I can recall, after the start up of the new process. So there was a gradual phase in of product from the new process, but I couldn't give you any data at all, exactly when material began to actually be sold from the new process.

Q That was going to be my next question, there was an overlap then between the old process and the new process?

A Correct.

Q And that was roughly 18 months, you said?

A On the order of 18 months, yes.

Q Was the old process eventually shut down in the 489 building?

A The old, yes, it was.

Q When you began your new responsibilities with regard to research on the new process, did someone else in the organic chemicals research department, was someone else assigned to doing any work or continuing with any work on the old process?

A I just simply don't recall how that -- the mind has gotten kind of vague as to specifically what was done, by whom, when, and all that.

Q Where there certain people within your department

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in 1975 that were assigned to the 2,4-D process beside yourself?

MR. WAGNER: This is the new process?

MR. SCHULER: The new or the old.

A Well, Harry Brust was certainly -- continued work on the new process. At this point I'll have to admit I simply don't recall who else.

Q Let me ask you this question, and if you don't know, just tell me and I'll move on, prior to 1975, when you became involved with organic chemicals research, do you know who was involved in the department, if anyone, doing research on 2,4-D?

A Harry Brust.

Q You said he's a chemist?

A Yes. And I know we had some engineers involved in that project, but I simply, at this point, don't remember who those individuals were.

Q Let me show you the report that we've talked about in this case, and I've highlighted some things. I'm just going to ask you to identify it for now, and if you have a copy of it, it will save me some time.



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A Yes, that's my report.

(Discussion held off the record.)

(Plaintiff's Exhibit 1 was marked for identification.)

MR. SCHULER: Back on the record.

Q Looking back at Plaintiff's Exhibit 1, here, this is your report from October 27th, is that 1978?

A Yes.

Q And you did this report for what purpose, Dr. Krumel?

A The purpose was to document some, essentially the research that is described in the report.

Q That's your answer, I take it?

A Does that answer your question?

Q I think so. There's some writing, I don't know, maybe this was from a prior lawsuit or something, but I've got some writing on top of mine that I see you don't have on top of yours. Do you recognize what that may be up there?

A Well, the report was obviously sent to somebody by somebody.

Q But you don't recognize it?

A No. Steve, Steve, it means nothing to me.



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Q In any event, this research was on the formation and removal of impurities in the 2,4-D process, correct?

A In the new 2,4-D process, yes.

Q And this was co-authored by Mr. R.F. Arnold?

A Ray Arnold is a laboratory technician who works with me. I was -- his part of the project is he ran the experiments or ran -- ran many of the experiments that are described in the report, but I'm the one that's responsible for the interpretation of the data. Ray was not qualified to do that.

Q And this was sent to, or it said receiver's signature, Peter Owen?

A Reviewer's signature, Peter Owen was my immediate supervisor. And the technique we use in report writing at Dow is the authors submit the report to the supervisor, and their supervisor has to sign the report before it can be issued.

Q What was Mr. Owen's position?

A He was, as I said, he was my immediate supervisor at that time.

Q Is he still with the company?



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A Yes.

Q Is he still in organic chemicals research?

A No. He's off in another department. At this point, I can't tell you exactly what his job is.

Q Up at the upper right-hand corner of Plaintiff's Exhibit 1, it says laboratory report code, OC, slash, 78, dash, 85. Do you know what that code stands for?

A OC is merely the designation for organic chemicals. It was the designation used by our library system to designate organic chemicals research. The number, it just means it's the 85th report written in 1978, to come out of this department.

Q And then below that, it's hard to make this out because of the copy I have, but it appears to be a lab number, is that right?

A Yes.

Q Let me --

A I beg your pardon?

Q Is it 05 or?

A 050.

Q And what is the significance of the 050 lab



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number, if any?

A That gets into some of the accounting and recharging of research dollars within the company. It has no meaning to the report, really, other than just to designate. The 050 is a laboratory number for accounting. The problem number is a method for internal recharging.

Q What do you mean by internal recharging?

A Well, how I'm paid, how my salary is paid.

Q And the problem number here is 9, six zeros?

A Correct. It has absolutely nothing to do with the report, itself.

Q With the subject matter?

A Yes.

Q Looking down at the descriptive summary with conclusions, let me just ask you a couple questions about that. One of the findings that you outline here is a new and unexpected class of non-acetic impurities, correct?

A Mm-hmm.

Q Yes?

A Yes.

Q And you mention two of the major components were



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tetrachloroxanthone and octachlorospirobixanthene?

A Yes.

Q And what type of impurities are those, I mean -- maybe that's a bad question, but can you categorize those impurities in any way?

MR. WAGNER: I object to the form of the question, compound, vague.

A Well, xanthone is an accepted organic nomenclature for a particular class of compounds. Spirobixanthene, again, is the same thing. It's accepted nomenclature. What they are is organic chemicals that were detected in the product.

Q In the final product of 2,4-D?

A That's where we first observed them, yes.

Q And when you mention that the impurities were causing problems in the subsequent formulation of 2,4-D as amine salts, what were you referring to, what did you mean by causing problems?

A The issue occurred as we stated before, the plant started up in May of '77. By that fall, what we started observing, we have a quality control test for our amines, where we mix a small amount of the amine salts with water, shake them up, centrifuge



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the samples and look at suspended solids, and we have a certain amount of solids in that that's an acceptable spec.

The problem that you run into, we started to see more of these solids, but where the problem really came up was when the formulated product was applied in the field, we started getting increasing customer complaints from plugged spray nozzles. At which point we went back and started looking specifically at those solids, and in these solids, that was where we first observed some of the compounds, the tetrachloroxanthene and the octachloro-spirobixanthene.

Q And this whole paper, if I understand it correctly, was devoted to exploring the possibility for attempting to control, minimize or eliminate these impurities in the 2,4-D?

A Correct. It was targeted at solving a customer complaint issue.

Q Do you recall whether there was a specific customer that did complain?

A I can't answer -- I just simply don't remember



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where the specific complaints came from.

Q Do you remember how you got notice of the complaint, that there was a complaint, and assigned this project?

MR. WAGNER: I object to the form of the question, compound.

A I don't recall the exact sequence of events. I believe people are mentioned in this report, a Joyce King, from formulations, in the 9001 building. It's on page 8 at the bottom. She is in our -- or she was in our formulations and TS&D area at the time. She would be working with our manufacturing supervision, who was working very closely with our R&D supervision in my department.

So the whole sequence of events I don't remember, but the bottom line came, I was assigned the job of getting involved in attempting to understand the formation and how we could get rid of them to solve a quality issue.

Q Do you know whether the old process that, from your earlier testimony, I understand was still ongoing at this time, was evaluated for these impurities, as well?



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A We tested the samples, and none were found.

Q When you say we, who are you referring to?

A Again, our team, the we in this case would have been someone from our analytical sciences department, and that someone was most likely, as best I can recall, Dale Humbert.

Q Humbert?

A Who is listed as a recipient on the back of this report under 574 building, D. Humbert. He was the chief analytical scientist supporting this area.

Q And from an overview standpoint, this report, you mention that the number of treatments and potential solutions that you examined, none appeared to be totally successful, correct?

MR. WAGNER: I object to the form of the question.

A That answer is -- yes, that's correct.

Q In my copy here, there's a blank that appears to be filled in on the one you have, the last paragraph. Can I see that for a second?

MR. WAGNER: Sure.

(Discussion held off the record.)

(Plaintiff's Exhibit 2 was marked for



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identification.)

MR. SCHULER: Back on the record.

Q Let me just follow through this report briefly with you. My page 1 is a table of contents, correct?

A Yes.

Q Page 2 appears to be an introductory section?

A Yes.

Q And that's where you mention at the top that the process, I think the word new is even blanked out, a new process for preparing high purity 2,4-D was started in May 1977 at the 943 building?

A 948.

Q Okay, it looks like 943 on mine, okay, 948 building. You mention that the high purity molten acid is transferred by pipeline to the 489 building where it is formulated into esters and water soluble amine salts, which would be the final product, correct?

A Yes.

Q You mention that the impurities that you found were never detected during laboratory or pilot plant development work, correct?



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A Correct.

Q Again, there's a word missing, I've got to ask, or there appears that there's a word missing, anyway. In any event, you mentioned, also, in this first paragraph, that the impurities were not found in the old process, correct?

A Yes.

Q And that was what you referred to earlier when you said there was some testing done in the old process, correct?

A Yes.

Q Who is R. McLachlan?

A He's an analytical scientist in the same department as Dale Humbert.

Q Is he still there?

A I don't believe he is. I have not -- I've lost track of him.

Q How about Mr. Humbert, is he still there?

A He's still in the company. He's not in analytical anymore, but I don't know specifically where he is.

Q Mr. McLachlan, in any event, was the one who analyzed precipitates and found the TCX and the



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OCSX?

A He's the one that wrote the report. Who actually did the work, I assume Dick did, but I don't know that for a fact.

Q But that's what you put in here, correct?

A Yes, that -- yes.

Q And the chemical formulas for the TCX and OCSX are outlined there, correct?

A Correct.

Q You mention that the TCX from the screening program at the plant showed levels of 200 to 500 parts per million in the crude reaction mass, and again, I'm missing words here. It says the recycle --

A Recycle sodium dichlorophenate.

Q -- solution and in the final product. Okay. Levels of 1,000 to 2,000 parts per million were found in the, and I'm missing --

A Would you want to just work off that, and we'll --

Q -- were found in the perc solvent, and as much as 10 percent in the still tars, perc still tars?

A Correct.

MR. WAGNER: I object.



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Q The toxicological significance of TCX and OCSX, is that unknown to you?

A Only what's reported in this report. I think on the next page, our page 6, is what I knew toxicologically about this material.

Q Where did you get the report on page 6?

A It should be referenced. It apparently is not --

Q So you don't know where that information comes from?

A Not specifically, anymore. There's a reference to, in the reference section on page 57, the very back of the report, reference two.

Q What reference are you referring to?

A Reference number two.

Q P. Keller?

A P. Keller, yes, that is from the --

Q Health and environmental toxicology?

A Yes, so --

Q Looking at that for a minute, on page 357 of Plaintiff's Exhibit 2, it says P. Keller et al, H-E-T, and some numbers, K, dash, 2372, dash, parentheses, 18. Do you know what that stands for?



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A I have no idea.

Q That would be the toxicology report?

A It is possible that that's the toxicology report.

Q And you're thinking --

A I don't know that for a fact.

Q Because it says HET?

A Correct.

Q Going back to page 3, it talks about 11 other minor components structurally similar to the above. When you say structurally similar to the above, what are you referring to there?

A Without having seen reference one for many, many years, I just simply don't recall.

Q Besides the TCX and the OCSX, though, there were other components that were discovered, as well?

A The compound shown as 8-5, and that is shown on page 4, and then on page 8 are two other impurities that were found, but specifically what the 11 minor impurities refer to, I have simply forgotten.

Q Go to page 4 for a second, the 8-5, you call this another significant impurity. What was the reason for calling it that?



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A Because it was detected in quantities that occasionally were comparable to what we were seeing for the OCSX and the TCX.

Q Do you know the toxicological significance of 8-5?

A I'm not aware of any data on that compound specifically.

Q Had the page 6 initial screening for toxicity report that you incorporated in this, that was research that you did not do yourself, correct?

A No, sir.

Q However, the report that you incorporated in Plaintiff's Exhibit 2 does appear to indicate chloracne response for different concentrations and different doses of the TCX and OCSX, correct?

A I only see, in this one, one concentration applied several times.

Q Well, correct me if I'm wrong, here, it looks to me like there are two. One is four grams per kilogram and the other is five grams per kilogram.

A Well, one is a tar sample that contains some TCX, some OCSX, and but you asked me, I thought you asked me specifically about TCX?

Q Well, I mentioned TCX and OCSX, as well.



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MR. WAGNER: Why don't we reask the question. Now, I'm confused about what's on the table.

Q My question was initially that the report that you incorporated in here by reference shows a chloracnegeneric response in various concentrations to both TCX and OCSX, correct?

MR. WAGNER: I object to the form of the question.

A The answer to the question is yes, to the best of my knowledge.

Q The diagram on page 7 is just a diagram of the process, would that be a fair statement?

A It is a very simplified diagram of the process, yes.

Q Do you know, when referring to the top of page 8, whether any data was obtained for long-term effects of these impurities that you found?

A I don't know.

Q At the bottom of page 8 you referenced earlier some other workers, and one is S. Siegel, OCR?

A Yes.

Q Organic chemicals research?



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A Yes.

Q And was that someone who worked with you?

A That was someone that was working alongside me, yes. As best I can recall, he was working more in the quality area directly with Joyce King and Susan Shell.

Q Susan Shell was in the production end?

A Yes, she was production supervisor.

Q Located in building 489?

A Yes, so she would have been production supervisor of the ester and amines portion of the process.

Q And Judy, was it?

A Joyce.

Q Joyce King was in the formulation end and located in Building 9001?

A Yes.

Q You mention in the last paragraph above the chemical symbols on page 8 that there were two other impurities called complex one and complex two, and you diagrammed those that were found, also, correct?

A Yes.

Q So we have, to keep track of all this, we have the



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TCX, the OCSX, the 8-5, and the complex one and complex two impurities, so far?

MR. WAGNER: I object to the form of the question.

Q Referenced in your report, correct?

A Yes.

Q Do you know the toxicological significance of the impurities, complex one and complex two?

A No, I don't. Incidentally, for correctness, there's a slight misprint on number four. The C shown in the middle shows CL; that should be CH. This should be -- may I?

Q That's CH there?

MR. WAGNER: If you're going to correct it --

MR. SCHULER: I'll correct it on this one because it's marked up already. That should be CH?

THE DEPONENT: Yes.

MR. WAGNER: How in the world you can remember that, I'll never know.

THE DEPONENT: Well, I just noticed it.

Q CH stands for?



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A The C stands for the chemical compound for carbon. The H is the chemical symbol for hydrogen. The CL is the chemical symbol or chlorine, and that would be an impossible structure.

Q And the OH is the chemical symbol --

A For the hydroxyl.

Q Oxygen and hydrogen?

A Yes.

Q K.E. First, referring to page 9, what role did that individual have in this report, if any?

A Ken First, at that time, was in process engineering, and I had actually even forgotten his involvement, but he did some computer modeling of rates of formulation based upon the data that I generated, or that Ray Arnold and I generated.

And the contribution I think in his report was to -- oh, goodness, I'm not sure what page it's on, but he talked about, if we maintained a certain level in the recirculating perc, we would maintain another level in the product. It's in the report someplace. I'm not sure exactly what page that's on.

Q We'll get to that. I just wanted to know who that



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was. Let's refer to page 9, Dr. Krumel, for a minute. At the bottom of page 9, after you essentially have outlined the impurities that we have already discussed, you decide to focus on TCX, correct?

A Yes.

Q And you stated the reason for the focus on TCX, one of the reasons was that it was a major impurity. What did you mean by that?

A Of these -- of the small amount of things that we found in the solids, it was a major component.

Q By volume, you mean, or some other yardstick?

A Typically what we're talking about would be by weight percent within these traces of solids that were found.

Q I want to ask you to skip over to page 21. One of the comments that you made on page 21 is that a recurring problem for the past several months was how to explain the fact that the plant observed TCX formation rates that were five times greater than the lab. Did you ever find the reason for that?

MR. WAGNER: I object to the form of the

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question.

A No, we never really did, nothing more than what's explained in this report.

Q In the first sentence of the last paragraph, full paragraph on page 21 of Plaintiff's Exhibit 2, you mention that in addition to TCX, OCSX and 8-5 are known to be formed measurable quantities during the reaction to 2,4-D -- maybe I didn't read that properly. In addition to TCX, OCSX and 8-5 are known to be formed in measurable quantities during the reaction to 2,4-D. When you say measurable quantities, can you tell me the relationship between the three, perhaps reflected in percentage as far as the ratio of the weights found?

MR. WAGNER: I object to the form.

A Without specifically reviewing data and numbers, I just simply don't recall, but we mentioned in the report 200 to 500 parts per million of TCX was found. Measurable quantities would, in that context, would mean comparable numbers, but specific data, I just simply don't recall.

Q On page 28, referring you to 28, and you can't tell because mine is the expurgated copy, here,

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but in the middle paragraphs you mention some TCX is formed in the reactor and was found throughout the 948 building process. When you say that, are you referring to the fact that the TCX was found at various points in the process or actually in the building, itself?

MR. WAGNER: I object to the form of the question.

A It was found in various process streams. As we indicated before, it was found in the reactor crude. It was found in the recycle dichlorophenate solution, and it was found in the recirculating perc, so it's found inside the chemical process, itself.

Q Was it found in the final product, 2,4-D?

A I think, back on page whatever, it was indicated that yes, we did find it in the product, itself.

Q Referring to the bottom of page 29, you make note of the fact that the 8-5 impurity is not efficiently removed with perc extraction, hence most of what is made goes out with the product. Why was that a concern?

MR. WAGNER: I object to the form of the



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question.

A Again, because it is, the trace levels that were in the product are insoluble in the amines formulating mixture and would again result in small amounts of solids that I think we discussed earlier.

Q In the table five above that statement you have some numbers for initial and final as far as TCX and 8-5 in parts per million, correct?

A Yes.

Q What does that refer to, initial and final, in that chart?

A I have to read the chart. What we did was simulate the process in the laboratory, and to take a sample of the crude sodium salt of 2,4-D, extract with perchloroethylene, in the laboratory, and analyze the sodium 2,4-D before and after extraction with perchloroethylene, and these are merely the results of those experiments.

Q Is the final referred to in the final product, or is that at some other juncture that you extracted the TCX and 8-5?

MR. WAGNER: You mean the columns,

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final, is that what you're referring to?

MR. SCHULER: Yes.

A This would refer to the sodium. This would not refer to the final product, but rather to the intermediate sodium 2,4-D.

Q At the bottom of page 30 you refer to the 2,4-D reaction as developed by H. Brust. Is that referring to this new process?

A Correct.

Q At the bottom of page 31, you mention that formation of the TCX cannot be limited to much less than 60 percent per million. Is that with reference to the final product of this new process, or sodium or the amine version of 2,4-D?

MR. WAGNER: I object to the form of the question.

A This refers to laboratory experiments which, as you can see, were run at 72 hours at 160 degrees in glass equipment. This is not refering to plant.

Q So this is the product that you were getting in the laboratory?

A Correct.

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Q Did you ever test the final product from the plant to determine a TCX concentration?

MR. WAGNER: I object to the form of the question.

A The product in the plant was analyzed routinely for these compounds.

Q And is there information here in this report with regard to that, or would that be located in some other report?

MR. WAGNER: I object to the form of the question.

A There may be a reference within the report here or there. I don't specifically recall talking about specific plant data. All of the numbers reported in various tables, to the best of my recollection, are all laboratory generated numbers.

Q So you were using, you simulated the process or reconstructed the process in the laboratory, and the numbers in this report are with regard to the product you produced in the laboratory?

A Correct, other than the numbers that we discussed at the very beginning, where we said we found 200 to 500 parts in the reactor crude and in the

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recycle, those were plant data.

Q With the plant data that you mentioned, it would be generally higher than the laboratory data for as far as the content of the impurities was concerned?

A We observed that, I think I mentioned it a little bit ago, where you were asking me, it's on page 21, where the plant observed TCX formation rates that were five times or so higher than laboratory.

Q Referring to page 35, you make reference to an earlier report, and it's got a number, footnote 16. Is that the report that's listed as 16 in the reference section on page 57?

A I recall the work. I do not recall the report.

Q What's listed as 16 on page 57 has some numbers behind it. Organic chemistry, I assume is the OC?

A Yes.

Q And then 78, dash, 17 stands for what, if you know?

A I guess I don't remember specifically. The thing that confuses me a little bit is the LR, because that is a code that we used to use for letter reports, which were a way of documenting results



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back at that time. I think I mentioned earlier the numbering code that we used. Well, we mentioned it on this report, but the 78-17 LR, I don't specifically remember how we used to number those.

Q What about the 39, dash, 78?

A That, I'm not sure about that, either.

Q There's a reference in the reference section, number 12, also, to some work done by, is it Dr. Brust?

A Yes.

Q And refers to organic chemicals, again, with a long number, dash, 2, and then a 2-26-73. Do you know what that refers to, number 12?

A That's one of Dr. Brust's research reports. I can't tell you from the number exactly which one. The date is the date that the report was issued. The numbering code is, the 0730013 is a coding system that was used for a period of years.

CHECK CHECK CHECK.

Q Any significance to that?

A Nothing as far as a -- I don't specificalloy recall.



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Q Was there a specific number that was assigned to subject matter, for example, like 2,4-D, was there a specific file or series of files pertaining to a particular chemical like that?

A Different coding systems were used at different times. Now, whether there was a coding system specifically designed to 2,4-D, I don't recall.

Q You don't remember whether there were specific codes that were assigned to certain chemicals, for example, to keep research, no matter what aspect it dealt with, but in regard to a certain chemical in that area that existed?

MR. WAGNER: I object to the form of the question.

A I don't specifically recall all that went into how they specifically assigned codes, because it changed at times. And what was used specifically at the time this report was issued, I don't really remember.

Q Was the research or the organization of the product of the research computerized back in 1975?

A Was the research computerized in 1975?

Q I mean the organization of the reports?



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A Oh, no, these were not done by, on computer.

Q But were they filed? Was there a computer index of the reports, if you know?

MR. WAGNER: In 1975?

MR. SCHULER: In 1975.

A In 1975 was there a computer? I don't know for certain.

Q At the bottom of page 36, or on page 36 I should say, you make a comparison in the first paragraph between the two processes, the 489 building and the new process in the 948 building, correct?

MR. WAGNER: I object to the form of the question.

A Are you talking about under item four?

Q Yes.

A Well, the process in 489 building did use a step involving the use of bleach that was not used in the new process, that's correct.

Q And were you making some type of an estimate as to whether adding a bleaching step would improve or reduce, help to reduce the impurities that were found in the new process, is that what you were doing there?



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A Yes. It was an option we wanted to consider.

Q And it is apparently submitted to somebody by the name of K.E. First?

A That's the same Ken First we discussed earlier.

Q And he estimated a cost of doing that at 500,000, is that what that is?

A Yes.

Q So that wasn't pursued because of the -- it wasn't cost effective?

MR. WAGNER: I object to the form of the question.

A Yeah, as stated in the report, it was dropped due to the marginal benefits that we concluded.

Q At the top of page 38 you mention the capacity of the 948 building up to that point in time, and I just want to know, need to know the numbers you're referring to there, it's 100 to 120 what per day?

A It's 100 to 120,000 pounds per day.

Q What, the new process?

A Yes.

Q Do you know at this time or, let me go back, do you know as of May of 1977 whether the 948 building was running at that capacity?



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A In May of '77 when we started up?

Q Yes.

A No, it was not.

Q What about when this report was done in October?

A The date would basically refer to the date this report was issued, so we're talking about, essentially now, October 1978. What the running rate was in October of '77, which is, I assume, the date you're asking about?

Q Yes.

A I don't know.

Q That's right, this report was October of '78, so you're referring to the full capacity as of October of '78?

A Correct.

Q And in your statement in the next sentence with regard to the impurities in the 2,4-D product is what, 20 parts per million of TCX?

A Yes.

Q And 20 parts per million of 8-5?

A Plus or minus some. What the ranges are, I don't recall.

Q You mention in a couple of paragraphs down that



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further work is justified only if the levels of impurities presently found in the product prove unacceptable in the future from a toxicity, environmental or performance standpoint. Do you recall whether there was any further research done in any of those areas to determine whether these impurities were unacceptable?

MR. WAGNER: I object to the form of the question.

A No, I don't recall.

Q You did not do any research in those areas, I take it?

A The work that we would have done in those areas would have been continuing to work in the plant, monitoring and making sure that we were, in fact, operating within these ranges.

Q You mean the ranges of 20 parts per million?

A Yes.

Q Was there a quality control laboratory set up in each building, for example, the 948 building for 2,4-D and the 489 building for 2,4-D?

A Yes.

Q And so the analyses that you referred to earlier

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with regard to quality control were performed right there in the plant, if you will?

A Correct.

Q As opposed to the organic chemicals research laboratory?

A We did very, very few analyses ourselves, in our department. We would rely on the quality control laboratories, as well as the analytical sciences laboratory.

Q Was there a quality control officer assigned, for example, to building 489?

A I can't answer how that was -- I don't know how that was managed those days.

Q Was that a separate department in 1975, quality control?

A The quality control work, during the time frame we're talking here, was done within the plants. How the data was managed in reference to a quality control officer, or as you brought up, I just -- I don't know.

MR. WAGNER: Let's take a quick break.

(Recess.)

BY MR. SCHULER:

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Q The acknowledgment section on page 56 of Plaintiff's Exhibit 2 mentions a number of people, some of whom you've already referred to, Dr. Krumel, but let me ask you about some of the others. Who is T. Evans?

A Tom Evans was an analytical scientist, as was Gary Jewett, as was Penn, P-E-N-N, Schloemann -- well, as I indicated, for their analytic support.

Q I just wanted to identify them. Did they all work on some aspect of preparing this report that we have marked as Plaintiff's Exhibit 2?

A They all would have provided input in the analytical results that were described within the report. I couldn't identify for you specifically what each one of those individuals did at this time, but they were all part of providing the analytical backup for this report.

Q Did any of them do any research on 2,4-D prior to the new process, the old process, we'll call it?

A Not that I recall.

Q I asked you about some of the documents listed on page 57, the reference section. Who is Mr. Dhingra, D-H-I-N-G-R-A?



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A Yes, Yog Dhingra.

Q Who is that?

A He's a chemist who was involved in the phenoxy area during the time I was in the cellulose ether area. So specifically what he was doing and what he was referring to in this reference, I can't tell you right now.

Q Mr. Fern or Ms. Fern, whatever that is, do you know who that is, it's the next one down, number 14?

A That's a misprint. That's what I was afraid of. You can -- back to page 31, I refer to Dhingra and Fear, reference 14.

Q So that's Fear?

A The name should be Fear, F-E-A-R, Dennis Fear. He was an engineer who was very much involved in process modeling. Now, we'd have to look at the report if you want to get specifically as to what he did.

Q The work that you did in the organic chemical research laboratory, was that originally committed to what's referenced here in some places as a lab book?



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MR. WAGNER: I object to the form of the question, over broad.

A Our standard way of initially documenting our work, as we're doing the experiments, is to write them up in research data books. The results of our work described in these research data books is then summarized in these research reports.

Q So the summary, this research report would be the summary of what's in the research data book for a particular experiment?

A Correct, or a particular project.

Q There's a reference at the bottom where it talks about laboratory notebook references, and it has your name and Mr. Arnold?

A OC 417 and OC 640, those are code numbers for the data books. The pages merely describe, so in research data back OC 417 for Ray Arnold, you will find the work that is summarized in this report described in pages 109 to 150. And in data book 640 from pages 1 to pages 73, and likewise in my research data book, OC 559, you will find work described in this report on pages 95 to 131. This is the way we have of referencing our reports back



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to the original data.

Q All right. After this was completed, did you do any further research with regard to these impurities in the new 2,4-D process?

MR. WAGNER: I object to the form of the question.

A Not that I can recall.

Q Did you do any further research into the old 2,4-D process after October of 1978?

MR. WAGNER: I object to the form of the question.

A Not that I can specifically recall.

Q At some point in this report, this 2,4-D was referred to as Rhone-Progil acid. Do you know what that means?

A Yes. Rhone-progil was a company in Europe that produced 2,4-D acid at that time. Their material happened to be particularly pure, so we had a sample of it that we used for research purposes only.

Q And that's why you refer to it by that name?

A Rhone-Progil, yes.

Q Was the new process for 2,4-D developed to reach

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the level of purity that had been developed by this Rhone-Progil company?

MR. WAGNER: I object to the form of the question.

A To my knowledge, there's no connection.

Q Did you, other than writing your report, and I assume, let me go back and ask this question, I assume this report, that we have marked as Plaintiff's Exhibit 2 here, was written for intercompany use?

A Yes.

Q Did you ever write any report for use outside the company, to anyone outside the company?

MR. WAGNER: On any subject at any time?

MR. SCHULER: No, on this subject.

A On this subject, no, I've not.

Q Did you ever communicate information to anyone outside the company regarding the fact that there were these impurities in this new 2,4-D process that were found and outlined in your report that we marked as Plaintiff's Exhibit 2?

A Not that I recall.

Q Do you know whether anyone else at Dow Chemical



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Company communicated information in this report that we marked as Plaintiff's Exhibit 2 to anyone else outside the company at any point in time?

A Not to my knowledge.

Q Do you know a Mr. Wisniewski, D.F Wisniewski?

A Dave Wisniewski.

Q What was his position back in '78 or '79, if you know?

A He was an analytical chemist that offered support to the general phenoxy area. Specifically what he was doing at that time, I can't tell you.

(Plaintiff's Exhibit 3 was marked for identification.)

Q Let me show you this document here and ask if you've seen this before, and you might show your counsel there, too. Let me see the date on that.

A December 16th, 1979.

Q Have you ever seen that document before?

A Not that I recall.

Q You weren't involved in any of the research that went into the preparation of that document?

A No, sir.

Q Mr. Wisniewski appears to at least have done some



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toxicological oriented research. Do you know if he's a toxicologist or not?

MR. WAGNER: I object to the form of the question.

A No. Mr. Wisniewski was definitely, he was an analytical chemist.

Q Is Mr. Wisniewski still with the company?

A Mr. Wisniewski passed away a number of years ago. So the right answer is no.

Q He may be with some company --

MR. WAGNER: Spiritually.

Q -- not with Dow Chemical Company. Do you know what his background was, Mr. Wisniewski's background, I'm talking about scientific specialty, obviously?

A Well, Wisniewski worked in the analytical department. What his specific scientific background training is, no, I don't know.

Q Well, I don't see your name on this one, either, but let me ask you if you've seen that before?

A This would be a document having been prepared within the analytical department, and no, I had no involvement in its preparation, nor do I recognize

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it specifically.

(Plaintiff's Exhibit 4 was marked for identification.)

Q There's a sheet attached here to this Plaintiff's Exhibit 4. It's very difficult for me to read, and probably it will be for you, too, but can you make out, it appears to say release rerouting sheet. Have you seen a form like that before?

A I have no idea what this is.

Q Have you ever testified in any form before the Environmental Protection Agency, for example, or the Department of Agriculture, regarding these type of chemicals?

A No, I haven't.

Q Have you ever written any reports that were furnished to the EPA that you're aware of?

MR. WAGNER: On any subject?

Q On the subject of these chemicals, 2,4-D, 2,4,5-T, Silvex?

A Not that I can recall at this time.

Q Do you know who Marguerite Leng is?

A Yes, I know Marguerite.

Q What is her position -- well, let's start with is



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she still with the company today?

A No, she's retired.

Q What was her position when she was last with the company, if you know?

A She was -- I can't give you her exact title. She was in the regulatory department in some capacity, but I don't know exactly.

Q Do you know if scientific reports were provided to her on a regular, continuing basis, particularly regarding these chemicals?

MR. WAGNER: I object to the form of the question.

A The only reports that I would know would have been distributed would have been, to whom I can say the reports were distributed were the ones that were listed on the back cover here, and if she isn't on that list, then I can't answer, then I don't know if she was or not.

Q Have you ever been involved with her in terms of, and I'm not just limiting it to these chemicals, but have you ever been involved with her in the sense that you submitted a copy of a scientific report to her and she reviewed it for some



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purpose?

A I don't specifically recall having done that.

Q Have you ever been involved with her in any type of work at Dow Chemical?

A Only very much on the periphery. Marguerite happens to be a personal friend, and I know her more from that standpoint than the work standpoint.

Q Outside of being a personal friend of hers, I'm talking about whether you actually worked with her on any type of reporting or scientific work?

A Not that I can specifically recall at this time.

Q And just so I'm clear on this, do you know whether she ever edited any reports that you submitted?

A Not to my knowledge.

Q Do you know an Andrew Watson?

A I know the name, but I don't know the individual.

Q Would the function of determining the effectiveness of end product 2,4-D, for example, for its ultimate purpose, killing weeds, would that be done by another department other than yours?

A Yes.

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Q What department would be involved in doing that?

A Well, at that time the department was known as the agricultural product department. In the 9008, 9001 building area, the person we mentioned before, Joyce King is one who is more likely to get involved in that type of activity.

Q Was she involved from the agricultural product standpoint with 2,4-D back in 1975?

A The only time I specifically know that she was involved with this project was when we were working on the product, on the issue of xanthones and related compounds over the time frame described in this report.

Q Have you been involved at all in the registration process for 2,4-D, to your knowledge?

MR. WAGNER: I object to the form of the question.

A The only involvement that I would have had is to supply process descriptions to the individuals who actually -- who prepare for reregistration packages, and I have provided information on occasion to those individuals.

Q Let me see if I understand this, process

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description for reregistration packages, what would that entail?

A Well, the reregistration -- a small piece of the reregistration process or package is to describe the chemical process for producing the product. And I would -- I have in the past provided information to that. I can't give you specific dates off the top of my head when I've done that, but I know I've done that.

Q Did you do that in connection with 2,4-D?

A Yes.

Q Can you give me an approximate time period when you did that with respect to 2,4-D?

A Early to mid eighties time frame.

Q Can you tell me what individuals you dealt with, in other words, who you furnished these process descriptions to for the reregistration package?

A I don't specifically recall at this time.

Q Was there a particular department that dealt with the registration process?

A The ag chemicals product department did that, so it would be an individual in that department.

Q Is that department presently located in any

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specific building?

A Well, since the formation of DowElanco, the organization is now very much different than it was during the time we're talking about here. All of the activities that were out of the 9001 building and 9008 building are now here in Indianapolis with DowElanco.

Q Have you ever had any input into the labeling process for 2,4-D?

A No.

Q Do you know whether the 2,4-D label ever reflected the impurities that you found in your report of October of 1978?

A Not to my knowledge.

Q Do you know whether the 2,4-D label ever reflected any impurities found in the product prior to October of 1978?

MR. WAGNER: I object to the form of the question, over broad.

A Not to my knowledge

Q Would the agricultural products department also have responsibility for labeling, to your knowledge?

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A I can't answer that specifically, but I would assume yes.

Q Do you know, for example, back in 1975, any individuals' names who might have had that responsibility?

A No, I don't -- I don't know any names since that was far removed from my involvement in the project.

Q Back in 1975, and I apologize if I asked this question or a version of it earlier, but I want to be clear about this, back in 1975, besides yourself, who else, if anyone, in the agricultural chemical process or products research section had responsibility for any aspect of the 2,4-D research?

MR. WAGNER: It was asked and answered. I don't think he remembered it.

MR. SCHULER: I think he mentioned Mr. Brust.

MR. WAGNER: That's right.

A I did happen to think of one more individual, a gentleman by the name of Quentin Hutchcroft.

Q Is he still with the company, Mr. Hutchcroft?

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A No. He left the company many years ago. He was a colleague of mine, and he and I worked together on an aspect of the process.

Q Anyone else that you recall?

A That's the only additional person that I can recall that I didn't mention earlier.

Q I think you testified that you, maybe I misunderstood you, but I want to be clear about this, you haven't done any further research on 2,4-D after this 1978 project, is that correct?

A I was -- I was the process chemist responsible for 2,4-D process research until approximately 1983, 1984, time frame. I think you asked the question in the context of specifically this report that we have been discussing, and --

Q Yes.

A -- and to the best of my knowledge, I've not done any work since that report.

Q When you say work since this report, you were responsible, but there was no, once the process got up and running, there was no further research from your department on the 2,4-D process or 2,4-D, itself?

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MR. WAGNER: I object to the form of the question.

A Oh, yes, oh, yes.

Q Can you give me an idea of what other research was done on 2,4-D after October of '78 up until '83?

A We were -- well, we did some further research on a modified process over what was described for, I think we discussed the plant in Aratu, Brazil, there was process research done in that area. There was process research done in the area of other trace impurities in the process. We were doing a lot of work during those days in the area of related -- related to waste brine treatment clean up. Those are three key areas that I can recall.

Q Waste brine being a by-product of the process?

A Yes, one of the by-products of the process was an 18 to 20 percent sodium chloride stream.

Q And what else, anything else comes to mind?

A Those are the key areas of our research, and continued support of the process. When plant problems crop up now and then, and these can be any one of a number of different things, that

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we're constantly asked to provide technical support to the plant, to the manufacturing staff.

Q Have you done any research with regard to 2,4,5-T or Silvex since 1975?

A Yes.

Q And can you give me some examples of research you've done and the time period it may have occurred?

A In addition to the 2,4-D acid process that was run in 489 building, we did have a process that produced 2,4,5-T and 2,4,5 -- well, Silvex esters. We called that the direct ester process. And, yes, I was involved in sampling and evaluating results in the areas of 2,3,7,8 TCDD and other polychlorinated dibenzo-para-dioxins, and we did some research in that time frame about further reducing those impurities from our product.

Q And when you say that time frame, you're referring to 1975, 1976, somewhere around there?

A The peak time frame of 1975 to 1979, when the direct ester process was shut down.

Q Did you generate reports?

A Yes.



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Q On that?

A Yes.

Q Do you have any of the reports with you today?

A No, sir.

MR. SCHULER: Are you taking the position that Dow has them, and he doesn't have them, that's why you're not producing it?

MR. WAGNER: Correct, they're not his reports.

Q From 1975 through 1979, did you find the presence of TCDD in either Silvex or 2,4,5-T end product?

A Yes.

Q And do you recall at what levels you found it?

A Typically the levels could range in the .03 to .07 parts per million of 2,3,7,8 TCDD.

Q Was there a fluctuation from batch to batch?

A Yes.

Q Did you ever find the presence of TCDD at a higher level than .07 parts per million in any batch that you sampled?

MR. WAGNER: I object to the form of the question.

A I don't recall specific data. When I tell you the

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.03 to .07, those are ranges that I recall that we would see in the product in that mid-1970 time frame.

Q Can you give me a rough idea how many reports were generated about that subject matter, the finding of TCDD or other dioxins in 2,4,5-T or Silvex?

A I couldn't give you an exact number or even a close number at this point.

Q Those reports, I assume, were written and used for intercompany purposes?

MR. WAGNER: I object to the form.

A Certainly anything that I wrote that would have summarized results would have been done for intercompany purposes. What happened to the data beyond that point, I can't comment.

Q Who else worked with you in this particular analysis or research into the presence of these dioxins in those end products?

A Well, Mr. Arnold would have provided technical support, laboratory support to me. Mr. Siegel that we mentioned earlier, has done work in that, during, again, this 1975-1979 time frame.

Q Other than Mr. Arnold and Mr. Siegel, anybody else



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that you can recall?

A Not that I recall specifically at this time.

Q Was this, for lack of a better term, kind of a continuing monitoring process when you tested these chemicals for the presence of TCDD or other dioxins?

MR. WAGNER: I object to the form of the question.

A Right.

Q How frequently would you test these products for the presence of those contaminants?

MR. WAGNER: I object to the form of the question.

A In our direct ester process, I don't recall the frequentcy that we did at that time. This was a quality control lab, analytical lab function that I was only off on the periphery of with access to the data.

Q When you say the direct ester process, would you also test the amine version of 2,4,5-T?

A I don't recall that we produced an amine form of 2,4,5-T at that time.

Q What about Silvex, was that tested?

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A The Silvex esters would have been tested, as would the 2,4,5-T esters.

Q The amine formulation of 2,4,5-T was not manufactured by Dow, you're saying from '75 to '79?

MR. WAGNER: I object to the form of the question.

Q Or did I misunderstand you?

A I don't recall that we manufactured the amine form of those compounds at that time.

Q At some earlier time did the company do that, if you know?

A Not that I know of specifically.

Q Where would these records be kept from your testing of these end products for TCDD or other dioxins?

A Well, the records we're talking about are records that were generated, as I said before, by the quality control labs and by the analytical lab, so it would be within whatever, wherever their documentation is maintained.

Q Would that be in the plant or some other place, if you know?

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A Some would be in the plant, and some would be within our central reporting index.

MR. WAGNER: Was your question directed to today or back then, Dick?

MR. SCHULER: During the period of 1975 to '79.

THE DEPONENT: Yes, that's when I was answering.

MR. WAGNER: I thought so.

Q During the period from 1975 to 1979, do you know whether there was any listing on the labels for 2,4,5-T or Silvex that those products contained either TCDD or any other dioxin contaminants?

MR. WAGNER: I object to the form of the question.

A I don't know.

Q Do you know whether any information from 1975 to 1979 was furnished to the government with regard to the dioxin contents of those end products?

MR. WAGNER: Same objection.

A I am not aware specifically of information that was submitted to the government on that subject.

Q Were you involved in the decision to shut down

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production of Silvex and 2,4,5-T?

A No, I wasn't.

Q Do you know who was involved in that decision?

A The managers of ag production and of the product department whose names -- who the specific individuals that would have met to make that decision, I couldn't answer at this time.

Q Do you know who the individuals were that may have been involved in making the decision?

A I can't give you a specific name.

Q Did you have, once a decision was made, did you have any role in shutting down of the process?

A No. Once the process was shut down, it was shut down, and being an organic chemist working in research, I had no involvement in the project.

Q Were you aware, between 1975 and 1979, of any hearings that were ongoing with regard to what's known as a rebuttable presumption against registration for either Silvex or 2,4,5-T?

A I knew about them, but I had no involvement in them, and I couldn't -- don't recall any of the specific details at this time.

Q You don't recall furnishing any information that



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was used in the course of those hearings?

A No, sir, no specific information that I recall.

MR. WAGNER: Let's take a quick break.

(Recess.)

BY MR. SCHULER:

Q Back in 1975, was the 2,4-D that was manufactured by Dow Chemical primarily sold in its amine form?

MR. WAGNER: I object, no predicate as to personal knowledge.

A It was sold. I can't comment as to whether it was sold primarily as the amine formulation. We certainly sold a significant quantity of it as the amine formulation, but I don't know the balance of esters, amines and acids sold.

Q Do you have any knowledge of the total amount of 2,4-D sold on an annualized basis, for example, back in 1975 and 1976?

A I couldn't give you a number from personal knowledge. It would be speculation.

Q You mentioned that the, in your report that we marked as Plaintiff's Exhibit 2, that this 948 building at capacity could crank out 100 to 120,000 pounds a day, correct?



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A Yes.

Q What did building 489, what was its capacity, if you know?

A I don't recall that number anymore.

Q Do you know if it was similar to the 948 building or not?

A It would have been in that magnitude, but a specific number, I just don't remember.

Q Were there any other buildings that Dow Chemical had, back in 1975 and '76, that produced 2,4-D other than those?

MR. WAGNER: In Midland?

Q In Midland, yes.

A No, sir. Those were the only places it was produced at that time.

Q Were there other locations back at that time that produced the chemical on behalf of Dow?

A The subsidiary produced 2,4-D for Dow in New Zealand, Ivan Watkins Dow, W-A-T-K-I-N-S.

Q Any other locations around the world?

MR. WAGNER: In 1975?

Q Yes, the '75-'76 time period.

A No. Those were it, those were the facilities.



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Q Do you know, and again, if you don't know this information just tell me and I'll move on, but do you know in what units the chemical 2,4-D was sold in '75 and '76? In other words, was it sold by the ton, by the pound, by the gallon?

A It was sold in a variety of different containers; gallons, five gallons, 55-gallons, tank cars, different products were sold in different containers, specifically, you know, the specific balance.

Q In 1975 and 1976, would you be aware of what the five gallon container looked like?

MR. WAGNER: For?

MR. SCHULER: 2,4-D.

A Amines, esters?

Q Amines.

MR. WAGNER: I object to the form of the question, not specific.

A I have seen the cans, but after 17 years, to recall exactly what was on the can and how it looks, I don't.

Q Were the cans metal or plastic back then?

A Metal.



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Q And do you recall the color of the cans?

A Not anymore.

Q Same question for Silvex, would you recall the color of the cans? Was it sold in cans?

MR. WAGNER: I object, compound, no predicate.

A Silvex, I can't recall specifically the way Silvex was supplied.

Q Same question with regard to 2,4,5-T?

MR. WAGNER: Same objection.

A And the same answer as for Silvex.

Q Do you know what the unit price was for a five-gallon can of 2,4-D back in '75 and '76?

A No, I don't remember that.

Q Who would know that information?

A That would be information that would available from the commercial function.

Q Agricultural products division?

A Yes -- well, DowElanco now, if those records still exist.

Q Do you have any opinions with regard to the toxicity of 2,4-D as it applies to human beings?

MR. WAGNER: No predicate as to



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expertise in that area. You mean his opinion today?

MR. SCHULER: Yes.

MR. WAGNER: Well, the question is whether or not you have an opinion. Go ahead.

A Well, as an organic chemist, not trained in toxicology, I don't feel I can render an opinion on that.

Q Have you participated in any other, had input in any reviews that the EPA has instituted with regard to the safety of 2,4-D?

MR. WAGNER: I think it's been asked and answered.

MR. SCHULER: I asked about Silvex and 2,4,5-T before.

MR. WAGNER: You're correct.

A I'm sorry, with the dialogs --

MR. SCHULER: Could you read that back.

(The requested material was read by the reporter.)

MR. WAGNER: I object to the form.

A No.

Q Back in 1975 and 1976, were you aware of any



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published literature that, I know you're not a toxicologist, but I'm asking you in your capacity as a scientist, were you aware of any published literature with regard to the potential for carcinogenicity of 2,4-D or Silvex?

A For the potential of carcinogenicity, no.

Q Same question with regard to 2,4-D, same time period?

A No.

Q Do you, yourself, subscribe to scientific journals other than what may be available to you in the Dow library?

A As a member of the American Chemical Society, I receive their weekly publication, Chemical and Engineering News. Otherwise, all of the scientific journals that I read are provided to me through Dow.

Q Do you know a fellow by the name of Leonard or Len Smith?

A Yes.

Q And what is his position or was his position at Dow?

A I don't know what his position was at the time,



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over the time frame that we're talking about here.

Q Is he still with the company?

A He's with DowElanco.

Q Here in Indianapolis now?

A Yes.

Q Do you know what his position is?

A He just moved, and I forget his new title.

Q When you were doing your analysis as reflected in your report of October of 1978, did you take hygienic precautions in dealing with those chemicals that are outlined in that report?

A Yes, I did. I used the standard, good laboratory practices that we follow in our department.

Q What kind of precautions did you take back in 1977-'78, when you were working on this report?

A Lab coat, impervious rubber gloves, glasses, goggles, all of our work was performed in a properly ventilated hood, the standard precautions that we take with toxic and hazardous chemicals.

Q Do you wear any special type of pants, for example, or does the coat come down pretty l-

A It was a typical knee-length laboratory coat.

Q And do you wear any type of special shoes or boots



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or anything like that?

A No.

Q When you say you work in a ventilated laboratory hood, what does that look like?

A The typical laboratory hood is a bench top, perhaps typically they're six feet wide, about 30 inches deep, with air movement sweeping across so that we're adequately protected.

Q The fumes are sucked up into the exhaust, if you will?

A Yes.

Q Did you ever wear a respirator in dealing with any of the materials outlined in your October '78 report?

A No.

Q Other than the research that we've discussed here today involving 2,4-D and 2,4,5-T and Silvex, have you done any other research with respect to those chemicals that we haven't discussed here today or touched on in your testimony?

MR. WAGNER: I object as to breadth.

A Yes.

Q What type of research?



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A Well, notably we did some research in the 2,4,5-T area where we learned how to further reduce the quantities of dioxins from the product. I think I gave you numbers to the best of my recollection of .03 to .07. We developed technology, again, I can't give you a concrete date, but in the '77-'78 time frame, to further reduce those levels in the ranges of, again, as best I can recall, .01, .02.

Q And what, do you recall the type of technology that was developed or methods that were developed to reduce the TCDD down to that level?

A The post treatment, prior to formulation, with activated carbon.

Q I'm not sure I understand -- post final product --

A The technical product, before it is formulated into the final product, was passed through a bed of activated carbon.

Q And the carbon helped to filter out some of those impurities, at least down to that level?

A It removed the impurities down to this level of, again, as best I recall, .01, .02, .03, in that range.

Q And to the best of your recollection, that would



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have been in the '77 to '78 time period?

A Plus or minus a little, yes.

Q Who else would have worked on that project with you?

A Sanford Siegel, in the laboratory.

Q Who else would have been involved with that project outside the laboratory as far as implementation of the carbon filters are concerned?

A That would have been, obviously, with the engineers in the plant. Specifically who the engineer or engineers were at this time, I don't recall.

Q Was anyone from agricultural products involved with that decision to approve the use of the carbon filters, for example?

A I don't remember the decision process for specific implementation of all that.

Q But you were involved doing the lab work?

A I was involved developing the technology, yes.

Q Any other research that you did with respect to 2,4-D, 2,4,5-T or Silvex between the 1975 and, say, 1977 time periods?



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MR. WAGNER: That he hasn't touched on?

MR. SCHULER: That he hasn't mentioned already, of course.

A We have touched on a number of topics at various times. I think we have covered them all.

Q Let me just ask you about the documentation. Do you have a CV, curriculum vitae, summarizing your educational background, experience, training in your profession?

A No. I haven't had a resume prepared since --

MR. WAGNER: He's not been job hunting.

A -- like almost 28 years.

Q You haven't looked for a job in a long time, that's right. Okay, in the notice of taking deposition I had, and by the way, you spell your name, K-A-R-L, correct?

A Yes, sir.

Q In the notice of deposition I had asked you to produce any and all documents produced by you or at your direction during the course of your employment with Dow Chemical Company or its subsidiaries that pertain to any research, analysis, formulation, study or production of the



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chemicals 2,4-D, 2,4,5-T, Silvex or any product or substance containing these chemicals or any ingredients used in making these chemicals or any contaminants or dioxins contained in any of these chemicals or their ingredients.

Today you produced no documents, correct? You gave me the October of '78 report that I already had. Did you bring any of those documents with you here today?

A Well, all the documents are owned by the Dow Chemical Company. I have no documents that are owned by me.

Q So the answer is, you did not bring any of those documents here with you today?

A That's right.

Q You have not served, I understand from your earlier testimony, as an expert witness in any case, correct?

A Correct.

Q You have not issued any documents, reports, articles or transcripts relating to any opinion you might have ever formed regarding the cause of soft tissue sarcoma or the toxicology or health



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effects of 2,4-D, 2,4,5-T, Silvex, 2,4,5-TP or any product or substance containing any of those chemicals?

A No, sir.

Q You mentioned your status as, I think you told me initially as senior scientist?

A My official title within Dow Chemical Company is an associate scientist.

Q Are there rankings within the company by title, and you get certain income, kind of like the military or an organized entity like that?

A Yes.

Q So when you reach, you have a certain title, you reach a certain level, you get a certain income that goes along with that, would that be a fair statement?

A Yes.

Q How long have you been with the company, the number of years?

A I joined the company in June of '65, so that puts me at 27 years, nine months.

Q Do you intend on staying with the company for the time until retirement?

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A Yes, I do.

Q When do you anticipate, if you do, retiring from the company?

A I have no plans for retirement at this point.

Q Prior to coming here to this deposition today, did you review any documents, other than obviously the document we have marked as Plaintiff's Exhibit 2?

A I reviewed one other letter that Allen showed me that was essentially a letter written by my manager at the time, I don't remember the exact date on that letter, to an analytical manager telling him we were going to be providing him with some samples for analysis for various chlorinated dioxins. Those are the only two documents that I've specifically reviewed for this deposition.

Q Who is your manager who wrote that letter?

A That was Dr. Mintz, Michael Mintz.

Q What was the date of that correspondence?

MR. WAGNER: I think he said he didn't remember.

A I don't remember the specific date. It would have been in the period of, around 1976, plus or minus a little.



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Q Prior to the time of this report that we have marked as Plaintiff's Exhibit 2?

A Yes.

MR. SCHULER: Did you have a copy of that? Can I see a copy of that?

MR. WAGNER: No.

MR. SCHULER: You have a copy present here today? You're just not going to let me see it?

MR. WAGNER: I don't know if it's present in this room.

Q When did you see the document?

A I saw it yesterday.

MR. SCHULER: For the record, I request a copy of the document. The copy of the document's been refused and --

MR. WAGNER: What's the basis that I would have to give you that document?

MR. SCHULER: Because I asked it be produced here today.

MR. WAGNER: It's a Dow document. It's not his document. If you would like documents from Dow, send me a request to produce.



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MR. SCHULER: Well, I understand the position that you've taken, but I disagree with it 100 percent, and particularly when the document is present here today and could be discussed with this witness. To refuse to produce it, I think is a violation of this request, and I'll seek court relief on that. I have no further questions, thank you.

MR. WAGNER: Before we let Aprille go, let's make this part of the record. Larry Silverstein faxed the statement which turns out to be an affidavit that he signed. That's my only copy. It was delivered here this morning, so let's mark it as an exhibit. From my review it does not contain any information that you didn't cover with him yesterday.

Why don't you take a minute to review it, if you want. We could probably have him come over and answer questions about it, but as I say, from my review of it, I think all those areas that were mentioned were covered.

MR. SCHULER: Well, I'm not -- I can't take a look at this. I mean, we had his



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deposition yesterday. This wasn't produced, and I'm taking the position that it was wrongfully withheld.

MR. WAGNER: Well, he didn't have it.

MR. SCHULER: Well, he was requested to produce it.

MR. WAGNER: I know he was requested, and I know it's here now. If you want him, I'll get him on the phone and see if he can come out here.

MR. SCHULER: That's not good enough for me. I was taking his deposition yesterday, and I'm handed a four-page document with 16 paragraphs today, and I'm not going to be put in that position of doing this now, and when it wasn't produced when it should have been produced, and asking him questions about it. We'll mark it for the purpose of discussion, since we talked about it at this deposition, as Plaintiff's Exhibit Number 5.

(Plaintiff's Exhibit 5 was marked for identification.)

MR. SCHULER: Is that it?



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MR. WAGNER: No questions.

AND FURTHER THE DEPONENT SAYETH NOT

_____

KARL KRUMEL, Ph.D.

FORM LASER BOND A PENGAD/INDY 1-800-631-6989

STATE OF INDIANA )
) ss:
COUNTY OF MARION )

I, Aprille Rigsbee Lucas, RPR, Notary Public in and for the County of Marion, State of Indiana, do hereby certify that the deponent herein was by me first duly sworn to tell the truth, the whole truth and nothing but the truth, in the aforementioned matter;

That the foregoing deposition was taken on behalf of the Plaintiff;

That said deposition was taken at the time and place heretofore mentioned between the hours of 8:00 a.m. and 6:00 p.m;

That said deposition was taken down in stenograph notes and afterwards reduced to typewriting under my direction and thereafter presented to said witness for signature; that this certificate does not purport to acknowledge or verify the signature hereto of the deponent;

I do further certify that I am a disinterested person in this cause of action; that I am not a relative or attorney of any of the



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parties, or otherwise interested in the event of this cause of action, and am not in the employ of the attorneys for any of the parties.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 15th day of March, 1993.

Aprille Rigsbee Lucas, RPR

My Commission Expires:
September 21, 1996

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KARL KRUMEL, Ph.D.- Kimberly Moyer Vs. Dow Chemical - March 9-10, 1993

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STATE OF FLORIDA )
) SS:
COUNTY OF ORANGE )
IN THE CIRCUIT COURT FOR ORANGE COUNTY, FLORIDA
KIMBERLY MOYER, as Personal ) Representative of the Estate of)
ROBERT W. MOYER, II, Deceased, )
)
Plaintiffs, )Case No. CI 89-8657
)Div: 32 Thompson
vs. )
)
DOW CHEMICAL COMPANY, et al., )
)
Defendants. )
The deposition upon oral examination of KARL KRUMEL, Ph.D., a deponent produced and sworn
to before me, Aprille Rigsbee Lucas, RPR, a Notary Public at large in and for the State of Indiana, taken on behalf of the Plaintiff at DowElanco, 9001 Purdue Road, Quad III, Indianapolis, Marion County, Indiana, on March 10,
1993, at 9:30 a.m., taken pursuant to the Florida Rules of Civil Procedure in the above-captioned matter.
ASSOCIATED REPORTING, INC.
TWO MARKET SQUARE CENTER
251 EAST OHIO STREET
SUITE 940
INDIANAPOLIS, INDIANA 46204

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KARL KRUMEL, Ph.D.,
having been first duly sworn to tell the truth, the whole truth and nothing but the truth, relating to said matter, was examined and testified as follows:
DIRECT EXAMINATION,
QUESTIONS BY MR. SCHULER:

*Q Would you state your name, please.*
**A My name is Karl Krumel.**
*Q What is your professional address?*
**A My professional address is 1710 Building, the Dow Chemical Company, Midland, Michigan, 48674.**
*Q Are you employed?*
**A Yes, I am.**
*Q By whom are you employed?*
**A By the Dow Chemical Company.**
*Q What is your position with Dow Chemical Company?*
**A My title is associate scientist.**
*Q As associate scientist, just in general, now, what are your duties and responsibilities?*
**A Well, the associate scientist is a generic title for people in research who have reached a certain level in the company. It doesn't in any way**

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**define the job.**
*Q Tell me a little bit about the structure, to give me some understanding of how the research department is organized. And if you would, could you also tell me, and you don't have to be completely thorough about this, but just tell me in general what the structure is and the various positions that are within the research department.*
MR. WAGNER: I object as to breadth, compound. You mean today?
MR. SCHULER: Right.
**A Are you asking me about the structure of research within the total Dow or within the structure within my department, which is a small part of the overall?**
*Q Let's start with your department.*
**A The department I'm in is agricultural chemicals process research. This department, the name has changed several times over the years that I've been in it, but that's the current name. Our structure, we have a technical director. We have two research managers, and these research managers then control groups of on the order of 30**

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**technical professionals each. I happen to be in one of those groups as a senior scientist in the department.**
*Q So there are roughly 62 or 65 people in the department?*
**A In the current department, yes.**
*Q Now, to expand that to the, to give me some idea of how the department of agricultural chemicals process research fits into the overall scheme of things, what other departments are there, other than that, if you know?*
**A Oh, goodness, there are a number of departments located in Midland that support other areas of Dow R&D, you know, of the Dow Chemical Company, including pharmaceuticals, analytical, polymers, resins.**
*Q You're the only department that has to do with agricultural chemicals in –*
**A In the Midland, area, yes.**
MR. WAGNER: You meant research of course?
MR. SCHULER: Right.
*Q Are there other research departments that deal*

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with agricultural chemicals in other areas of the country?
**A Well, we have small groups that will support the production of ag chemicals in other locations other than Midland, yes.**
Q That are right within the factories, themselves, you mean?
**A They're within the plant area, themselves, yes.**
Q Who is the technical director presently?
**A The gentleman's name is Jim Love, L-O-V-E.**
Q How long has he been technical director at the agricultural chemicals process research department?
**A He's been there since 1988.**
Q Do you know who his predecessor was?
**A His predecessor was, yes, the gentleman's name is Alex Vogel, V-O-G-E-L.**
Q How long was he there, if you know?
**A I can't give you the exact time frame. It's on the order of four years or so.**
Q Would that position of technical director of the agricultural chemicals process research department have been in existence back in 1975, let's say?

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**A In '75, the organization was pretty much the same. The name of the department at that point was different.**
Q What was the name at that time?
**A Organic chemicals research.**
Q And who was the head of the department back in 1975, if you recall?
**A 1975, the technical director was a gentleman named Don Morehouse.**
Q Were there also residents or research managers back in 1975?
**A Yes.**
Q Do you recall who the research managers were in 1975?
**A Well, I certainly recall my research manager at that point, which was Michael Mintz, M-I-N-T-Z.**
Q Is Mr. Morehouse still with the company?
**A No. He retired a number of years ago.**
Q Is he still in Midland or has he moved away?
**A He moved – well, where he is today, I really don't know. He moved away to Florida, but I've lost track of him.**
Q How about Mr. Mintz, it is he still with the

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company?
**A Yes, he still works for Dow.**
Q And what is his position now, the same?
**A Oh, no, no, no. He's off in another area. I can't tell you exactly what his job is today.**
Q What is your educational background, Dr. Krumel?
**A In 1960, I received a Bachelor of Arts degree at Grinnell College, Grinnell, Iowa; in 1962, a Master in chemistry; in 1962, a Master of Arts in chemistry from DePauw University, D-E-P-A-U-W, in Greencastle; and then in 1965, Ph.D. in organic chemistry from Michigan State University.**
MR. LUTZ: What year was that?
THE DEPONENT: 1965.
Q After '65, what did you do?
**A I joined Dow in June of '65, right out of college.**
Q So you have worked for Dow basically all of your working professional life?
**A Correct, since graduation from college.**
Q Trace for me, if you would, the positions that you've held at Dow, starting from when you began work there after graduating in 1965.
**A From the standpoint of the departments in which I**

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**worked?**
Q Yes, and the positions that you held.
**A In 1965, I joined Dow as a research chemist, which was an entry-level position for a Ph.D. at that time. I joined the benzene research lab, which was part of the laboratory organization at that time known as organic chemicals production research.**
**In 1969, I moved over to an area of polymer chemistry, cellulose ether chemistry. The department I moved into was –**
Q I'm sorry, that last statement was?
**A Cellulose, C-E-L-L-U-L-O-S-E, cellulose ether chemistry.**
Q Cellulose ether?
**A Yes. And the name of that department changed a couple of times during the time I was there, but in 1975, I then moved into what was then known as organic chemicals research, and I've been in that department, or whatever that department was renamed, since that time.**
Q So I can save myself some time here, prior to 1975, would it be fair to say that you did not

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have any experience, within Dow Chemical Company, with the agricultural chemicals that the company was producing?
**A No, because I hired into benzene research, and benzene research, at that time, one of their responsibilities was supporting the agricultural chemicals business at that time. The period of time of '69 to '75, I had no involvement at all in ag.**
Q Go back to '65, from '65 to '69, then, did you have any involvement with polychlorinated phenols, I think they're called, those type of chemicals?
**A The polychlorinated phenols, yes. In 1966, I began doing production research on dichlorophenol.**
Q Any others?
**A And, of course, by association, I was aware of what was going on in the other chlorinated phenol areas of research at that time.**
Q To be more specific, did you produce any documentation from 1965 through 1969 with regard to any research on 2,4-D or 2,4,5-T or Silvex?
**A No.**
Q Did you work on any projects that involved 2,4-D,

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2,4,5-T or Silvex during that time period?
**A No.**
Q Did you produce any research during that time period, from '65 through '69, that had to do with any of the component parts that went either 2,4-D, 2,4,5-T or Silvex?
MR. WAGNER: I object as vague.
**A I'm sorry, would you rephrase the first part of your question?**
Q Between '65 and '69, did you produce any research at Dow Chemical Company on any of the component chemicals that went into making 2,4-D or 2,4,5-T or Silvex?
**A Yes, I did.**
Q And which chemicals are those, as you recall?
**A 2,4-dichlorophenol.**
Q And that is involved with the production of 2,4-D?
**A Yes.**
Q Did you have one or were there many projects involving 2,4-dichlorophenal?
**A It was one major project.**
Q And without getting too technical on me, can you tell me basically, in laymen's terms, what the

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project involved?
**A The project involved trying to improve the isomer purity of the raw material, of the 2,4-dichlorophenol.**
Q And did you produce a paper or papers regarding that?
**A Yes.**
Q Was the process that you were involved with ultimately implemented commercially?
**A No.**
Q And do you recall the reason why?
**A Subsequently some additional work was done that found something better.**
Q And who did that additional work, do you recall?
**A Let's see, one of the gentlemen's names was W. David Watson. Dave Watson was the primary researcher. He would have been the primary researcher in that area.**
Q Was there a fellow by the name of Brust or –
**A Harry Brust, yes.**
Q Was he also working in that area in the process for 2,4-dichlorophenol, or attempting to improve the isomer from which 2,4-D is made?

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**A By the time I got to know – well, I didn't actually get to know Harry until I came back into organic chemicals research in 1975. I'm aware of what he did in years before that, but only because I knew – I got to know him when I came back into the department. And he was not involved in the dichlorophenol part, as best I can recall.**
Q Between '65 and '69, though, he was not directly involved in the research and development for 2,4-D as far as you know –
**A I don't know what Harry Brust did in that period of time.**
Q Between '65 and '69, did you have occasion in your research to analyze or write about any potential contaminants of 2,4-dichlorophenol or 2,4-D, itself, such as any of the dioxins, TCDD or any of the dioxins, for example?
MR. WAGNER: I object as to the breadth.
**A Are we specifically talking about polychlorinated dibenzo-para-dioxins when we use the term dioxin?**
Q Yes.
**A Not that I recall.**
Q What about furans? I know that's a broad

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statement, but did you do any papers or analysis with regard to the presence of –
**A Again, polychlorinated dibenzofurans?**
Q Yes.
**A Not that I recall.**
MR. WAGNER: He sounds like a scientist.
THE DEPONENT: Well, I'm going to do that.
Q Did you do any toxicological research between '65 and '69?
**A I have – no.**
Q Let me ask you a very general question here as well, do you consider yourself, I know you're an organic chemistry researcher, do you consider yourself to have expertise in toxicology?
**A No, I have no training whatsoever in that area.**
Q Again, a general question, which will save time later on, as far as the, when I'm going to ask you some questions about the report you did, I think in 1978, although the date is hard to make out here, but with regard to any contaminants that you ultimately may have dealt with in your research with 2,4-D or 2,4-dichlorophenol, you would not be

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an expert on the toxicological impact of those contaminants?
**A That's correct.**
Q That type of research would be carried on by others at Dow?
**A Yes.**
Q Between '65 and '69, did you do any research that was connected with any Dow involvement with any claims that either 2,4-D or 2,4,5-T or Silvex caused various injuries or diseases?
MR. WAGNER: I object, over broad and vague.
**A Are you asking me did I consult with Dow attorneys?**
Q Yes, that would be part of it, I assume.
**A No, I never did.**
Q Did you ever testify in any form regarding 2,4-D or 2,4,5-T or Silvex from, excuse me, from '65 to '69, again, I'm talking about?
**A No.**
Q Did you ever relate any communications to any governmental agencies regarding 2,4-D or 2,4,5-T or Silvex or their component parts?

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**A No.**
Q Did you, and I'm going to open this up to the entire time all the way to the present, did you ever give a deposition in any case involving allegations of personal injury as a result of exposure to 2,4-D, 2,4,5-T or Silvex?
**A This is my first deposition.**
Q This is your first deposition, period, you've never given one before?
MR. WAGNER: You're it.
Q I have to get the answer from you, though. This is your first one?
**A Yes, sir.**
Q There has been testimony in this case that, I'm not sure as I look back at it, the exact date, but there was a meeting regarding contaminants found in 2,4,5-trichlorophenol of various manufacturers, I think either in '64 or 65. You wouldn't have attended that meeting, would you?
**A Well, no, obviously not, because I didn't join the company until June of '65, and I had no involvement whatsoever in the area of halogenated phenols until after 1966.**

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Q So you wouldn't have attended any meetings with regard to the presence or absence of TCDD in any of the Dow chemicals from 1965 to 1969?
**A Correct. I'm sorry, would you ask that question again? I want to make sure –**
(THE REQUESTED MATERIAL WAS READ BY THE REPORTER.)
**A The question should probably be, I attended no meetings, I was not involved in anything dealing with 2,4-D, 2,4,5-T or Silvex.**
Q Nothing whatever during that time period?
**A Correct.**
Q Let's skip forward to your moving into the organic chemicals research in 1975. Were you assigned responsibilities when you went into that particular department back in 1975, any responsibilities with respect to 2,4-D or 2,4,5-T or Silvex or their component parts with respect to doing research?
**A Yes, I was.**
Q What responsibilities were you assigned initially when you first went into the department?
**A When I first went to that department, I was**

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**assigned the responsibility of doing process research for the new 2,4-D plant that was scheduled for start up in approximately two years from the time that I joined the group.**

*Q And when you say process research for the new 2,4-D plant, 1975, when you went back to organic chemistry research or the organic chemicals research department, 2,4-D was being made by Dow Chemical Company at that time?*

**A Correct.**

*Q It was being made pursuant to a process that they had been using for a number of years, correct?*

**A That's also correct.**

*Q Do you know the history of the process of 2,4-D, in other words, the process that was being used in 1975? When you went to the organic chemicals research department, do you know, was there a name for the process they were using at that time?*

**A Well, it was just simply called the 2,4-D plant.**

*Q And what building was it located in?*

**A 489 building.**

*Q And there wasn't any specific name for the process, who put the process together or anything*

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*like that?*

MR. WAGNER: I object, compound.

**A Not to my knowledge. It was just known as the 2,4-D plant.**

*Q What was the purpose, if you recall, for attempting to put together a new process for the manufacture of 2,4-D?*

**A We developed some new technology that was much more efficient, produced much higher yield, and produced isomer purity in the final product.**

*Q When you say we developed?*

**A Our department.**

*Q I understand, but were there certain individuals that were responsible for developing that new process?*

**A Well, the scientists. David Watson, that I mentioned before, was the primary investigator in improving the quality of our 2,4-dichlorophenol from an isomer specific standpoint. Harry Brust is the chemist who developed the chemistry that was eventually implemented in the 2,4-D process.**

*Q Is Mr. Watson still with the company, by the way?*

**A Yes.**

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*Q Is he in your department?*

**A No. He's in another department. He's located at Midland.**

*Q Do you know what department he's located in?*

**A The department is called design thermoplastics research.**

*Q What about Mr. Brust, is he still with the company?*

**A No. Harry retired a number of years ago.**

*Q Is he still in Midland, or did he move away somewhere?*

**A I believe he's moved away, although I see him in town every once in a while.**

*Q Did you know whether or not, with the process that was being used in 1975, for the manufacture of 2,4-D, whether there were any problems, from an organic chemistry standpoint, with contaminants being found in the 2,4-D being manufactured, I'll call it by the old process that was in existence, 1975?*

**A No.**

MR. WAGNER: I object, vague.

*Q You don't know one way or the other?*

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**A No, I don't.**

*Q Do you know who might have, if anyone, done research on the 2,4-D that was manufactured in 1975, to determine its purity or to determine whether there were any contaminants in the 2,4-D?*

MR. WAGNER: Calls for speculation.

**A Could you be more specific?**

*Q Well, it's relatively specific. Let me see if I can make it more clear. Do you know who the individual was in the organic chemicals research department, if anyone, who might have done research on the 2,4-D being manufactured in 1975, to determine whether there were any contaminants in the 2,4-D?*

MR. WAGNER: Same objection.

**A No, I can't recall.**

*Q Let me ask the question this way, maybe this will make it more clear, was there anyone that you knew back in 1975, in the organic chemicals research department, that was responsible for doing the basic research on 2,4-D back then?*

**A Well, Dr. Brust was responsible for the research on the new developing process. I did some**

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**research in the, as it relates to the old process, not specifically targeted at trace impurities.**

*Q In other words, you weren't just looking for trace impurities; you were just doing research on it for other purposes?*

**A For other purposes, yes.**

*Q Did you produce tapes that outlined your research back in 1975?*

**A Yes, I would have.**

*Q Do you recall whether, in the course of doing your research, you found any impurities in the process for making 2,4-D in 1975?*

**A For me to answer that question properly, I guess I'd like to know what impurities you're specifically asking about.**

*Q TCDD, for example.*

**A No.**

*Q No, you did not find TCDD?*

**A No, nor did we analyze – was I responsible for determining TCDD in that time frame?**

*Q You were not looking for that?*

**A Correct.**

*Q Do you know if there was anyone that was looking*

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*for TCDD, for example, in 2,4-D back in 1975?*

**A No.**

*Q You don't know, no, or –*

**A No, I don't know.**

*Q How big was the department back then in 1975?*

MR. WAGNER: Organic chemistry research?

MR. SCHULER: Yes.

**A More or less the same size. At this point I don't recall exactly how many people we had.**

*Q What I'm getting at, do you have an idea of who may have been involved in that type of research, or you're just not sure who it was?*

**A I just simply don't recall anyone doing any research at that time, and I would, if it were done, I'm sure.**

*Q Okay, to get back to my earlier question, I asked you about whether in your research I think you found any TCDD. I know you weren't looking for these things, but in the course of your research on the 1975 process, did you find any of the other polychlorinated dibenzo-p-dioxins, did I pronounce it properly?*

**A What you're specifically asking me about is did we**

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look for these compounds in the old 2,4-D process, in the 1975 time frame?
Q Correct.
A No.
Q Let me change the question a little bit to, even though you weren't looking for them, did you find any of those?
A No.
Q Did you work with someone in doing your research on 2,4-D in 1975?
A Within our department?
Q Yes.
A No. I was doing the work. Excuse me, are you asking about the old process work?
Q The old process, that's right.
A Yes, that was done by me.
Q You didn't have someone that worked with you in the department, it was just you?
MR. WAGNER: Asked and answered.
A As best I can recall at this point.
Q In your work on the old process, can you just tell me what your research did involve back in 1975?
A At that time, again, we were just – one of my

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roles as a process chemist is to make sure we're using the most modern, up-to-date technology and chemistry that we can do. And my research was essentially aimed at doing just that, making sure the plant was operating, that the chemistry in the lab was operating most efficiently within the boundaries in which we could operate in the plant, maximizing yield, maximizing product quality, that sort of thing.
Q Would you try different things in the laboratory to see if you could improve the quality to maximize yield and maximize purity?
A Correct.
Q And if they appeared to be, the things that you did were improvements and appeared to be things that could be incorporated into the process, then that suggestion would be made, is that how it worked?
A It would certainly be considered.
Q Who would make the ultimate decisions as to whether a particular change in the process would be incorporated? I know there's probably a number of people it went through, but just give me a

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general idea how it worked.
A At that time the, well, the ultimate – the person ultimately responsible for the plant would be the plant superintendent.
Q Who was the –
A But the plant superintendent would work with people in the agricultural chemicals production department because we had some senior level experienced engineers that were located in that department, whose responsibility it was to maintain high standards of technology from the engineering perspective.
Q That was the agricultural chemical production department, you say?
A Yes.
Q Who was the plant superintendent for the 489 2,4-D process back in 1975?
A At the time I joined the group, the man's name was Bill Jones, William Jones.
Q Is he still with the company, to your knowledge?
A As far as I know he is.
Q Do you know where he is in the company, what department?

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A I haven't any idea at this point.
Q In the plant, would records be kept about the process, in other words, the yields that were being obtained, the quality of the product, would that periodically be tested and records be kept on that?
MR. WAGNER: 1975 time period?
MR. SCHULER: Right.
A During that time period, yes.
Q Do you know what other records that would be kept in the plant, primarily?
A Well, they would keep operational records of how the plant was running, product quality, the results of quality control testing, records on plant maintenance and et cetera, et cetera.
Q Would the plant superintendent be specifically responsible for the quality control testing?
A He's the person who is in charge of the people who do the work, yes.
Q Some of these questions, I'm sure, seem very basic to you, but I need to know, do these plants run continuously?
A Yes.

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Q 24 hours a day?
A Yes.
Q And besides operational records and records dealing with yield and purity and quality control testing, are there any other types of records kept in the plant back in 1975, I'm talking about?
A I think I covered the ones that certainly I'm aware of.
Q Was it ever your function to go and review the records in the plant to see how the plant was doing?
A Oh, yes, I would, on a regular basis, review records on how the plant was operating and how the product quality was holding up. I didn't have any reason to review records on maintenance or scheduling or things like that.
Q When you say product quality, and taking 2,4-D specifically in 1975, and again, as generically as you can, what would you look for to determine product quality?
MR. WAGNER: I object to the form of the question.
A We – well, we had certain specific indications

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that we – that the product was required to meet by our customers, and we would maintain a track of that and try to maintain an awareness of how the product quality was related to the specs that we were – specifications that we were expected to meet. And if problems or issues came up with regards to meeting specs, then we would attempt to solve the problem or issue.
Q What type of specs are you talking about?
A Assays, A-S-S-A-Y, the tracking of normal isomer, isomeric impurities. We had several final product quality control tests that we would monitor on a regular basis.
Q When you talk about assays, what are you talking about, what type of assays? You mean concentration of the product?
A Well, the quality of the technical product, the assay at that time was expected to be 95 percent pure 2,4-D, so that's what I mean by assay. Now, what I'm talking about is the technical 2,4-D assay, which is 2,4-dichlorophenoxyacetic acid, A-C-E-T-I-C, acid.
Q And the spec at that time was 95 percent purity?

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A Yes.
Q And when you say 95 percent purity, was that in what form, was that in liquid or powder?
A Powder form.
Q Was the powder put in suspension before the product was shipped, or was it shipped both ways, how did that work, if you know?
MR. WAGNER: I object to the form of the question.
A It was – we did supply, some of our materials were supplied to the customer as the acid form, but then it was supplied in a number of other physical forms.
Q Depending on the customers' requirements, more or less?
A Right.
Q Now, when you said they were tested for isomeric impurities, was there any test for the dioxins that we discussed earlier, for example, TCDD?
A I simply don't recall how that was handled in those days.
Q What about any of the other polychlorinated dibenzo-p-dioxins, were there tests for any of the

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others?
A Not that I specifically recall.
Q Same question with regard to the furans, were there any tests for those?
A Not that I specifically recall.
Q What type of impurities, when you say isomeric impurities, do you recall any that was tested for?
A We would, our quality control procedures at that time did not require that we analyze for other isomeric impurities.
Q I thought you told me earlier that there was testing for isomeric impurities. Did I misunderstand you?
A I'm trying to recall 18 years ago. If I said that, I guess I must have misspoken. At that time, the specs that we were required to meet in our quality control was 95 percent assay, a 95 percent assay. We had the ability to analyze for other isomeric impurities, but that was not an official specification. That may be where we got confused a little bit.
Q Does that mean that it wasn't done or it was done periodically or what, testing for isomeric

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impurities?
MR. WAGNER: I object to the form of the question.
A It was more likely to be done on an irregular basis, and most likely from a research standpoint.
Q As opposed to a quality control standpoint?
A As opposed to a quality control standpoint, yes.
Q You mentioned initially you did some research on the old process for manufacturing 2,4-D, and at some point you were given responsibilities to do process research for what was potentially going to be a new process, correct?
A Correct.
Q Was there any other research, before we get to that, that you did with regard to the old process? I know I've focused on impurities, and you've told me basically what you did, but was there any other aspect of your research that we haven't covered from the old process?
MR. WAGNER: This is 1975, before he started working on the new one?
A As it relates to the 2,4-D acid process in the 489 building?

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Q Right.
A As best I recall, I've told you essentially everything I did at this time.
Q From a chronological standpoint, how long were you involved in the research in the old process before you turned your attention or your responsibilities were directed to doing research on the new process?
A Only a few months.
Q And when your attention was directed to the new process, what was your initial assignment with regard to that?
A Essentially to provide chemistry support to the construction of the new plant, focusing on gaining a personal understanding of the way the new process was going to operate.
Q Let me get some time parameters in here, too, so perhaps this can save me some effort later on. Did the new process – was it implemented?
A Yes.
Q Can you tell me at what point in time the new process was implemented?
A We started the new 2,4-D process in the spring of

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'77, I think. I see you've got my report. I think it talks about May of '77.
Q Okay, was it May of '77, is that when the process was began?
A That's when we started the production of 2,4-D.
Q And up until May of 1977, the old process was being used?
A Yes.
Q Was the new process, did the new process, was that put in the same building, 489?
A No. It was a new structure.
Q What was the new building?
A 948 building – 948-949 building.
Q From your recollection, if you know, when the new process was started in the spring of '77, was the product, in May of '77, was the product sold right away or was there any delay in the sale of the product?
MR. WAGNER: I object to the form of the question, vague.
A I have no personal knowledge as to when we actually began – the old process continued to operate for approximately 18 months after, as best

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I can recall, after the start up of the new process. So there was a gradual phase in of product from the new process, but I couldn't give you any data at all, exactly when material began to actually be sold from the new process.
Q That was going to be my next question, there was an overlap then between the old process and the new process?
A Correct.
Q And that was roughly 18 months, you said?
A On the order of 18 months, yes.
Q Was the old process eventually shut down in the 489 building?
A The old, yes, it was.
Q When you began your new responsibilities with regard to research on the new process, did someone else in the organic chemicals research department, was someone else assigned to doing any work or continuing with any work on the old process?
A I just simply don't recall how that – the mind has gotten kind of vague as to specifically what was done, by whom, when, and all that.
Q Where there certain people within your department

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in 1975 that were assigned to the 2,4-D process beside yourself?
MR. WAGNER: This is the new process?
MR. SCHULER: The new or the old.
**A Well, Harry Brust was certainly – continued work on the new process. At this point I'll have to admit I simply don't recall who else.**
Q Let me ask you this question, and if you don't know, just tell me and I'll move on, prior to 1975, when you became involved with organic chemicals research, do you know who was involved in the department, if anyone, doing research on 2,4-D?
**A Harry Brust.**
Q You said he's a chemist?
**A Yes. And I know we had some engineers involved in that project, but I simply, at this point, don't remember who those individuals were.**
Q Let me show you the report that we've talked about in this case, and I've highlighted some things. I'm just going to ask you to identify it for now, and if you have a copy of it, it will save me some time.

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**A Yes, that's my report.**
**(DISCUSSION HELD OFF THE RECORD.)**
**(Plaintiff's Exhibit 1 was marked for identification.)**
MR. SCHULER: Back on the record.
Q Looking back at Plaintiff's Exhibit 1, here, this is your report from October 27th, is that 1978?
**A Yes.**
Q And you did this report for what purpose, Dr. Krumel?
**A The purpose was to document some, essentially the research that is described in the report.**
Q That's your answer, I take it?
**A Does that answer your question?**
Q I think so. There's some writing, I don't know, maybe this was from a prior lawsuit or something, but I've got some writing on top of mine that I see you don't have on top of yours. Do you recognize what that may be up there?
**A Well, the report was obviously sent to somebody by somebody.**
Q But you don't recognize it?
**A No. Steve, Steve, it means nothing to me.**

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Q In any event, this research was on the formation and removal of impurities in the 2,4-D process, correct?
**A In the new 2,4-D process, yes.**
Q And this was co-authored by Mr. R.F. Arnold?
**A Ray Arnold is a laboratory technician who works with me. I was – his part of the project is he ran the experiments or ran – ran many of the experiments that are described in the report, but I'm the one that's responsible for the interpretation of the data. Ray was not qualified to do that.**
Q And this was sent to, or it said receiver's signature, Peter Owen?
**A Reviewer's signature, Peter Owen was my immediate supervisor. And the technique we use in report writing at Dow is the authors submit the report to the supervisor, and their supervisor has to sign the report before it can be issued.**
Q What was Mr. Owen's position?
**A He was, as I said, he was my immediate supervisor at that time.**
Q Is he still with the company?

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**A Yes.**
Q Is he still in organic chemicals research?
**A No. He's off in another department. At this point, I can't tell you exactly what his job is.**
Q Up at the upper right-hand corner of Plaintiff's Exhibit 1, it says laboratory report code, OC, slash, 78, dash, 85. Do you know what that code stands for?
**A OC is merely the designation for organic chemicals. It was the designation used by our library system to designate organic chemicals research. The number, it just means it's the 85th report written in 1978, to come out of this department.**
Q And then below that, it's hard to make this out because of the copy I have, but it appears to be a lab number, is that right?
**A Yes.**
Q Let me –
**A I beg your pardon?**
Q Is it 05 or?
**A 050.**
Q And what is the significance of the 050 lab

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number, if any?
**A That gets into some of the accounting and recharging of research dollars within the company. It has no meaning to the report, really, other than just to designate. The 050 is a laboratory number for accounting. The problem number is a method for internal recharging.**
Q What do you mean by internal recharging?
**A Well, how I'm paid, how my salary is paid.**
Q And the problem number here is 9, six zeros?
**A Correct. It has absolutely nothing to do with the report, itself.**
Q With the subject matter?
**A Yes.**
Q Looking down at the descriptive summary with conclusions, let me just ask you a couple questions about that. One of the findings that you outline here is a new and unexpected class of non-acetic impurities, correct?
**A Mm-hmm.**
Q Yes?
**A Yes.**
Q And you mention two of the major components were

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tetrachloroxanthone and octachlorospirobixanthene?
**A Yes.**
Q And what type of impurities are those, I mean – maybe that's a bad question, but can you categorize those impurities in any way?
MR. WAGNER: I object to the form of the question, compound, vague.
**A Well, xanthone is an accepted organic nomenclature for a particular class of compounds. Spirobixanthene, again, is the same thing. It's accepted nomenclature. What they are is organic chemicals that were detected in the product.**
Q In the final product of 2,4-D?
**A That's where we first observed them, yes.**
Q And when you mention that the impurities were causing problems in the subsequent formulation of 2,4-D as amine salts, what were you referring to, what did you mean by causing problems?
**A The issue occurred as we stated before, the plant started up in May of '77. By that fall, what we started observing, we have a quality control test for our amines, where we mix a small amount of the amine salts with water, shake them up, centrifuge**

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**the samples and look at suspended solids, and we have a certain amount of solids in that that's an acceptable spec. The problem that you run into, we started to see more of these solids, but where the problem really came up was when the formulated product was applied in the field, we started getting increasing customer complaints from plugged spray nozzles. At which point we went back and started looking specifically at those solids, and in these solids, that was where we first observed some of the compounds, the tetrachloroxanthene and the octachloro-spirobixanthene.**

*Q And this whole paper, if I understand it correctly, was devoted to exploring the possibility for attempting to control, minimize or eliminate these impurities in the 2,4-D?*

**A Correct. It was targeted at solving a customer complaint issue.**

*Q Do you recall whether there was a specific customer that did complain?*

**A I can't answer – I just simply don't remember**

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**where the specific complaints came from.**

*Q Do you remember how you got notice of the complaint, that there was a complaint, and assigned this project?*

MR. WAGNER: I object to the form of the question, compound.

**A I don't recall the exact sequence of events. I believe people are mentioned in this report, a Joyce King, from formulations, in the 9001 building. It's on page 8 at the bottom. She is in our – or she was in our formulations and TS&D area at the time. She would be working with our manufacturing supervision, who was working very closely with our R&D supervision in my department. So the whole sequence of events I don't remember, but the bottom line came, I was assigned the job of getting involved in attempting to understand the formation and how we could get rid of them to solve a quality issue.**

*Q Do you know whether the old process that, from your earlier testimony, I understand was still ongoing at this time, was evaluated for these impurities, as well?*

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**A We tested the samples, and none were found.**

*Q When you say we, who are you referring to?*

**A Again, our team, the we in this case would have been someone from our analytical sciences department, and that someone was most likely, as best I can recall, Dale Humbert.**

*Q Humbert?*

**A Who is listed as a recipient on the back of this report under 574 building, D. Humbert. He was the chief analytical scientist supporting this area.**

*Q And from an overview standpoint, this report, you mention that the number of treatments and potential solutions that you examined, none appeared to be totally successful, correct?*

MR. WAGNER: I object to the form of the question.

**A That answer is – yes, that's correct.**

*Q In my copy here, there's a blank that appears to be filled in on the one you have, the last paragraph. Can I see that for a second?*

MR. WAGNER: Sure.

(DISCUSSION HELD OFF THE RECORD.)

**(Plaintiff's Exhibit 2 was marked for identification.)**

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MR. SCHULER: Back on the record.

*Q Let me just follow through this report briefly with you. My page 1 is a table of contents, correct?*

**A Yes.**

*Q Page 2 appears to be an introductory section?*

**A Yes.**

*Q And that's where you mention at the top that the process, I think the word new is even blanked out, a new process for preparing high purity 2,4-D was started in May 1977 at the 943 building?*

**A 948.**

*Q Okay, it looks like 943 on mine, okay, 948 building. You mention that the high purity molten acid is transferred by pipeline to the 489 building where it is formulated into esters and water soluble amine salts, which would be the final product, correct?*

**A Yes.**

*Q You mention that the impurities that you found were never detected during laboratory or pilot plant development work, correct?*

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**A Correct.**

*Q Again, there's a word missing, I've got to ask, or there appears that there's a word missing, anyway. In any event, you mentioned, also, in this first paragraph, that the impurities were not found in the old process, correct?*

**A Yes.**

*Q And that was what you referred to earlier when you said there was some testing done in the old process, correct?*

**A Yes.**

*Q Who is R. McLachlan?*

**A He's an analytical scientist in the same department as Dale Humbert.**

*Q Is he still there?*

**A I don't believe he is. I have not – I've lost track of him.**

*Q How about Mr. Humbert, is he still there?*

**A He's still in the company. He's not in analytical anymore, but I don't know specifically where he is.**

*Q Mr. McLachlan, in any event, was the one who analyzed precipitates and found the TCX and the*

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*OCSX?*

**A He's the one that wrote the report. Who actually did the work, I assume Dick did, but I don't know that for a fact.**

*Q But that's what you put in here, correct?*

**A Yes, that – yes.**

*Q And the chemical formulas for the TCX and OCSX are outlined there, correct?*

**A Correct.**

*Q You mention that the TCX from the screening program at the plant showed levels of 200 to 500 parts per million in the crude reaction mass, and again, I'm missing words here. It says the recycle –*

**A Recycle sodium dichlorophenate.**

*Q – solution and in the final product. Okay. Levels of 1,000 to 2,000 parts per million were found in the, and I'm missing –*

**A Would you want to just work off that, and we'll –**

*Q – were found in the perc solvent, and as much as 10 percent in the still tars, perc still tars?*

**A Correct.**

MR. WAGNER: I object.

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Q The toxicological significance of TCX and OCSX, is that unknown to you?
**A Only what's reported in this report. I think on the next page, our page 6, is what I knew toxicologically about this material.**
Q Where did you get the report on page 6?
**A It should be referenced. It apparently is not –**
Q So you don't know where that information comes from?
**A Not specifically, anymore. There's a reference to, in the reference section on page 57, the very back of the report, reference two.**
Q What reference are you referring to?
**A Reference number two.**
Q P. Keller?
**A P. Keller, yes, that is from the –**
Q Health and environmental toxicology?
**A Yes, so –**
Q Looking at that for a minute, on page 357 of Plaintiff's Exhibit 2, it says P. Keller et al, H-E-T, and some numbers, K, dash, 2372, dash, parentheses, 18. Do you know what that stands for?

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**A I have no idea.**
Q That would be the toxicology report?
**A It is possible that that's the toxicology report.**
Q And you're thinking –
**A I don't know that for a fact.**
Q Because it says HET?
**A Correct.**
Q Going back to page 3, it talks about 11 other minor components structurally similar to the above. When you say structurally similar to the above, what are you referring to there?
**A Without having seen reference one for many, many years, I just simply don't recall.**
Q Besides the TCX and the OCSX, though, there were other components that were discovered, as well?
**A The compound shown as 8-5, and that is shown on page 4, and then on page 8 are two other impurities that were found, but specifically what the 11 minor impurities refer to, I have simply forgotten.**
Q Go to page 4 for a second, the 8-5, you call this another significant impurity. What was the reason for calling it that?

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**A Because it was detected in quantities that occasionally were comparable to what we were seeing for the OCSX and the TCX.**
Q Do you know the toxicological significance of 8-5?
**A I'm not aware of any data on that compound specifically.**
Q Had the page 6 initial screening for toxicity report that you incorporated in this, that was research that you did not do yourself, correct?
**A No, sir.**
Q However, the report that you incorporated in Plaintiff's Exhibit 2 does appear to indicate chloracne response for different concentrations and different doses of the TCX and OCSX, correct?
**A I only see, in this one, one concentration applied several times.**
Q Well, correct me if I'm wrong, here, it looks to me like there are two. One is four grams per kilogram and the other is five grams per kilogram.
**A Well, one is a tar sample that contains some TCX, some OCSX, and but you asked me, I thought you asked me specifically about TCX?**
Q Well, I mentioned TCX and OCSX, as well.

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MR. WAGNER: Why don't we reask the question. Now, I'm confused about what's on the table.
Q My question was initially that the report that you incorporated in here by reference shows a chloracnegeneric response in various concentrations to both TCX and OCSX, correct?
MR. WAGNER: I object to the form of the question.
**A The answer to the question is yes, to the best of my knowledge.**
Q The diagram on page 7 is just a diagram of the process, would that be a fair statement?
**A It is a very simplified diagram of the process, yes.**
Q Do you know, when referring to the top of page 8, whether any data was obtained for long-term effects of these impurities that you found?
**A I don't know.**
Q At the bottom of page 8 you referenced earlier some other workers, and one is S. Siegel, OCR?
**A Yes.**
Q Organic chemicals research?

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**A Yes.**
Q And was that someone who worked with you?
**A That was someone that was working alongside me, yes. As best I can recall, he was working more in the quality area directly with Joyce King and Susan Shell.**
Q Susan Shell was in the production end?
**A Yes, she was production supervisor.**
Q Located in building 489?
**A Yes, so she would have been production supervisor of the ester and amines portion of the process.**
Q And Judy, was it?
**A Joyce.**
Q Joyce King was in the formulation end and located in Building 9001?
**A Yes.**
Q You mention in the last paragraph above the chemical symbols on page 8 that there were two other impurities called complex one and complex two, and you diagrammed those that were found, also, correct?
**A Yes.**
Q So we have, to keep track of all this, we have the

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TCX, the OCSX, the 8-5, and the complex one and complex two impurities, so far?
MR. WAGNER: I object to the form of the question.
Q Referenced in your report, correct?
**A Yes.**
Q Do you know the toxicological significance of the impurities, complex one and complex two?
**A No, I don't. Incidentally, for correctness, there's a slight misprint on number four. The C shown in the middle shows CL; that should be CH. This should be – may I?**
Q That's CH there?
MR. WAGNER: If you're going to correct it –
MR. SCHULER: I'll correct it on this one because it's marked up already. That should be CH?
THE DEPONENT: Yes.
MR. WAGNER: How in the world you can remember that, I'll never know.
THE DEPONENT: Well, I just noticed it.
Q CH stands for?

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A The C stands for the chemical compound for carbon. The H is the chemical symbol for hydrogen. The CL is the chemical symbol or chlorine, and that would be an impossible structure.
Q And the OH is the chemical symbol –
A For the hydroxyl.
Q Oxygen and hydrogen?
A Yes.
Q K.E. First, referring to page 9, what role did that individual have in this report, if any?
A Ken First, at that time, was in process engineering, and I had actually even forgotten his involvement, but he did some computer modeling of rates of formulation based upon the data that I generated, or that Ray Arnold and I generated. And the contribution I think in his report was to – oh, goodness, I'm not sure what page it's on, but he talked about, if we maintained a certain level in the recirculating perc, we would maintain another level in the product. It's in the report someplace. I'm not sure exactly what page that's on.
Q We'll get to that. I just wanted to know who that

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was. Let's refer to page 9, Dr. Krumel, for a minute. At the bottom of page 9, after you essentially have outlined the impurities that we have already discussed, you decide to focus on TCX, correct?
A Yes.
Q And you stated the reason for the focus on TCX, one of the reasons was that it was a major impurity. What did you mean by that?
A Of these – of the small amount of things that we found in the solids, it was a major component.
Q By volume, you mean, or some other yardstick?
A Typically what we're talking about would be by weight percent within these traces of solids that were found.
Q I want to ask you to skip over to page 21. One of the comments that you made on page 21 is that a recurring problem for the past several months was how to explain the fact that the plant observed TCX formation rates that were five times greater than the lab. Did you ever find the reason for that?
MR. WAGNER: I object to the form of the

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question.
A No, we never really did, nothing more than what's explained in this report.
Q In the first sentence of the last paragraph, full paragraph on page 21 of Plaintiff's Exhibit 2, you mention that in addition to TCX, OCSX and 8-5 are known to be formed measurable quantities during the reaction to 2,4-D – maybe I didn't read that properly. In addition to TCX, OCSX and 8-5 are known to be formed in measurable quantities during the reaction to 2,4-D. When you say measurable quantities, can you tell me the relationship between the three, perhaps reflected in percentage as far as the ratio of the weights found?
MR. WAGNER: I object to the form.
A Without specifically reviewing data and numbers, I just simply don't recall, but we mentioned in the report 200 to 500 parts per million of TCX was found. Measurable quantities would, in that context, would mean comparable numbers, but specific data, I just simply don't recall.
Q On page 28, referring you to 28, and you can't tell because mine is the expurgated copy, here,

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but in the middle paragraphs you mention some TCX is formed in the reactor and was found throughout the 948 building process. When you say that, are you referring to the fact that the TCX was found at various points in the process or actually in the building, itself?
MR. WAGNER: I object to the form of the question.
A It was found in various process streams. As we indicated before, it was found in the reactor crude. It was found in the recycle dichlorophenate solution, and it was found in the recirculating perc, so it's found inside the chemical process, itself.
Q Was it found in the final product, 2,4-D?
A I think, back on page whatever, it was indicated that yes, we did find it in the product, itself.
Q Referring to the bottom of page 29, you make note of the fact that the 8-5 impurity is not efficiently removed with perc extraction, hence most of what is made goes out with the product. Why was that a concern?
MR. WAGNER: I object to the form of the

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question.
A Again, because it is, the trace levels that were in the product are insoluble in the amines formulating mixture and would again result in small amounts of solids that I think we discussed earlier.
Q In the table five above that statement you have some numbers for initial and final as far as TCX and 8-5 in parts per million, correct?
A Yes.
Q What does that refer to, initial and final, in that chart?
A I have to read the chart. What we did was simulate the process in the laboratory, and to take a sample of the crude sodium salt of 2,4-D, extract with perchloroethylene, in the laboratory, and analyze the sodium 2,4-D before and after extraction with perchloroethylene, and these are merely the results of those experiments.
Q Is the final referred to in the final product, or is that at some other juncture that you extracted the TCX and 8-5?
MR. WAGNER: You mean the columns,

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final, is that what you're referring to?
MR. SCHULER: Yes.
A This would refer to the sodium. This would not refer to the final product, but rather to the intermediate sodium 2,4-D.
Q At the bottom of page 30 you refer to the 2,4-D reaction as developed by H. Brust. Is that referring to this new process?
A Correct.
Q At the bottom of page 31, you mention that formation of the TCX cannot be limited to much less than 60 percent per million. Is that with reference to the final product of this new process, or sodium or the amine version of 2,4-D?
MR. WAGNER: I object to the form of the question.
A This refers to laboratory experiments which, as you can see, were run at 72 hours at 160 degrees in glass equipment. This is not refering to plant.
Q So this is the product that you were getting in the laboratory?
A Correct.

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Q Did you ever test the final product from the plant to determine a TCX concentration?
MR. WAGNER: I object to the form of the question.
**A The product in the plant was analyzed routinely for these compounds.**
Q And is there information here in this report with regard to that, or would that be located in some other report?
MR. WAGNER: I object to the form of the question.
**A There may be a reference within the report here or there. I don't specifically recall talking about specific plant data. All of the numbers reported in various tables, to the best of my recollection, are all laboratory generated numbers.**
Q So you were using, you simulated the process or reconstructed the process in the laboratory, and the numbers in this report are with regard to the product you produced in the laboratory?
**A Correct, other than the numbers that we discussed at the very beginning, where we said we found 200 to 500 parts in the reactor crude and in the**

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**recycle, those were plant data.**
Q With the plant data that you mentioned, it would be generally higher than the laboratory data for as far as the content of the impurities was concerned?
**A We observed that, I think I mentioned it a little bit ago, where you were asking me, it's on page 21, where the plant observed TCX formation rates that were five times or so higher than laboratory.**
Q Referring to page 35, you make reference to an earlier report, and it's got a number, footnote 16. Is that the report that's listed as 16 in the reference section on page 57?
**A I recall the work. I do not recall the report.**
Q What's listed as 16 on page 57 has some numbers behind it. Organic chemistry, I assume is the OC?
**A Yes.**
Q And then 78, dash, 17 stands for what, if you know?
**A I guess I don't remember specifically. The thing that confuses me a little bit is the LR, because that is a code that we used to use for letter reports, which were a way of documenting results**

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**back at that time. I think I mentioned earlier the numbering code that we used. Well, we mentioned it on this report, but the 78-17 LR, I don't specifically remember how we used to number those.**
Q What about the 39, dash, 78?
**A That, I'm not sure about that, either.**
Q There's a reference in the reference section, number 12, also, to some work done by, is it Dr. Brust?
**A Yes.**
Q And refers to organic chemicals, again, with a long number, dash, 2, and then a 2-26-73. Do you know what that refers to, number 12?
**A That's one of Dr. Brust's research reports. I can't tell you from the number exactly which one. The date is the date that the report was issued. The numbering code is, the 0730013 is a coding system that was used for a period of years. CHECK CHECK CHECK.**
Q Any significance to that?
**A Nothing as far as a – I don't specificalloy recall.**

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Q Was there a specific number that was assigned to subject matter, for example, like 2,4-D, was there a specific file or series of files pertaining to a particular chemical like that?
**A Different coding systems were used at different times. Now, whether there was a coding system specifically designed to 2,4-D, I don't recall.**
Q You don't remember whether there were specific codes that were assigned to certain chemicals, for example, to keep research, no matter what aspect it dealt with, but in regard to a certain chemical in that area that existed?
MR. WAGNER: I object to the form of the question.
**A I don't specifically recall all that went into how they specifically assigned codes, because it changed at times. And what was used specifically at the time this report was issued, I don't really remember.**
Q Was the research or the organization of the product of the research computerized back in 1975?
**A Was the research computerized in 1975?**
Q I mean the organization of the reports?

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**A Oh, no, these were not done by, on computer.**
Q But were they filed? Was there a computer index of the reports, if you know?
MR. WAGNER: In 1975?
MR. SCHULER: In 1975.
**A In 1975 was there a computer? I don't know for certain.**
Q At the bottom of page 36, or on page 36 I should say, you make a comparison in the first paragraph between the two processes, the 489 building and the new process in the 948 building, correct?
MR. WAGNER: I object to the form of the question.
**A Are you talking about under item four?**
Q Yes.
**A Well, the process in 489 building did use a step involving the use of bleach that was not used in the new process, that's correct.**
Q And were you making some type of an estimate as to whether adding a bleaching step would improve or reduce, help to reduce the impurities that were found in the new process, is that what you were doing there?

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**A Yes. It was an option we wanted to consider.**
Q And it is apparently submitted to somebody by the name of K.E. First?
**A That's the same Ken First we discussed earlier.**
Q And he estimated a cost of doing that at 500,000, is that what that is?
**A Yes.**
Q So that wasn't pursued because of the – it wasn't cost effective?
MR. WAGNER: I object to the form of the question.
**A Yeah, as stated in the report, it was dropped due to the marginal benefits that we concluded.**
Q At the top of page 38 you mention the capacity of the 948 building up to that point in time, and I just want to know, need to know the numbers you're referring to there, it's 100 to 120 what per day?
**A It's 100 to 120,000 pounds per day.**
Q What, the new process?
**A Yes.**
Q Do you know at this time or, let me go back, do you know as of May of 1977 whether the 948 building was running at that capacity?

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**A In May of '77 when we started up?**
*Q Yes.*
**A No, it was not.**
*Q What about when this report was done in October?*
**A The date would basically refer to the date this report was issued, so we're talking about, essentially now, October 1978. What the running rate was in October of '77, which is, I assume, the date you're asking about?**
*Q Yes.*
**A I don't know.**
*Q That's right, this report was October of '78, so you're referring to the full capacity as of October of '78?*
**A Correct.**
*Q And in your statement in the next sentence with regard to the impurities in the 2,4-D product is what, 20 parts per million of TCX?*
**A Yes.**
*Q And 20 parts per million of 8-5?*
**A Plus or minus some. What the ranges are, I don't recall.**
*Q You mention in a couple of paragraphs down that*

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*further work is justified only if the levels of impurities presently found in the product prove unacceptable in the future from a toxicity, environmental or performance standpoint. Do you recall whether there was any further research done in any of those areas to determine whether these impurities were unacceptable?*
MR. WAGNER: I object to the form of the question.
**A No, I don't recall.**
*Q You did not do any research in those areas, I take it?*
**A The work that we would have done in those areas would have been continuing to work in the plant, monitoring and making sure that we were, in fact, operating within these ranges.**
*Q You mean the ranges of 20 parts per million?*
**A Yes.**
*Q Was there a quality control laboratory set up in each building, for example, the 948 building for 2,4-D and the 489 building for 2,4-D?*
**A Yes.**
*Q And so the analyses that you referred to earlier*

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*with regard to quality control were performed right there in the plant, if you will?*
**A Correct.**
*Q As opposed to the organic chemicals research laboratory?*
**A We did very, very few analyses ourselves, in our department. We would rely on the quality control laboratories, as well as the analytical sciences laboratory.**
*Q Was there a quality control officer assigned, for example, to building 489?*
**A I can't answer how that was – I don't know how that was managed those days.**
*Q Was that a separate department in 1975, quality control?*
**A The quality control work, during the time frame we're talking here, was done within the plants. How the data was managed in reference to a quality control officer, or as you brought up, I just – I don't know.**
MR. WAGNER: Let's take a quick break.
(RECESS.)
BY MR. SCHULER:

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*Q The acknowledgment section on page 56 of Plaintiff's Exhibit 2 mentions a number of people, some of whom you've already referred to, Dr. Krumel, but let me ask you about some of the others. Who is T. Evans?*
**A Tom Evans was an analytical scientist, as was Gary Jewett, as was Penn, P-E-N-N, Schloemann – well, as I indicated, for their analytic support.**
*Q I just wanted to identify them. Did they all work on some aspect of preparing this report that we have marked as Plaintiff's Exhibit 2?*
**A They all would have provided input in the analytical results that were described within the report. I couldn't identify for you specifically what each one of those individuals did at this time, but they were all part of providing the analytical backup for this report.**
*Q Did any of them do any research on 2,4-D prior to the new process, the old process, we'll call it?*
**A Not that I recall.**
*Q I asked you about some of the documents listed on page 57, the reference section. Who is Mr. Dhingra, D-H-I-N-G-R-A?*

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**A Yes, Yog Dhingra.**
*Q Who is that?*
**A He's a chemist who was involved in the phenoxy area during the time I was in the cellulose ether area. So specifically what he was doing and what he was referring to in this reference, I can't tell you right now.**
*Q Mr. Fern or Ms. Fern, whatever that is, do you know who that is, it's the next one down, number 14?*
**A That's a misprint. That's what I was afraid of. You can – back to page 31, I refer to Dhingra and Fear, reference 14.**
*Q So that's Fear?*
**A The name should be Fear, F-E-A-R, Dennis Fear. He was an engineer who was very much involved in process modeling. Now, we'd have to look at the report if you want to get specifically as to what he did.**
*Q The work that you did in the organic chemical research laboratory, was that originally committed to what's referenced here in some places as a lab book?*

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MR. WAGNER: I object to the form of the question, over broad.
**A Our standard way of initially documenting our work, as we're doing the experiments, is to write them up in research data books. The results of our work described in these research data books is then summarized in these research reports.**
*Q So the summary, this research report would be the summary of what's in the research data book for a particular experiment?*
**A Correct, or a particular project.**
*Q There's a reference at the bottom where it talks about laboratory notebook references, and it has your name and Mr. Arnold?*
**A OC 417 and OC 640, those are code numbers for the data books. The pages merely describe, so in research data back OC 417 for Ray Arnold, you will find the work that is summarized in this report described in pages 109 to 150. And in data book 640 from pages 1 to pages 73, and likewise in my research data book, OC 559, you will find work described in this report on pages 95 to 131. This is the way we have of referencing our reports back**

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**to the original data.**
*Q All right. After this was completed, did you do any further research with regard to these impurities in the new 2,4-D process?*
MR. WAGNER: I object to the form of the question.
**A Not that I can recall.**
*Q Did you do any further research into the old 2,4-D process after October of 1978?*
MR. WAGNER: I object to the form of the question.
**A Not that I can specifically recall.**
*Q At some point in this report, this 2,4-D was referred to as Rhone-Progil acid. Do you know what that means?*
**A Yes. Rhone-progil was a company in Europe that produced 2,4-D acid at that time. Their material happened to be particularly pure, so we had a sample of it that we used for research purposes only.**
*Q And that's why you refer to it by that name?*
**A Rhone-Progil, yes.**
*Q Was the new process for 2,4-D developed to reach*

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*the level of purity that had been developed by this Rhone-Progil company?*
MR. WAGNER: I object to the form of the question.
**A To my knowledge, there's no connection.**
*Q Did you, other than writing your report, and I assume, let me go back and ask this question, I assume this report, that we have marked as Plaintiff's Exhibit 2 here, was written for intercompany use?*
**A Yes.**
*Q Did you ever write any report for use outside the company, to anyone outside the company?*
MR. WAGNER: On any subject at any time?
MR. SCHULER: No, on this subject.
**A On this subject, no, I've not.**
*Q Did you ever communicate information to anyone outside the company regarding the fact that there were these impurities in this new 2,4-D process that were found and outlined in your report that we marked as Plaintiff's Exhibit 2?*
**A Not that I recall.**
*Q Do you know whether anyone else at Dow Chemical*

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*Company communicated information in this report that we marked as Plaintiff's Exhibit 2 to anyone else outside the company at any point in time?*
**A Not to my knowledge.**
*Q Do you know a Mr. Wisniewski, D.F Wisniewski?*
**A Dave Wisniewski.**
*Q What was his position back in '78 or '79, if you know?*
**A He was an analytical chemist that offered support to the general phenoxy area. Specifically what he was doing at that time, I can't tell you.**
**(Plaintiff's Exhibit 3 was marked for identification.)**
*Q Let me show you this document here and ask if you've seen this before, and you might show your counsel there, too. Let me see the date on that.*
**A December 16th, 1979.**
*Q Have you ever seen that document before?*
**A Not that I recall.**
*Q You weren't involved in any of the research that went into the preparation of that document?*
**A No, sir.**
*Q Mr. Wisniewski appears to at least have done some*

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*toxicological oriented research. Do you know if he's a toxicologist or not?*
MR. WAGNER: I object to the form of the question.
**A No. Mr. Wisniewski was definitely, he was an analytical chemist.**
*Q Is Mr. Wisniewski still with the company?*
**A Mr. Wisniewski passed away a number of years ago. So the right answer is no.**
*Q He may be with some company –*
MR. WAGNER: Spiritually.
*Q – not with Dow Chemical Company. Do you know what his background was, Mr. Wisniewski's background, I'm talking about scientific specialty, obviously?*
**A Well, Wisniewski worked in the analytical department. What his specific scientific background training is, no, I don't know.**
*Q Well, I don't see your name on this one, either, but let me ask you if you've seen that before?*
**A This would be a document having been prepared within the analytical department, and no, I had no involvement in its preparation, nor do I recognize**

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**it specifically.**
**(Plaintiff's Exhibit 4 was marked for identification.)**
*Q There's a sheet attached here to this Plaintiff's Exhibit 4. It's very difficult for me to read, and probably it will be for you, too, but can you make out, it appears to say release rerouting sheet. Have you seen a form like that before?*
**A I have no idea what this is.**
*Q Have you ever testified in any form before the Environmental Protection Agency, for example, or the Department of Agriculture, regarding these type of chemicals?*
**A No, I haven't.**
*Q Have you ever written any reports that were furnished to the EPA that you're aware of?*
MR. WAGNER: On any subject?
*Q On the subject of these chemicals, 2,4-D, 2,4,5-T, Silvex?*
**A Not that I can recall at this time.**
*Q Do you know who Marguerite Leng is?*
**A Yes, I know Marguerite.**
*Q What is her position – well, let's start with is*

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*she still with the company today?*
**A No, she's retired.**
*Q What was her position when she was last with the company, if you know?*
**A She was – I can't give you her exact title. She was in the regulatory department in some capacity, but I don't know exactly.**
*Q Do you know if scientific reports were provided to her on a regular, continuing basis, particularly regarding these chemicals?*
MR. WAGNER: I object to the form of the question.
**A The only reports that I would know would have been distributed would have been, to whom I can say the reports were distributed were the ones that were listed on the back cover here, and if she isn't on that list, then I can't answer, then I don't know if she was or not.**
*Q Have you ever been involved with her in terms of, and I'm not just limiting it to these chemicals, but have you ever been involved with her in the sense that you submitted a copy of a scientific report to her and she reviewed it for some*

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purpose?
**A I don't specifically recall having done that.**
*Q Have you ever been involved with her in any type of work at Dow Chemical?*
**A Only very much on the periphery. Marguerite happens to be a personal friend, and I know her more from that standpoint than the work standpoint.**
*Q Outside of being a personal friend of hers, I'm talking about whether you actually worked with her on any type of reporting or scientific work?*
**A Not that I can specifically recall at this time.**
*Q And just so I'm clear on this, do you know whether she ever edited any reports that you submitted?*
**A Not to my knowledge.**
*Q Do you know an Andrew Watson?*
**A I know the name, but I don't know the individual.**
*Q Would the function of determining the effectiveness of end product 2,4-D, for example, for its ultimate purpose, killing weeds, would that be done by another department other than yours?*
**A Yes.**

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*Q What department would be involved in doing that?*
**A Well, at that time the department was known as the agricultural product department. In the 9008, 9001 building area, the person we mentioned before, Joyce King is one who is more likely to get involved in that type of activity.**
*Q Was she involved from the agricultural product standpoint with 2,4-D back in 1975?*
**A The only time I specifically know that she was involved with this project was when we were working on the product, on the issue of xanthones and related compounds over the time frame described in this report.**
*Q Have you been involved at all in the registration process for 2,4-D, to your knowledge?*
MR. WAGNER: I object to the form of the question.
**A The only involvement that I would have had is to supply process descriptions to the individuals who actually – who prepare for reregistration packages, and I have provided information on occasion to those individuals.**
*Q Let me see if I understand this, process*

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*description for reregistration packages, what would that entail?*
**A Well, the reregistration – a small piece of the reregistration process or package is to describe the chemical process for producing the product. And I would – I have in the past provided information to that. I can't give you specific dates off the top of my head when I've done that, but I know I've done that.**
*Q Did you do that in connection with 2,4-D?*
**A Yes.**
*Q Can you give me an approximate time period when you did that with respect to 2,4-D?*
**A Early to mid eighties time frame.**
*Q Can you tell me what individuals you dealt with, in other words, who you furnished these process descriptions to for the reregistration package?*
**A I don't specifically recall at this time.**
*Q Was there a particular department that dealt with the registration process?*
**A The ag chemicals product department did that, so it would be an individual in that department.**
*Q Is that department presently located in any*

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*specific building?*
**A Well, since the formation of DowElanco, the organization is now very much different than it was during the time we're talking about here. All of the activities that were out of the 9001 building and 9008 building are now here in Indianapolis with DowElanco.**
*Q Have you ever had any input into the labeling process for 2,4-D?*
**A No.**
*Q Do you know whether the 2,4-D label ever reflected the impurities that you found in your report of October of 1978?*
**A Not to my knowledge.**
*Q Do you know whether the 2,4-D label ever reflected any impurities found in the product prior to October of 1978?*
MR. WAGNER: I object to the form of the question, over broad.
**A Not to my knowledge**
*Q Would the agricultural products department also have responsibility for labeling, to your knowledge?*

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**A I can't answer that specifically, but I would assume yes.**
*Q Do you know, for example, back in 1975, any individuals' names who might have had that responsibility?*
**A No, I don't – I don't know any names since that was far removed from my involvement in the project.**
*Q Back in 1975, and I apologize if I asked this question or a version of it earlier, but I want to be clear about this, back in 1975, besides yourself, who else, if anyone, in the agricultural chemical process or products research section had responsibility for any aspect of the 2,4-D research?*
MR. WAGNER: It was asked and answered. I don't think he remembered it.
MR. SCHULER: I think he mentioned Mr. Brust.
MR. WAGNER: That's right.
**A I did happen to think of one more individual, a gentleman by the name of Quentin Hutchcroft.**
*Q Is he still with the company, Mr. Hutchcroft?*

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**A No. He left the company many years ago. He was a colleague of mine, and he and I worked together on an aspect of the process.**
*Q Anyone else that you recall?*
**A That's the only additional person that I can recall that I didn't mention earlier.**
*Q I think you testified that you, maybe I misunderstood you, but I want to be clear about this, you haven't done any further research on 2,4-D after this 1978 project, is that correct?*
**A I was – I was the process chemist responsible for 2,4-D process research until approximately 1983, 1984, time frame. I think you asked the question in the context of specifically this report that we have been discussing, and –**
*Q Yes.*
**A – and to the best of my knowledge, I've not done any work since that report.**
*Q When you say work since this report, you were responsible, but there was no, once the process got up and running, there was no further research from your department on the 2,4-D process or 2,4-D, itself?*

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MR. WAGNER: I object to the form of the question.

**A Oh, yes, oh, yes.**

*Q Can you give me an idea of what other research was done on 2,4-D after October of '78 up until '83?*

**A We were – well, we did some further research on a modified process over what was described for, I think we discussed the plant in Aratu, Brazil, there was process research done in that area. There was process research done in the area of other trace impurities in the process. We were doing a lot of work during those days in the area of related – related to waste brine treatment clean up. Those are three key areas that I can recall.**

*Q Waste brine being a by-product of the process?*

**A Yes, one of the by-products of the process was an 18 to 20 percent sodium chloride stream.**

*Q And what else, anything else comes to mind?*

**A Those are the key areas of our research, and continued support of the process. When plant problems crop up now and then, and these can be any one of a number of different things, that**

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**we're constantly asked to provide technical support to the plant, to the manufacturing staff.**

*Q Have you done any research with regard to 2,4,5-T or Silvex since 1975?*

**A Yes.**

*Q And can you give me some examples of research you've done and the time period it may have occurred?*

**A In addition to the 2,4-D acid process that was run in 489 building, we did have a process that produced 2,4,5-T and 2,4,5 – well, Silvex esters. We called that the direct ester process. And, yes, I was involved in sampling and evaluating results in the areas of 2,3,7,8 TCDD and other polychlorinated dibenzo-para-dioxins, and we did some research in that time frame about further reducing those impurities from our product.**

*Q And when you say that time frame, you're referring to 1975, 1976, somewhere around there?*

**A The peak time frame of 1975 to 1979, when the direct ester process was shut down.**

*Q Did you generate reports?*

**A Yes.**

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*Q On that?*

**A Yes.**

*Q Do you have any of the reports with you today?*

**A No, sir.**

MR. SCHULER: Are you taking the position that Dow has them, and he doesn't have them, that's why you're not producing it?

MR. WAGNER: Correct, they're not his reports.

*Q From 1975 through 1979, did you find the presence of TCDD in either Silvex or 2,4,5-T end product?*

**A Yes.**

*Q And do you recall at what levels you found it?*

**A Typically the levels could range in the .03 to .07 parts per million of 2,3,7,8 TCDD.**

*Q Was there a fluctuation from batch to batch?*

**A Yes.**

*Q Did you ever find the presence of TCDD at a higher level than .07 parts per million in any batch that you sampled?*

MR. WAGNER: I object to the form of the question.

**A I don't recall specific data. When I tell you the**

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**.03 to .07, those are ranges that I recall that we would see in the product in that mid-1970 time frame.**

*Q Can you give me a rough idea how many reports were generated about that subject matter, the finding of TCDD or other dioxins in 2,4,5-T or Silvex?*

**A I couldn't give you an exact number or even a close number at this point.**

*Q Those reports, I assume, were written and used for intercompany purposes?*

MR. WAGNER: I object to the form.

**A Certainly anything that I wrote that would have summarized results would have been done for intercompany purposes. What happened to the data beyond that point, I can't comment.**

*Q Who else worked with you in this particular analysis or research into the presence of these dioxins in those end products?*

**A Well, Mr. Arnold would have provided technical support, laboratory support to me. Mr. Siegel that we mentioned earlier, has done work in that, during, again, this 1975-1979 time frame.**

*Q Other than Mr. Arnold and Mr. Siegel, anybody else*

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*that you can recall?*

**A Not that I recall specifically at this time.**

*Q Was this, for lack of a better term, kind of a continuing monitoring process when you tested these chemicals for the presence of TCDD or other dioxins?*

MR. WAGNER: I object to the form of the question.

**A Right.**

*Q How frequently would you test these products for the presence of those contaminants?*

MR. WAGNER: I object to the form of the question.

**A In our direct ester process, I don't recall the frequency that we did at that time. This was a quality control lab, analytical lab function that I was only off on the periphery of with access to the data.**

*Q When you say the direct ester process, would you also test the amine version of 2,4,5-T?*

**A I don't recall that we produced an amine form of 2,4,5-T at that time.**

*Q What about Silvex, was that tested?*

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**A The Silvex esters would have been tested, as would the 2,4,5-T esters.**

*Q The amine formulation of 2,4,5-T was not manufactured by Dow, you're saying from '75 to '79?*

MR. WAGNER: I object to the form of the question.

*Q Or did I misunderstand you?*

**A I don't recall that we manufactured the amine form of those compounds at that time.**

*Q At some earlier time did the company do that, if you know?*

**A Not that I know of specifically.**

*Q Where would these records be kept from your testing of these end products for TCDD or other dioxins?*

**A Well, the records we're talking about are records that were generated, as I said before, by the quality control labs and by the analytical lab, so it would be within whatever, wherever their documentation is maintained.**

*Q Would that be in the plant or some other place, if you know?*



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A Some would be in the plant, and some would be within our central reporting index.
MR. WAGNER: Was your question directed to today or back then, Dick?
MR. SCHULER: During the period of 1975 to '79.
THE DEPONENT: Yes, that's when I was answering.
MR. WAGNER: I thought so.
Q During the period from 1975 to 1979, do you know whether there was any listing on the labels for 2,4,5-T or Silvex that those products contained either TCDD or any other dioxin contaminants?
MR. WAGNER: I object to the form of the question.
A I don't know.
Q Do you know whether any information from 1975 to 1979 was furnished to the government with regard to the dioxin contents of those end products?
MR. WAGNER: Same objection.
A I am not aware specifically of information that was submitted to the government on that subject.
Q Were you involved in the decision to shut down

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production of Silvex and 2,4,5-T?
A No, I wasn't.
Q Do you know who was involved in that decision?
A The managers of ag production and of the product department whose names – who the specific individuals that would have met to make that decision, I couldn't answer at this time.
Q Do you know who the individuals were that may have been involved in making the decision?
A I can't give you a specific name.
Q Did you have, once a decision was made, did you have any role in shutting down of the process?
A No. Once the process was shut down, it was shut down, and being an organic chemist working in research, I had no involvement in the project.
Q Were you aware, between 1975 and 1979, of any hearings that were ongoing with regard to what's known as a rebuttable presumption against registration for either Silvex or 2,4,5-T?
A I knew about them, but I had no involvement in them, and I couldn't – don't recall any of the specific details at this time.
Q You don't recall furnishing any information that

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was used in the course of those hearings?
A No, sir, no specific information that I recall.
MR. WAGNER: Let's take a quick break.
(RECESS.)
BY MR. SCHULER:
Q Back in 1975, was the 2,4-D that was manufactured by Dow Chemical primarily sold in its amine form?
MR. WAGNER: I object, no predicate as to personal knowledge.
A It was sold. I can't comment as to whether it was sold primarily as the amine formulation. We certainly sold a significant quantity of it as the amine formulation, but I don't know the balance of esters, amines and acids sold.
Q Do you have any knowledge of the total amount of 2,4-D sold on an annualized basis, for example, back in 1975 and 1976?
A I couldn't give you a number from personal knowledge. It would be speculation.
Q You mentioned that the, in your report that we marked as Plaintiff's Exhibit 2, that this 948 building at capacity could crank out 100 to 120,000 pounds a day, correct?

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A Yes.
Q What did building 489, what was its capacity, if you know?
A I don't recall that number anymore.
Q Do you know if it was similar to the 948 building or not?
A It would have been in that magnitude, but a specific number, I just don't remember.
Q Were there any other buildings that Dow Chemical had, back in 1975 and '76, that produced 2,4-D other than those?
MR. WAGNER: In Midland?
Q In Midland, yes.
A No, sir. Those were the only places it was produced at that time.
Q Were there other locations back at that time that produced the chemical on behalf of Dow?
A The subsidiary produced 2,4-D for Dow in New Zealand, Ivan Watkins Dow, W-A-T-K-I-N-S.
Q Any other locations around the world?
MR. WAGNER: In 1975?
Q Yes, the '75-'76 time period.
A No. Those were it, those were the facilities.

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Q Do you know, and again, if you don't know this information just tell me and I'll move on, but do you know in what units the chemical 2,4-D was sold in '75 and '76? In other words, was it sold by the ton, by the pound, by the gallon?
A It was sold in a variety of different containers; gallons, five gallons, 55-gallons, tank cars, different products were sold in different containers, specifically, you know, the specific balance.
Q In 1975 and 1976, would you be aware of what the five gallon container looked like?
MR. WAGNER: For?
MR. SCHULER: 2,4-D.
A Amines, esters?
Q Amines.
MR. WAGNER: I object to the form of the question, not specific.
A I have seen the cans, but after 17 years, to recall exactly what was on the can and how it looks, I don't.
Q Were the cans metal or plastic back then?
A Metal.

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Q And do you recall the color of the cans?
A Not anymore.
Q Same question for Silvex, would you recall the color of the cans? Was it sold in cans?
MR. WAGNER: I object, compound, no predicate.
A Silvex, I can't recall specifically the way Silvex was supplied.
Q Same question with regard to 2,4,5-T?
MR. WAGNER: Same objection.
A And the same answer as for Silvex.
Q Do you know what the unit price was for a five-gallon can of 2,4-D back in '75 and '76?
A No, I don't remember that.
Q Who would know that information?
A That would be information that would available from the commercial function.
Q Agricultural products division?
A Yes – well, DowElanco now, if those records still exist.
Q Do you have any opinions with regard to the toxicity of 2,4-D as it applies to human beings?
MR. WAGNER: No predicate as to

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expertise in that area. You mean his opinion today?
MR. SCHULER: Yes.
MR. WAGNER: Well, the question is whether or not you have an opinion. Go ahead.
**A Well, as an organic chemist, not trained in toxicology, I don't feel I can render an opinion on that.**
*Q Have you participated in any other, had input in any reviews that the EPA has instituted with regard to the safety of 2,4-D?*
MR. WAGNER: I think it's been asked and answered.
MR. SCHULER: I asked about Silvex and 2,4,5-T before.
MR. WAGNER: You're correct.
**A I'm sorry, with the dialogs –**
MR. SCHULER: Could you read that back.
(THE REQUESTED MATERIAL WAS READ BY THE REPORTER.)
MR. WAGNER: I object to the form.
**A No.**
*Q Back in 1975 and 1976, were you aware of any*

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*published literature that, I know you're not a toxicologist, but I'm asking you in your capacity as a scientist, were you aware of any published literature with regard to the potential for carcinogenicity of 2,4-D or Silvex?*
**A For the potential of carcinogenicity, no.**
*Q Same question with regard to 2,4-D, same time period?*
**A No.**
*Q Do you, yourself, subscribe to scientific journals other than what may be available to you in the Dow library?*
**A As a member of the American Chemical Society, I receive their weekly publication, Chemical and Engineering News. Otherwise, all of the scientific journals that I read are provided to me through Dow.**
*Q Do you know a fellow by the name of Leonard or Len Smith?*
**A Yes.**
*Q And what is his position or was his position at Dow?*
**A I don't know what his position was at the time,**

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**over the time frame that we're talking about here.**
*Q Is he still with the company?*
**A He's with DowElanco.**
*Q Here in Indianapolis now?*
**A Yes.**
*Q Do you know what his position is?*
**A He just moved, and I forget his new title.**
*Q When you were doing your analysis as reflected in your report of October of 1978, did you take hygienic precautions in dealing with those chemicals that are outlined in that report?*
**A Yes, I did. I used the standard, good laboratory practices that we follow in our department.**
*Q What kind of precautions did you take back in 1977-'78, when you were working on this report?*
**A Lab coat, impervious rubber gloves, glasses, goggles, all of our work was performed in a properly ventilated hood, the standard precautions that we take with toxic and hazardous chemicals.**
*Q Do you wear any special type of pants, for example, or does the coat come down pretty –*
**A It was a typical knee-length laboratory coat.**
*Q And do you wear any type of special shoes or boots*

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*or anything like that?*
**A No.**
*Q When you say you work in a ventilated laboratory hood, what does that look like?*
**A The typical laboratory hood is a bench top, perhaps typically they're six feet wide, about 30 inches deep, with air movement sweeping across so that we're adequately protected.**
*Q The fumes are sucked up into the exhaust, if you will?*
**A Yes.**
*Q Did you ever wear a respirator in dealing with any of the materials outlined in your October '78 report?*
**A No.**
*Q Other than the research that we've discussed here today involving 2,4-D and 2,4,5-T and Silvex, have you done any other research with respect to those chemicals that we haven't discussed here today or touched on in your testimony?*
MR. WAGNER: I object as to breadth.
**A Yes.**
*Q What type of research?*

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**A Well, notably we did some research in the 2,4,5-T area where we learned how to further reduce the quantities of dioxins from the product. I think I gave you numbers to the best of my recollection of .03 to .07. We developed technology, again, I can't give you a concrete date, but in the '77-'78 time frame, to further reduce those levels in the ranges of, again, as best I can recall, .01, .02.**
*Q And what, do you recall the type of technology that was developed or methods that were developed to reduce the TCDD down to that level?*
**A The post treatment, prior to formulation, with activated carbon.**
*Q I'm not sure I understand – post final product –*
**A The technical product, before it is formulated into the final product, was passed through a bed of activated carbon.**
*Q And the carbon helped to filter out some of those impurities, at least down to that level?*
**A It removed the impurities down to this level of, again, as best I recall, .01, .02, .03, in that range.**
*Q And to the best of your recollection, that would*

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*have been in the '77 to '78 time period?*
**A Plus or minus a little, yes.**
*Q Who else would have worked on that project with you?*
**A Sanford Siegel, in the laboratory.**
*Q Who else would have been involved with that project outside the laboratory as far as implementation of the carbon filters are concerned?*
**A That would have been, obviously, with the engineers in the plant. Specifically who the engineer or engineers were at this time, I don't recall.**
*Q Was anyone from agricultural products involved with that decision to approve the use of the carbon filters, for example?*
**A I don't remember the decision process for specific implementation of all that.**
*Q But you were involved doing the lab work?*
**A I was involved developing the technology, yes.**
*Q Any other research that you did with respect to 2,4-D, 2,4,5-T or Silvex between the 1975 and, say, 1977 time periods?*

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MR. WAGNER: That he hasn't touched on?
MR. SCHULER: That he hasn't mentioned already, of course.
**A We have touched on a number of topics at various times. I think we have covered them all.**
*Q Let me just ask you about the documentation. Do you have a CV, curriculum vitae, summarizing your educational background, experience, training in your profession?*
**A No. I haven't had a resume prepared since –**
MR. WAGNER: He's not been job hunting.
**A – like almost 28 years.**
*Q You haven't looked for a job in a long time, that's right. Okay, in the notice of taking deposition I had, and by the way, you spell your name, K-A-R-L, correct?*
**A Yes, sir.**
*Q In the notice of deposition I had asked you to produce any and all documents produced by you or at your direction during the course of your employment with Dow Chemical Company or its subsidiaries that pertain to any research, analysis, formulation, study or production of the*

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*chemicals 2,4-D, 2,4,5-T, Silvex or any product or substance containing these chemicals or any ingredients used in making these chemicals or any contaminants or dioxins contained in any of these chemicals or their ingredients.*
*Today you produced no documents, correct? You gave me the October of '78 report that I already had. Did you bring any of those documents with you here today?*
**A Well, all the documents are owned by the Dow Chemical Company. I have no documents that are owned by me.**
*Q So the answer is, you did not bring any of those documents here with you today?*
**A That's right.**
*Q You have not served, I understand from your earlier testimony, as an expert witness in any case, correct?*
**A Correct.**
*Q You have not issued any documents, reports, articles or transcripts relating to any opinion you might have ever formed regarding the cause of soft tissue sarcoma or the toxicology or health*

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*effects of 2,4-D, 2,4,5-T, Silvex, 2,4,5-TP or any product or substance containing any of those chemicals?*
**A No, sir.**
*Q You mentioned your status as, I think you told me initially as senior scientist?*
**A My official title within Dow Chemical Company is an associate scientist.**
*Q Are there rankings within the company by title, and you get certain income, kind of like the military or an organized entity like that?*
**A Yes.**
*Q So when you reach, you have a certain title, you reach a certain level, you get a certain income that goes along with that, would that be a fair statement?*
**A Yes.**
*Q How long have you been with the company, the number of years?*
**A I joined the company in June of '65, so that puts me at 27 years, nine months.**
*Q Do you intend on staying with the company for the time until retirement?*

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**A Yes, I do.**
*Q When do you anticipate, if you do, retiring from the company?*
**A I have no plans for retirement at this point.**
*Q Prior to coming here to this deposition today, did you review any documents, other than obviously the document we have marked as Plaintiff's Exhibit 2?*
**A I reviewed one other letter that Allen showed me that was essentially a letter written by my manager at the time, I don't remember the exact date on that letter, to an analytical manager telling him we were going to be providing him with some samples for analysis for various chlorinated dioxins. Those are the only two documents that I've specifically reviewed for this deposition.**
*Q Who is your manager who wrote that letter?*
**A That was Dr. Mintz, Michael Mintz.**
*Q What was the date of that correspondence?*
MR. WAGNER: I think he said he didn't remember.
**A I don't remember the specific date. It would have been in the period of, around 1976, plus or minus a little.**

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*Q Prior to the time of this report that we have marked as Plaintiff's Exhibit 2?*
**A Yes.**
MR. SCHULER: Did you have a copy of that? Can I see a copy of that?
MR. WAGNER: No.
MR. SCHULER: You have a copy present here today? You're just not going to let me see it?
MR. WAGNER: I don't know if it's present in this room.
*Q When did you see the document?*
**A I saw it yesterday.**
MR. SCHULER: For the record, I request a copy of the document. The copy of the document's been refused and –
MR. WAGNER: What's the basis that I would have to give you that document?
MR. SCHULER: Because I asked it be produced here today.
MR. WAGNER: It's a Dow document. It's not his document. If you would like documents from Dow, send me a request to produce.

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MR. SCHULER: Well, I understand the position that you've taken, but I disagree with it 100 percent, and particularly when the document is present here today and could be discussed with this witness. To refuse to produce it, I think is a violation of this request, and I'll seek court relief on that. I have no further questions, thank you.
MR. WAGNER: Before we let Aprille go, let's make this part of the record. Larry Silverstein faxed the statement which turns out to be an affidavit that he signed. That's my only copy. It was delivered here this morning, so let's mark it as an exhibit. From my review it does not contain any information that you didn't cover with him yesterday.
Why don't you take a minute to review it, if you want. We could probably have him come over and answer questions about it, but as I say, from my review of it, I think all those areas that were mentioned were covered.
MR. SCHULER: Well, I'm not – I can't take a look at this. I mean, we had his

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deposition yesterday. This wasn't produced, and I'm taking the position that it was wrongfully withheld.
MR. WAGNER: Well, he didn't have it.
MR. SCHULER: Well, he was requested to produce it.
MR. WAGNER: I know he was requested, and I know it's here now. If you want him, I'll get him on the phone and see if he can come out here.
MR. SCHULER: That's not good enough for me. I was taking his deposition yesterday, and I'm handed a four-page document with 16 paragraphs today, and I'm not going to be put in that position of doing this now, and when it wasn't produced when it should have been produced, and asking him questions about it. We'll mark it for the purpose of discussion, since we talked about it at this deposition, as Plaintiff's Exhibit Number 5.
**(Plaintiff's Exhibit 5 was marked for identification.)**
MR. SCHULER: Is that it?

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MR. WAGNER: No questions.
AND FURTHER THE DEPONENT SAYETH NOT

KARL KRUMEL, Ph.D.

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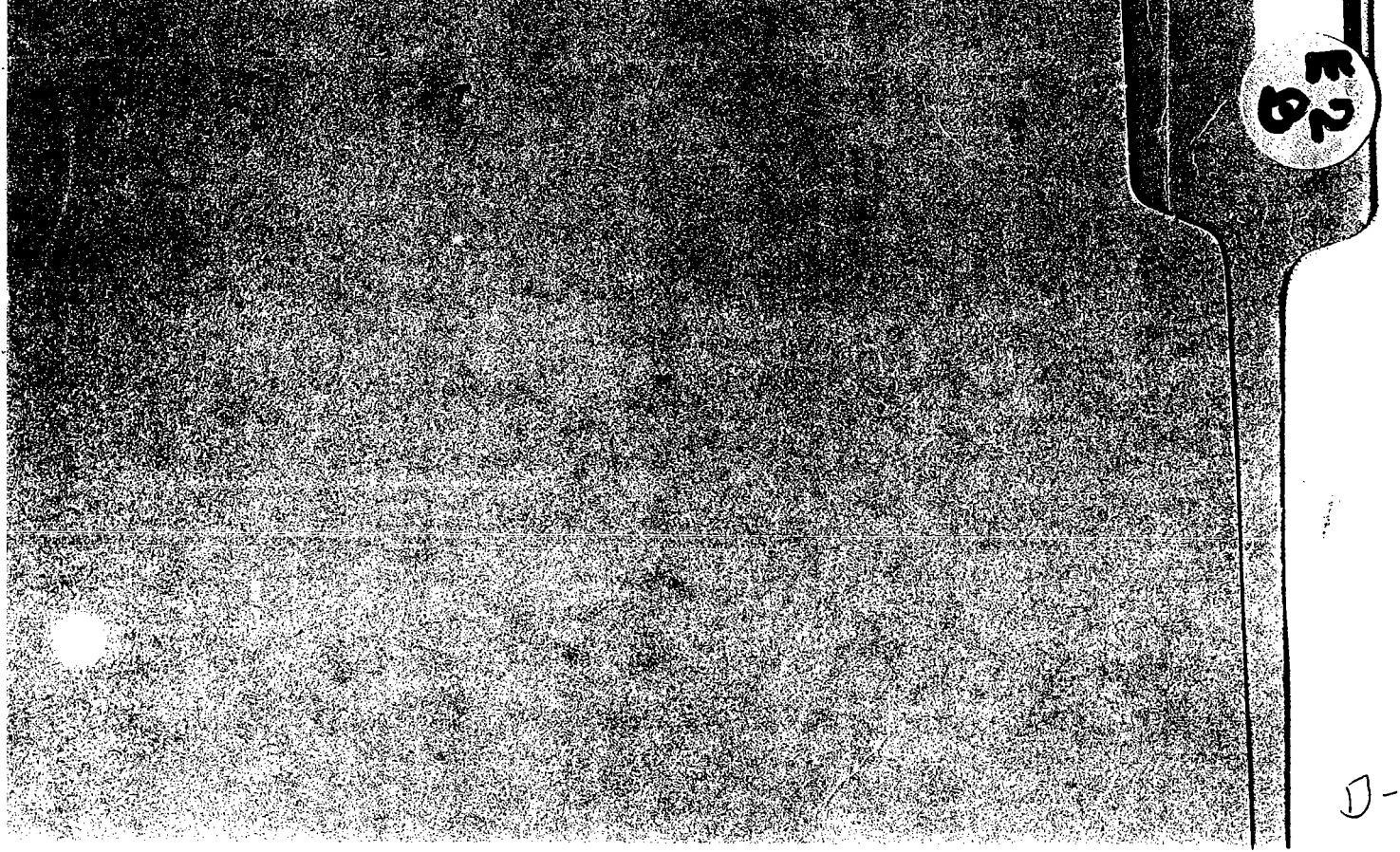
STATE OF INDIANA )
) ss:
COUNTY OF MARION )
I, Aprille Rigsbee Lucas, RPR, Notary Public in and for the County of Marion, State of Indiana, do hereby certify that the deponent herein was by me first duly sworn to tell the truth, the whole truth and nothing but the truth, in the aforementioned matter;
That the foregoing deposition was taken on behalf of the Plaintiff;
That said deposition was taken at the time and place heretofore mentioned between the hours of 8:00 a.m. and 6:00 p.m;
That said deposition was taken down in stenograph notes and afterwards reduced to typewriting under my direction and thereafter presented to said witness for signature; that this certificate does not purport to acknowledge or verify the signature hereto of the deponent;
I do further certify that I am a disinterested person in this cause of action; that I am not a relative or attorney of any of the

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parties, or otherwise interested in the event of this cause of action, and am not in the employ of the attorneys for any of the parties.
IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 15th day of March, 1993.

Aprille Rigsbee Lucas, RPR
My Commission Expires:
September 21, 1996


AGENT ORANGE PACK. FROM DR. T.
MOYER V DOW





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THE DOW CHEMICAL COMPANY

BARSTOW BUILDING
2020 DOW CENTER
MIDLAND, MICHIGAN 48640

June 15, 1970

DOW 424633

The Honorable Melvin R. Laird
Secretary of Defense
The Pentagon
Washington, D. C.

Sir:

Subject: Defoliants for the Department of Defense

Several weeks ago the Department of Defense announced the temporary suspension of the use of Agent Orange (a mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid) as a defoliant in Southeast Asia. It has now come to our attention that the use of Agent Orange may be reinstituted.

There is abundant evidence that 2,3,7,8-tetrachlorodibenzo-p-dioxin occurring as an impurity in 2,4,5-T is highly toxic. 2,4,5-T can be produced that contains only minute quantities of this impurity (less than one part per million), and such a product is available to the government from various sources. We at Dow are convinced that 2,4,5-T containing less than one part per million of 2,3,7,8-tetrachlorodibenzo-p-dioxin can be used safely. Certainly such a product is safer in use than one containing larger quantities.

The Dow Chemical Company again recommends strongly that the government set appropriate specifications and controls to insure that no 2,4,5-T be used if it contains more than one part per million 2,3,7,8-tetrachlorodibenzo-p-dioxin. More specifically, we would make this recommendation with respect to the use of 2,4,5-T as a component of Agent Orange if it is to be used as a defoliant in Vietnam. Such specification should apply to stocks on hand as well as new procurement.

EXHIBIT II

INSTA-TAB™ Pat. Pend.

LETTER TO
LAIRD

DOW 424631

Because of our strong feelings in this matter, we are sending copies of this letter to those listed below.

Dr. Lee A. DuBridge
Science Adviser to the President

The Honorable Clifford M. Hardin
Secretary of Agriculture

The Honorable Elliot Richardson
Secretary of Health, Education, and Welfare

The Honorable Walter J. Hickel
Secretary of the Interior.

Yours very truly,

G. J. Williams

G. J. Williams
Vice President

GJW:lm

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

IN RE

"AGENT ORANGE"

Products Liability Litigation

MDL No. 381
(all cases)

ADDENDUM TO PLAINTIFFS'MEMORANDUM ON THE APPLICABILITY OF THE LEGAL THEORIES OF FAILURE TO WARN, CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

Plaintiffs submit the following material which was inadvertantly omitted from their Memorandum and should be inserted after Page 15.

In a Dow document entitled "Report on the Chloracne Problem Meeting on 3/24/65", dated March 29, 1965, it is clear once again that all the participants at that meeting were fully apprised of the fact that the 2,4,5-T they were manufacturing was contaminated with dioxin. It is further patently clear that the method available for the detection of dioxin was completely explained as well. Expressed at that meeting was a serious concern that the users of the finished contaminated product were at greater risk than the plaint 2,4,5-T workers in view of the fact that the multitude of safety precautions used by workers were not available to them. L. G. Silverstein, of the Biochemical

Research Laboratories at Dow specifically recalled the aforementioned concern and stated in that report at the bottom of Page 4 that:

> "The question of specification, quality control specification that is, was raised and we were asked if we could give levels of dioxin contamination which were permissible limits. V. K. mentioned that at present we are using zero with a confidence of 1 ppm in process samples. There was some discussion on the problem of customers using finished products under far less desireable conditions of health control that we can provide our workmen in our own plant."

Mr. Silverstein, in that document, further went on to state on the bottom of Page 4 that:

> "There seemed to be agreement among the group that we could not afford to sell contaminated products."

Thus, it is clear that by the end of that meeting, the representatives of Hooker Chemical Corporation, Diamond Alkali Company, Hercules Powder Company and Dow knew full well that the products they manufactured, which contained dioxin, should not be sold, yet chose to disregard this knowledge when they proceeded to sell mass amounts to the United States Government.

In a postscript to the aforementioned document, V. K. Rowe stated:

> "All participants seemed to appreciate well the problem and all indicated that they would return home and attempt to convince their management to institute safety specifications (really quality control) for their various products in this area. All agreed that the industry should meet its own responsibility. All were very appreciative of Dow's effort to steer them away from a danger area. Time will tell whether we accomplished our mission, but as of now I feel satisfied with our effort and the reception it received."

Appended hereto is a copy of the aforesaid document entitled "Report on the Chloracne Problem Meeting on 3/24/64" dated 3/29/65 and authored by L. G. Silverstein, Biochemical Research Laboratory as Exhibit 1.

Plaintiffs respectfully submit the following information which was omitted from its Memorandum because at the time of filing we were not in possession of the transcript hereinafter referred to. The material which follows should have been inserted at the end of Page 30b.

The Deposition of Robert R. Rumer, who was the Vice President of the Monsanto Agricultural Chemical Division from 1965 to 1969 and also served as the General Manager of that same division from 1964 to 1969 was held on November 18, 1983. (T-112) It was learned that somewhere between 1965 and 1967, Mr. Rowe contacted Mr. William Allen, the individual in charge of Dow's Agricultural Chemicals operations, (T-91), to ascertain if "... Dow would be willing to sell or license Monsanto information from Dow's process know-how to reduce the impurities in the trichlorophenol and produce a higher quality product. (T-88) Mr. Allen flatly refused to share with Monsanto the knowledge they had regarding how to reduce the dioxin in Monsanto trichlorophenol because "... it wouldn't be in their interest." (T-91,92)

Thus, it is obvious that Dow, who was willing to share the wherewithall to detect the level of dioxin contamination in 2,4,5-T, chose not to share with its competitors the means with which to reduce the dioxin level of its competitors product.



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Appended hereto are Pages 112, 91, 92, 88, 89 and 90 of the deposition of Robert R. Rumer taken on November 18, 1983, as Exhibit 2.

Dated: December 5, 1983

Respectfully submitted,

Plaintiffs' Management Committee
By: David J. Dean

Stephen J. Schlegel, Esq.

Benton Musselwhite, Esq.

Thomas Henderson, Esq.

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

In re

"AGENT ORANGE"

Product Liability Litigation

MDL No. 381
(all cases)

ADDENDUM TO PLAINTIFFS' MEMORANDUM ON THE APPLICABILITY OF THE LEGAL THEORIES OF FAILURE TO WARN, CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

December 2, 1983

PLAINTIFFS' MANAGEMENT COMMITTEE

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
----------X

In Re

"Agent Orange"

Products Liability Litigation
----------X

MDL No. 381
(All Cases)

PLAINTIFFS' MEMORANDUM ON THE APPLICABILITY OF THE LEGAL THEORIES OF FAILURE TO WARN, CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

## INTRODUCTION

Plaintiffs' Memorandum addresses the issue of whether the legal theories of concerted action, enterprise liability, or alternative liability may be applied here in the absence of evidence enabling plaintiffs to identify which defendants' tortious conduct caused the injuries complained of. However, plaintiffs do not solely rely on the aforementioned theories.

It is plaintiffs' position that: (1) each defendant breached its duty to warn the government of the dioxin hazards to health known or which should have known by it to be associated with its own dioxin contaminated Agent Orange herbicide product and with the dioxin contaminated products sold by the other defendants to the military; (2) that


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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
----------X

In Re

"AGENT ORANGE"

Product Liability Litigation
----------X

MDL No. 381
(All Cases)

# PLAINTIFFS' MEMORANDUM ON THE APPLICABILITY OF THE LEGAL THEORIES OF FAILURE TO WARN, CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

December 1, 1983

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chloracne appeared at the Ingelheim plant and 18 cases appeared at the Hamburg plant. The problem became so serious that production was halted at the Ingelheim plant in December of 1954. In the spring of 1955, production was halted at the Hamburg plant. The plants were closed.

To test for toxicity in the plants, rabbits were placed on each of the floors with the doors and windows closed. All the rabbits died within five days. Autopsies showed pronounced liver changes and liver necrosis. By June of 1955, Dr. K.H. Schulz of the University Skin Clinic in Hamburg-Eppendorf had found that the "chloracne inciters" were present in the phenol and the 2,4,5-trichlorophenolate solution. Dr. Schulz further determined that the anisole fraction was the carrier of the chloracnegenic substance. In 1956, Dr. Schulz identified the offending substance as 2,3,6,7-tetrachlorodibenzodioxine.

Because C.H. Boehringer was having such difficulty with chloracne in the manufacture of 2,4,5-TCP, it sought outside help. C.H. Boehringer was put in touch with Dow.

On January 27, 1955 Dow wrote to Boehringer, "[E]nclosing a data sheet describing the hazards due to toxicity and precautions for safe handling and use of 2,4,5-trichlorophenol and answered seven specific questions regarding experience in our own plant." In the course of

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1. Caustic Hydrolysis

   a. A solution of caustic (believed to be sodium hydroxide) in methanol was formed;

   b. The caustic and methanol were mixed with tetrachlorobenzene;

   c. The solution of caustic and methanol and tetrachlorobenzene were placed in a reactor under pressure and heat.

2. Preparation of Sodium Salt of 2,4,5-TCP

   a. Distillation of methanol under heat;

   b. Distillation of water under heat;

   c. Driving off of trichloroanisole under heat;

3. Coupling Sodium 2,4,5-tricholophenate and Monochloroacetic Ester

In 1945, Dow conducted the first rabbit skin test on the trichlorophenol process material. At that time the caustic insoluble oil from the 2,4,5-TCP process was found to cause acneform dermatitis on the rabbit's skin. As early as 1945, Dow knew that exposure to trichlorophenol process materials could cause acneform dermatitis. In 1952 Dow went from a "batch" process to a "continuous" process. By 1956, Dow learned of the particular substance in the 2,4,5-TCP and 2,4,5-T which was responsible for the acneform dermatitis.

Knowledge of the toxic contaminant in 2,4,5-TCP was learned by Dow from the C.H. Boehringer Sohn Company of Germany. In 1951, C.H. Boehringer began experimenting with the production of 2,4,5-TCP. Between 1952 and 1954, 19 cases of serious

In the manufacture of its commercial 50/50 mixtures of 2,4-D and 2,4,5-T, Dow developed internal specifications. Those specifications dealt with the manufacturing processes and the compositions of the final products. In addition to product specifications, Dow developed "accepted quality control procedures" and "quality requirements."

Prior to selling "Agent Orange" to the United States Military, Dow was thoroughly familiar with commercial 50/50 mixtures of 2,4,5-T and 2,4-D. Prior to selling "Agent Orange" to the United States military, Dow had developed internal specifications and quality control programs for the production of commercial herbicides containing a 50/50 mixture of 2,4,5-T and 2,4-D. As the result of direct manufacturing experience since 1948 of commercial products containing 2,4,5-T, Dow developed a tremendous expertise with respect to that particular phenoxy herbicide.

B. Dow was Knowledgeable About the Manufacturing Process of 2,4,5-T and Its Toxic Impurities

Though Dow has withheld as proprietary and confidential the specific manufacturing processes it utilized from 1948 to 1970, it is generally known that Dow produced 2,4,5-T through the following process:

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
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In Re

"Agent Orange"

Products Liability Litigation
----------X

MDL No. 381
(All Cases)

PLAINTIFFS' MEMORANDUM ON THE APPLICABILITY OF THE LEGAL THEORIES OF FAILURE TO WARN, CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

## INTRODUCTION

Plaintiffs' Memorandum addresses the issue of whether the legal theories of concerted action, enterprise liability, or alternative liability may be applied here in the absence of evidence enabling plaintiffs to identify which defendants' tortious conduct caused the injuries complained of. However, plaintiffs do not solely rely on the aforementioned theories.

It is plaintiffs' position that: (1) each defendant breached its duty to warn the government of the dioxin hazards to health known or which should have known by it to be associated with its own dioxin contaminated Agent Orange herbicide product and with the dioxin contaminated products sold by the other defendants to the military; (2) that

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President and Director of Research for Dow, gave a statement before a subcommittee of the United States Senate Committee on Commerce. Mr. Johnson stated:

> Since 1950 we have been keenly aware of the possibility of a highly toxic impurity being formed in 2,4,5-trichlorophenol as a side reaction under conditions of elevated processing temperatures...We also knew that if the impurity was present in the 2,4,5-trichlorophenol it could be carried forward to the end product, 2,4,5-T.

A review of Dow's history of 2,4,5-trichlorophenol (hereafter "2,4,5-TCP") and 2,4,5-T production confirms that statement.

Dow began making 2,4,5-TCP in mid-1946. In 1948, Dow registered its first 2,4,5-T product under the Federal Insecticide, Fungicide and Rodenticide Act.

Since 1948, Dow has manufactured a number of products containing by volume (minus inert ingredients) a 50/50 mixture of 2,4,5-T and 2,4-D.[2/] One such product was Brush Killer 50-50. Absent inert ingredients, that product contained a 50/50 mixture of 2,4,5-T and 2,4-D. In addition to Brush Killer 50-50, Dow also manufactured Brush Killer LV 2-2, Tippon 2-2, Verton CE, and Veon Brush Killer, each of which is approximately a 50/50 mixture of 2,4-D and 2,4,5-T. Dow patented Tippon 2-2 and Brush Killer 50-50.

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2/ "Agent Orange" was a 50/50 mixture of 2,4,5-T and 2,4-D.

## I. DEFENDANTS WERE KNOWLEDGEABLE ABOUT THE MANUFACTURING PROCESS, DIOXIN AS A CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN.

### A. Prior to Becoming a "Government Contractor," Dow had Invented, Patented and Sold Commercial Herbicides Containing a 50/50 Mixture of 2, 4-D and 2,4,5-T

Dow admits to have known about a highly toxic impurity in 2,4,5-T since 1950.[1/] On April 15, 1970, Julius E. Johnson, Vice-

1/ The record suggests Dow's earlier knowledge.

1. 1937---Four hundred (400) lumber workers using Dowicide H (tetrachlorophenol), some of whom developed among other things, comedones, cysts and pustules (chloracne), urinary disturbances, skin leisons lasting seven years and marked hyperkeratosis;

2. 1937---Twenty-one (21) workers at a Dow plant which manufactured tetrachlorophenol, some of whom developed the same symptoms as the 400 lumber workers;

3. 1949---Ten (10) workers exposed in Nordheim, W. Fahlen in the manufacture of 2,4,5-TCP, some of whom developed neuralgic pains, heart disorders and chloracne;

4. 1949---One hundred seventeen (117) workers exposed in the manufacture of 2,4,5-T and 228 family members and medical personnel dealing with the exposed workers, at a Monsanto plant in Nitro, West Virginia some of whom developed chloracne, liver damage, vomiting, papable liver and tiredness;

5. 1954---Thirty-one (31) workers at a C.H. Boehringer plant exposed in the manufacture of 2,4,5-TCP and 2,4,5-T, some of whom developed liver damage and chloracne;

6. 1956---Twenty-nine (29) workers in a Diamond Alkali (now Diamond Shamrock) plant exposed in the manufacture of 2,4,5-T some of whom developed porphyria cutanea tarda, hyperpigmentation and hirsutism; and

7. 1964---Forty (40) plus workers in a Dow plant in Midland, Michigan exposed in the manufacture of 2,4,5-T, some of whom developed chloracne and complaints of tiredness, weakness, and depression with some reduction in hemoglobin and red cel counts. Some workers with metaplastic changes were examined.

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## FACTUAL BACKGROUND

In order to address the issues of failure to warn and applicability of the theories of concerted action, enterprise liability and alternative liability, it is necessary to review in historical sequence, the factual record as it has been developed to date. The record is far from complete, but enough is already known upon which the Court may reach a preliminary judgment that the conduct, transactions and relationships between the defendants (horizontal) and between the defendants and the Government (vertical) are such as to warrant a finding that defendants have breached their duty to warn and that one or more of the above theories of liability are applicable in this case. It is likely that additional discovery will, if anything, buttress the appropriateness of applying these theories.

We begin the review of the historical record with an examination of the knowledge and conduct of the defendant Dow Chemical Company, a key player in the events which followed and a linchpin connecting many of the horizontal and vertical relationships between the defendants and the Government in connection with the sale of the dioxin-contaminated Agent Orange herbicides which caused plaintiffs' injuries.

Where necessary to present the full context of factual statements in this part of plaintiffs' [illegible], a limited number of documents have been appended which have previously been used as exhibits or referred to in plaintiffs' prior submissions or in depositions of the defendants and Government witnesses.

Instead, they conspired secretely and persistently to deceive the military and other government agencies about the matters hereinafter detailed which were of profound importance to the health of American soldiers and to the national security let alone to the American people generally. The defendants used every device available to keep their dioxin problems confined to their inner circle and to keep the military and government agencies in the dark - secret meetings, confidential documents, misrepresentations, half truths, suppression and withholding of data and technology, task and trade association fronts and position papers, ad hoc committees, and a myriad of other regrettable activites, which, if they had not occurred, might have led to military decisions which would have prevented the injuries inflicted by defendants. The full story is now told.

alternative liability, enterprise liability, and that, should the Court deem it necessary to address the defendant identification causation issue, the defendants may be held jointly and severally liable under any of these three theories.

In the detailed factual background statement which follows, a tragic hitherto unrecorded chapter of the Vietnam war is told of the misdeeds of chemical war contractors which injured American and allied soldiers.

The defendant chemical companies owned or controlled virtually all of the Agent Orange herbicide production capacity.

They supplied to the military, the sole source purchaser over 99% of the herbicides contracted for and received over 99% of the purchase price paid. (Exhibit 1)

Each of the defendant's herbicides was contaminated with dioxin, in varying degrees and violated their contractual obligations to the military. Each defendant knew its product was contaminated and hazardous to human health. Each defendant knew that the other defendants' herbicides were dioxin contaminated and hazardous. Each knew, with varying degrees of expertise, how to eliminate or reduce the dioxin. None ever warned the trusting, less expert, military, or informed it of the dioxin problem and the means of its avoidance or elimination.



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each defendant's breach of duty to warn was a substantial factor leading the military to decide to mix and deploy the dioxin contaminated Agent Orange herbicides supplied by defendants, which caused plaintiffs' injuries; and (3) that consequently defendants are liable as tortfeasors jointly and severally for such injuries without any burden on the part of plaintiffs to identify and prove which defendant caused their injuries.

If this Court agrees that the defendants' breach of their duty to warn carries such legal consequences, it need not decide with regard to the failure to warn issue, whether the theories of concerted activities, enterprise liability or alternative liability need to be applied on the identification/ causation issue. However, so that the Court may be in a position to consider the legal implications of all these theories, plaintiffs present herein a comprehensive historical record of defendants' conduct in the manufacturing and sale of dioxin contaminated Agent Orange herbicides to the military for use in Vietnam, focusing on the realtions between the defendants and with the military and other government agencies during the period of the Vietnam era.

Plaintiffs believe that this historical record fully supports any and all of the theories of concerted activities,

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attempting to identify the cause of the chloracne, researchers at C.H. Boehringer identified tetrachlorodibenzodioxine in 1956. As a result of C.H. Boehringer's identification of dioxin as the chloracnegenic agent in 2,4,5-TCP, C.H. Boehringer instituted certain process changes to prevent the formation of dioxin.

Since Dow had provided C.H. Boehringer information in 1955 concerning the chloracne problem, C.H. Boehringer sent to Dow, on February 11, 1957, information on the preparation of trichlorophenoxyacetic acid in a manner to avoid the formation of "chlorakne exciters." information was sent by C.H. Boehringer to all known producers of chlorophenol.[3/]

In April, 1957, Dr. Schulz reported his findings with respect to 2,3,7,8-tetrachlorodibenzodioxine together with Professor Kimmig in "Die Naturwissenshaften" 44:337-338 (1957). In the article, Kimmig and Schulz described the appearance of workers at C.H. Boehringer's plants who had been exposed to the trichlorophenol containing the 2,3,6,7-tetrachlorodibenzodioxine which they believed to be the culprit:

> The appearance of the illness was characterized by a scattering of comedones, pustules, small sebum retaining cysts in the regions of the face, neck, breasts, back, and extremities. Damages to liver functioning was determined in individual cases.

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3/ This suggests that the other defendants knew at the time that Dow did, how to avoid the formation of the toxic impurity that was causing the chloracne problem.

Kimmig and Schulz noted the "high general toxicity" of the compound and found upon autopsy of exposed rabbits "severe necroses as well as diffuse adiposis of the liver." The article states: "It was also possible to isolate a tetrachlorodibenzo-dioxane, identical to the synthesized model substance, from the by-products resulting in the industrial pressure phenol process."

Dow either had a copy of the Kimmig and Schulz article in 1957 or should have had a copy of that article in light of their extensive dealings with C.H. Boehringer. In September, 1962, Dow made a two-week pilot plant run using an approximate 24% caustic solution diluted with water. Again, the temperature was raised.[4/]

In July, 1963, Dow shut down building 199, where 2,4,5-TCP was manufactured, to install new equipment to increase Dow's capacity to hydrolyze tetrachlorobenzene to 2,4,5-TCP using the 22% caustic solution. After reopening, Dow was "running at the limit of (its) hydrolyzing capacity". Dow was "pushing (the) existing plant to (its) limit." "Whenever production is increased it is usually done by increasing the temperature of the synthesis run."

---

4/ The caustic insoluble oil from the production of 2,4,5-TCP was studied by the Biochemical Research Laboratory of Dow and found to be an active chloracnegen.

On July 3, 1963, an event occurred which illustrates that Dow and the defendant Hercules were both fully aware of the hazards associated with the use of 2,4-D and 2,4,5-T. On that date, Dr. John P. Frawley, Hercules' Chief Toxicologist, wrote to V.K. Rowe, Chief Toxicologist for the Dow Chemcial Company, to discuss the hazards associated with the use of 2,4,-D and 2,4,5-T. The letter reads in part as follows:

"Dear V.K.:

Several weeks ago I mentioned to Don McCallister that Dr. Jack Leary of U.S.D.A. has approached Hercules and Monsanto with a request to conduct subacute dermal toxicity studies on at least one chlorinated phenoxy herbicide.

On June 27th, I had an opportunity to review this request with Leary and I will try to report to you the background.

Undoubtedly you have seen the clinical reports of four cases of neuropathy which allegedly have been caused by 2,4-D salts and esters. (Archives of Internal Medicine, Vol. 3, 1963, pp. 133-134; J.A.M.A. November 7, 1959 pp. 1306 to 1389) In addition, I have heard of one previously unreported case involving a product liability claim which was successfully defended by a formulator. To my knowledge, Leary has not heard of this case...

On the basis of these reports Leary feels that the hazards associated with the use of 2,4,-D and 2,4,5-T products should be understood more thoroughly. He specifically wishes to know whether repeated dermal exposure of animals to the free acids and the various salts and esters will cause peripheral neuropathy or the other related symptoms. He plans to make an informal request of each manufacturer to study at least one such product... Frankly I believe Leary's request is reasonable. It could have been made in the form of a demand and not a request, and certainly could have involved far more extensive design. I believe it is desirable for you, Bill Hunt and myself to confer on the desirability of conducting such studies and to consider carefully the design and the selection of minimum number of these products for such study... I also suggest that we handle such discussions by requesting NACA to appoint an ad hoc toxicology sub-committee consisting of the three of us. After we have crystalized our own thinking we can invite others to serve as we see fit and can negotiate with USDA as a technical committee...

Since Dow is generally regarded as the largest manufacturer of phenoxy herbicides, I suggest that you serve as Chairman of this committee...

Sincerely,

John P. Frawley, P.H.D.

Chief Toxicologist..."

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This letter reveals three significant facts. First, the United States Department of Agriculture as early as July, 1963, was relying upon the phenoxy herbicide industry to make the studies necessary to determine whether phenoxy herbicides were toxic to humans. Second, both Dow and Hercules had seminal knowledge of problems associated with consumer use of 2,4,5-T, and third, in order to insure against any adverse findings, NACA (National Agricultural Chemical Association), an industry operated lobbying group would appoint industry representatives to "negotiate" with USDA so that the design and study of toxicity and potential hazards to human health would be minimal and not get out of hand.[5/]

Incredible as it may seem, given its extensive knowledge of health hazards associated with the use of 2,4-D and 2,4,5-T in 1963, Dow affirmatively misrepresented to the United States military:

> (W)e have been manufacturing 2,4-D and 2,4,5-T for over ten years. To the best of our knowledge, none of the workmen in these factories have shown any ill effects as a result of working with these chemicals.

---

5/ From this seminal undertaking later emerged in the years 1965, 1966, and 1967, an industry-wide conspiracy whose sole function was to defraud the military and the government by concealing from them the knowledge which and the phenoxy herbicide industry possessed about dioxin as a contaminant poison in 2,4,5-T and its potential hazards to human health.

Dow made that representation knowing about the prior occupational health problems in its own and other chemical company plants, and knowing about C.H. Boehringers' horrifying experiences with chloracne and liver damage in 1954.

Apparently Dow thought in 1963 that the military would be interested in Dow's industrial health history in the manufacture of 2,4,5-T as a benchmark of safety.

As the result of pushing its production capacities to the limit where the temperatures employed were increased, workers in the Dow plants began to experience chloracne. In August of 1964, Dow utilized vapor phase chromatography to detect dioxin in the waste oils. The waste oils were fractionated, dioxin isolated and identified. Dow then proceeded to synthesize dioxin in the laboratory. In November, 1964 Dow prepared internally a confidential memorandum on an analytical method for "The Determination of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in 2,4,5-Trichlorophenoxyacetic Acid by Gas-Liquid Chromatography."

The analytical method was for detection of dioxin in 2,4,5-T, the end product and not only for 2,4,5-TCP, the intermediary. Dow apparently thought it was necessary to analyze its end product.



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Thus, by November, 1964, the Dow Chemical Company had identified dioxin as the toxic compound causing chloracne, an admittedly hideous disfiguring disease. This identification of dioxin as the causative factor in the known health problems as set forth in the November 30, 1964 memorandum on the stationary of "The Dow Chemical Company", titled "The Determination of Compounds Capable of Causing Chloracne in 2,4,5-Trichlorophenol Process Samples By Gas-Liquid Chromatography." This memorandum describing the methods and means for detecting dioxin was later to be distributed to those attending the secret March 24, 1965 "dioxin" conference, described infra. Dow sought to advise the other manufacturers of 2,4,5-T that Dow knew their products were contaminated.

Dr. R.C. Dosser of Dow pointed out to Mr. E.T. Upton of T.H. (Defendant T.H. Agriculture & Nutrition, Inc.) in a telephone conversation on or before January 12, 1965:



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> [t]hat if a compound, found in 2,4,5-T acid or its esters, proved to be damaging that this might lead to a flurry of successful claims by users of the herbicide who allegedly had been injured by it.

On February 18, 1965, Dow held an internal "Exciter" Problem, Meeting. Minutes of that meeting state:

> Otis introduced the meeting by indicating that recent information indicates "Exciter" components may be present in Dow 2,4,5-trichlorophenol. Bioproducts is concerned about 2,4,5-T acid, esters, formulations, silvex, ronnel, and Erbon. This meeting is to review status of our knowledge of this subject, potential hazards, possible effect on Dow image, legal implications, and need for possible quarantine. These basic decisions are to be made without consideration of economic impact.

As a result of that meeting, Dow determined to meet with the other producers of 2,4,5-T.

In February, 1965, Dr. Frawley, Chief Toxicologist of defendant Hercules learned from V.K. Rowe, Dow's Chief Toxicologist that 2,4,5-T was contaminated with an acnegen. This is the toxic impurity which was more accurately identified by Dr. Rowe at the secret conference called March 24, 1965 at Dow's headquarters in Midland, Michigan.

Prior to March 1, 1965, V.K. Rowe of Dow contacted the Medical Director (Emett Kelly, M.D.) and Assistant Medical Director at Monsanto and the Chief Toxicologist at Hercules (John P. Frawley) concerning dioxin contamination.

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On March 19, 1965, Dow entered into a letter agreement with C.H. Boehringer, concerning the disclosure of processes and/or apparatus and/or production information regarding the prevention of incidence of chloracne arising out of the production of 2,4,5-T. The agreement provided for C.H. Boehringer to disclose to Dow technical know-how designed to prevent the occurrence of chloracne. The documentation and information was submitted within a covenant of secrecy. The agreement was to come into force December 7, 1964 and be valid for a period of ten years until December 6, 1974. The importance of secrecy was emphasized in the following provisions:

> "You agree to keep any documents concerning the process as well as all verbal or written information and data strictly secret. You will bind your collaborators who get knowledge of this information, documents and data to the same obligation as that assumed by Dow by requiring them to execute an individual commitment.
>
> The obligation of secrecy hereunder shall not apply to any item of information disclosed hereunder which:
>
> 1. Dow can demonstrate was known to Dow and in its possession prior to disclosure by Boehringer on or after December 7th, 1964, or
>
> 2. Is now or hereafter becomes generally available to the public without fault of Dow, or
>
> 3. Dow can demonstrate was obtained by it in good faith from a third party having a bona fide right to make such disclosure."

We do not know at this time whether or the extent to which or at what time if ever, the existence of this agreement was made known by Dow to the other defendant chemical companies or the Government.

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On March 19, 1965, V.K. Rowe of Dow wrote an identical letter to Emmett Kelley, M.D., Dr. J. Wilkenfeld of Hooker Chemical Corporation, Mr. Raymond Verhoeze of Hooker Chemical Corporation, Mr. Francis Kennedy, Plant Manager of Diamond Alkali Company, Dr. Ed Chandler, Technical Services, Diamond Alkali Company, and Dr. John P. Frawley. That letter stated:

> [I] am inviting each of you to come to Midland to discuss the toxicological problems caused by the presence of certain highly toxic impurities in certain samples of 2,4,5-trichlorophenol and related materials.
>
> ...
>
> Our discussions will deal only with toxicological and analytical aspects of the problem. We will not discuss manufacturing know how, sales, or anything else not dealing with the problems of health.

See, Exhibit 2. The meeting occurred on March 24, 1965. Present at that meeting were: Dr. Wilkenfeld and Raymond Verhoeze of Hooker Chemical Corporation, Mr. Francis Kennedy and Dr. Edward Chandler of Diamond Alkali Company, and Mr. C.L. Dunn and Dr. John P. Frawley of Hercules Powder Company. At the meeting "V.K. Rowe recapped the Dow situation in terms of the problem and the initial studies by Toxicology and Environmental Research Laboratory regarding the in-plant situation. He expanded this in general terms to the study of end products, ours and other peoples." See. Exhibit 3. A number of the attendees at the March 25, 1965 meeting drafted memos to file. Those memos are worth reviewing in their entirety.

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A memo to file from E.L. Chandler of Diamond A Company notes, among other things:

> The Dow people state that they intend to set a limit of zero with sensitivity of plus or minus 1 ppm on this material. They have analyzed materials from other companies, including our company, and have found amounts as high as 10 ppm in 2,4,5-T acid (end product) and 20 to 30 ppm in phenates.
>
> They have made a single application to the ears of test rabbits and have found that 20 ppm will not give folliculitis. Forty ppm does give a slight effect, and 100 ppm is severe. They have made repeated applications of from 10 to 100 ppb, and 25 of these treatments do not cause a response; however, 1000 ppb (1 ppm) gives a slight response with nine applications and a severe reaction with 11 applications.
>
> They conclude, therefore, that 1 ppm with repeat exposure can create a real problem.

See, Exhibit 4 . (Emphasis added). It is clear that Dow believed in 1965 that 1 ppm with repeated exposures presented a significant health hazard.

C.L. Dunn of Hercules Powder Company also prepared a memo to file. In that memo Mr. Dunn notes, "Rowe expressed concern that carry-through of toxic materials into final formulated herbicide products may occur unless precautions are taken." See, Exhibit 5 , p. 1. On page 2 of that memo to file is found: "Evidence that the chloracnegens may be systemic."; and "Hooker and Diamond people were quite aware of chloroacne. One of the Hooker people said that some cases are believed to relate to exposures occurring 20 years before." On page 4

of that memo to file Mr. Dunn recorded the detection limits for Dow's gas chromatography: "2,4,5-TCP - 1 p.p.m." and "2,4,5-T acid - 1 p.p.m." See, Exhibit 5 , p. 4. On page 5 is found: "Competitor products - Dow has examined all manufacturer's 2,4,5-T products. Some have "surprisingly high" amounts of chloroacnegens. This defined as 10 p.p.m. in 2,4,5-T acid, and up to 30 p.p.m. in 2,4,5-trichlorophenate." Id., p. 5.

Similarly, J. Wilkenfeld of Hooker Chemical Company recorded the information he had received at Dow on March 24, 1965. Dr. Wilkenfeld noted:

> Work with rabbits with washing after exposure, sometimes as soon as 15 minutes after application, did not stop the development of the chloracne and single, oral dose toxicity tests (not (?) m 50) resulted in the death of some rabbits at 17 micrograms per kilo. Peripheral liver cell necrosis occurred in some rabbits where the washing was done.
>
> ...
>
> The current inplant working limit is "no response" with less than one ppm by chromatography considered safe. When they were having difficulty, chloracne causers were in the order of 20 - 30 ppm.

See, Exhibit 6 (parenthetical unclear). Not a single government representative was invited to attend the March, 1965 meeting. Dow nor any of the other defendants has produced any evidence suggesting that the information conveyed by Dow to the other defendants at the March 24, 1965 meeting was conveyed to any government representative or more properly, a high-ranking military official.

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Defendants other than Dow were also communicating with each other as to their chloracne and dioxin problems.

On April 9, 1965, Dr. Frawley (Hercules) sent a memorandum to Mr. C.L. Dunn. In the memorandum, Dr. Frawley refers to obtaining information from Monsanto,

> "...regarding the problems they and Badische have had on chloracne..."

He then goes on to report that,

> "...from the data provided, a sample which contained 5 ppm of the Dioxin would be acutely toxic. Whether this refers to death or liver damage is not clear..."

On June 24, 1965, V.K. Rowe of Dow's Biochemical Research Laboratory wrote a letter to Ross Mulholland, Manager, Bioproducts, Dow Chemical of Canada. In that letter, Mr. Rowe stated:

> As you well know, we had a serious situation in our operating plants because of contamination of 2,4,5-trichlorophenol with impurities, the most active of which is 2,3,7,8-tetrachlorodibenzodioxin. This material is exceptionally toxic; it has tremendous potential for producing chloracne and systemic injury. If it is present in the trichlorophenol, it will be carried through into the T acid and into the esters and hence into formulations which are to be sold to the public. One of the things which we want to avoid is the occurrence of any acne in consumers. I am particularly concerned here with persons who are using the material on a

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daily, repeated basis such as custom operators may use it. If this should occur, the whole 2,4,5-T industry will be hard hit and I would expect restrictive legislation, either barring the material or putting very ridged controls upon it. This is the main reason why we are so concerned that we clean up our own house from within, rather than having someone from without do it for us. In this way, we can approach the problem in an orderly manner. If the producers and handlers of this material will cooperate, there is no reason why we cannot get this problem under strict control and thereby hopefully avoid restrictive legislation; in other words, let us practice good citizenship.

. . .

We are not in any way attempting to hide our problem under a heap of sand, but we certainly do not want to have any situations arise which will cause the regulatory agencies to become restrictive. Our primary objective is to avoid this.

. . .

I trust that you will be very judicious in your use of this information. It could be quite embarrassing if it were misinterpreted or misused.

See, Exhibit 7, (emphasis added). In keeping with the desire to maintain secrecy, V.K. Rowe wrote as a postscript, "under no circumstances may this letter be reproduced, shown, or sent to anyone outside of Dow." Id.

Later, a telephone conversation took place on July 9, 1965 between Dr. John P. Frawley, Chief Toxicologist for Hercules, and Earl Farnham, a Dow Company executive, who, according to this memorandum, was calling Dr. Frawley on behalf of Dow Vice-President, Donald Baldwin. The document dated July 12, 1965, and marked "Confidential", reads as follows: (Exhibit 8)

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The documents reveal that the chemical companies were all aware that their dioxin level in Agent Orange was totally unacceptable and a potential health hazard. No such communication or any of the information described above was ever transmitted by any chemical company to the Government or the military, even though the chemical companies knew that the dioxin level of some of the herbicides ranged from 20-140 ppm, and they all knew that their contaminated herbicides were being mixed together in drums before use in Vietnam.

Silence and confidentiality were the code words utilized to conceal the knowledge which these defendants had amassed concerning the potential health hazards associated with the contaminated Agent Orange herbicides.

It is clear from the record that no one in the military was advised of the contamination of the defendants' Agent Orange herbicides with dioxin and of the concomitant health hazards until March 6, 1970.

On that date, representatives of Dow provided a briefing to representatives of the United States military. The subject of that briefing was dioxin as an impurity in 2,4,5-TCP and 2,4,5-T. At that briefing, Dow representatives presented the following information on 2,4,5-T:

> Since 1950 it has been known that 2,3,7,8-tetrachlorodibenzo-p-dioxin is an impurity associated with 2,4,5-trichlorophenol (TP). The latter material is used in the manufacture of 2,4,5 T. Dioxin is a highly toxic material...In 1964, Dow closed their plant which manufactured 2,4,5T due to widespread acne among plant workers. Dioxin and other impurities were found in the 2,4,5T. The plant was cleaned and the manufacturing process was changed to eliminate the dioxin and other impurities. The Dow 2,4,5T now contains less than 0.5 ppm of dioxin.

See, Exhibit 9.

The deposition of Dr. Robert Darrow is instructive on the level of the United States military's knowledge with respect to dioxin as late as March of 1970. Dr. Robert Darrow attended the meeting on March 6, 1970 at the Pentagon with Dr. Charles Minarik as representatives of the Crops Division at Fort Detrick. During examination by defendant's counsel, the following transpired:

> Question: Can you recall a meeting which took place on or about March 11, 1970, at which various representatives of Dow met with Gen. William Sloan (sic) and various others concerning Agent Orange?
>
> Mr. O'Brien: (Objection)
>
> Mr. Krohley: (question rephrased)
>
> Mr. O'Brien: (Objection)
>
> Answer: I was at a meeting with Dow's representatives but I don't recall the date of it. The name General Sloan doesn't register with me. I'm not sure.

...

Question: Do you recall what if anything you said at that meeting.

Answer: I just listened. I didn't say anything.

Question: Do you recall what if anything Dr. Minarik said at that meeting?

Mr. O'Brien: Same Objection.

Answer: The presentation was given by the Dow people. That was it. They presented information.

Question: Anyone at the meeting, Dr. Darrow, did they say in words or in substance to the Dow representatives why didn't you tell us about this before?

Answer: I think the feeling was there but I'm not sure it was said. We were surprised when we got the information at this time.

Question: By "we" who are you referring to?

Answer: Dr. Minarik and myself.

---

Question: Do you recall what if anything was said in that regard by anyone at the meeting?

Answer: No specific comments, no. In other words, this represented information that we were receiving for the first time in this respect on the dioxin situation.

Question: Where was that meeting held? Do you recall that?

Answer: It was in the Pentagon. It was in Washington, D.C., in the Pentagon.

Without any doubt, Dow and the other defendants in this litigation had conspired to withhold information from the United States military concerning dioxin contamination of the Agent Orange herbicides.

On June 15, 1970, Dow wrote a letter addressed as follows:

The Honorable Melvin R. Laird
Secretary of Defense
The Pentagon
Washington, D.C.

See, Exhibit 10. In that letter, Dow advised the Secretary of Defense that Dow's Agent Orange contained one part per million of dioxin and that "certainly such a product is safer in use than one containing larger quantities".

Thus was culminated a period of relationship between the government and defendants which began with Dow's misrepresentations in 1963 of the safety of its herbicides and ended in 1970 after a continued conspiracy of silence and failure to warn, with admissions of their high toxicity, and the fact higher dioxin levels meant greater safety hazards.

It is clear also that during the period of time of their relationship with the military, the defendants also withheld from the military their considerable knowledge about detection and manufacturing risk reduction techniques.

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C. Defendants were Knowledgeable About Detection and Manufacturing Risk Reduction Techniques

Risk reduction requires a problem, method for investigating the problem, remedial action and a method for monitoring to prevent recurrence. The "highly toxic impurity" problem defined itself in 1937 when 400 lumber workers developed chloracne. The method for investigating the problem was animal testing which Dow did not undertake. The remedial action was a change in the manufacturing process. Plaintiffs are unaware whether such a change was made. As of 1941, the method for monitoring to prevent the recurrence was the rabbit skin test.

In 1964, the problem was the same. The method for investigating the problem was gas liquid chromotagraphy and sample preparation techniques. The remedial action, at least with respect to Dow was the purchase and implementation of C.H. Boehringer technology to produce 2,4,5-TCP and 2,4,5-T with less than one ppm of dioxin.[6] The method for monitoring the problem to prevent recurrence was liquid gas chromatography and separation techniques pioneered by Dow.

6/ The C.H. Boehringer technology called for, among other things, reducing the temperature of the reactor (autoclave) to a maximum of 175 degrees centigrade; no more than 20 atmospheres (hereinafter "atms") of pressure in the reactor; rinsing salt deposits from the reactor after each use; cessation of the introduction of sodium hydroxide if the temperature or pressure in the reactor went above the maximum; distillation of methanol under heat and 5 atms until temperature at head has risen to 88-90 degrees centigrade with a cessation of distillation when trichloroanisole appears; maximum temperature of 115 degrees centigrade in the sump phase to prevent excess water evaporation from the phenolate solution; addition of water before driving off the trichloroanisole solution (primary carrier of dixion) by steam./



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There can be no doubt that Dow was familiar with risk reduction techniques of a detection and manufacturing nature and the Dow had total discretion in the decision of whether to employ those techniques.

The military placed no restrictions on the defendants with respect to their manufacturing processes. Dow had clear discretion in the choice of processes to use. Dow well understood that the process used determined the amount of dioxin in the 2,4,5-T. Dr. B.B. Holder, Medical Director, Medical Department of Dow admitted:

> In 1964 at the trichlorophenol production area a process alteration was made changing the temperature and pressure levels previously used. It was well understood by all involved that we had to be extremely careful in process changes to prevent the formation of excessive chlorinated dioxins and similar toxic compounds.

Dow was fully aware of process alternatives. In fact, to lower the dioxin contamination of its 2,4,5-TCP and 2,4,5-T, Dow purchased, in 1965, parts of a 2,4,5-TCP process from C.H. Boehringer. Dow had absolute freedom to do so. Dow was so concerned about end product contamination that on May 4, 1965, it established a specification requiring a gas liquid chromatographic analysis of all 2,4,5-T leaving the plant. Had the military known that different temperatures, pressures, alcohols, and phenolate water content resulted in different levels of dioxin contamination, there can be no doubt, the military would have required the safest method.

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Nothing speaks more clearly to the effect of different processes on the level of dioxin contamination and to defendants' knowledge on that subject than the following excerpt from an internal document:

> Chlorophenol and derivatives producers are Dow, Monsanto, Hercules, Diamond and Hooker. Dow and Hooker isolate and distill the trichlorphenol prior to sales and use, and analyses of samples of their sales products show no exciter present. It is suspected that Hercules also distills the trichlorophenol as samples of their 2,4,5-T acid shows no exciter. Diamond and Monsanto do not isolate the trichlorophenol to purify it, but make all derivatives from the sodium salt. Analysis of Monsanto's 2,4,5-T acid shows 3 - 8 ppm. exciter, and analyses of Diamond's sodiumtrichlorophenate shows 8 - 24 ppm. exciter.

Clearly, different manufacturing processes resulted in different levels of dioxin contamination and Dow and the other defendants were clearly aware of that fact. Of equal clarity is the fact that the military was ignorant of this matter. The evidence indicates that the military did not know independently and was not informed by the defendants of the relationship between process selected and level of dioxin.

A particularly irrational instance of "cover up" was in the defendants' withholding from the government of the technology necessary to analyze the products and to detect its deadly impurities. The Air Force was working on a method of analysis, gas chromotrography which it hoped would prove more effective than the army's infrared spectrography, analysis and preliminary tests looked promising. The government was well behind the defendants in developing this technology, however.

In a Hercules memorandum marked "confidential" and dated September 5, 1967, from M.A. Taves, Synthetic Research Division, to Mr. J.M. Eagan, Synthetic Department, the government procedure (infrared) was described as "very tedious" and possibly was inaccurate. The report states that "they apparently are not aware of the components which we knew to be present." The memorandum conjectures that the government would probably be receptive to adopting Hercules' analytical method, but Taves cautioned, "we must carefully compare both methods because it is possible that their method may be giving beneficially higher analysis, particularly on 2,4-D, than our own method."

During the years that the defendants supplied contaminated herbicides to the military, Dow was not the only defendant possessed of expertise as to dioxin hazards and means of risk reduction. While their expertise may have varied in depth and time acquired, each of the defendants failed to warn the military of what defendant knew about its and other defendants' products and sooner or later became a party to the conspiracy to conceal or misrepresent the matters which the military needed to know in order to make informed choices and decisions as to herbicide procurement.

We turn next to an historical review of the conduct of the other defendants.

## DEFENDANT MONSANTO'S KNOWLEDGE ABOUT MANUFACTURING PROCESS, DIOXIN AS CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS, AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN

Perhaps the most malevolent participant in the Chemical Company conspiracy to withhold from the Government and the general public the toxic effects of the dioxin content in their 2,4,5-T is the Monsanto Chemical Company.

It was in 1949, at their Nitro, West Virginia plant that Monsanto was first alerted to the existence of a contaminant present in their 2,4,5-T process. As a result of the "process upset", (Monsanto's term), workers participating in the refinement of sodium trichlorophenol (the precurser of 2,4,5-T) were exposed

to the product. Ultimately, more than 200 workers in the 2,4,5-T department began to develop manifestations of toxic exposure.

Multiple workers' compensation claims were filed in which there were made acute complaints of liver damage, peripheral nerupathy, chloracne and severe systemic effects.

Monsanto's extensive knowledge of the health problems associated with 2,4,5-T exposure is further illustrated by the communication from Elmer Wheeler, a key Monsanto employee, in which he discussed an incident at Badische, the German manufacturer of 2,4,5-T. Referring to a November, 1953 process disruption similar to that of the Nitro incident four years before, Mr. Wheeler acknowledged that approximately 50-60 cases of Badische worker health problems occurred following the incident. Stated the Monsanto hygienist, not only did Badische 2,4,5-T workers show "horrible skin eruptions" but that "In addition to the skin manifestations, their men reported all the additional symptoms as experienced in our workers, i.e. fatigue, vertigo, loss of libido, painful joints, etc."

Through the 1950's Monsanto continued to be alerted to the problem of worker 2,4,5-T exposure. A 1955 confidential memorandum acknowledged widespread employee toxic reaction. It stated, "You also know that the 2,4,5-T problem has not been solved and chloracne remained as the outstanding problem of the Nitro plant in dealing with hourly personnel". (Exhibit 11 ).

Throughout the '50's, the worker illness problem in the 2,4,5-T plant became so acute that the workers refused to labor in that environment. Monsanto was required to pay an hourly bonus to those volunteer workers who did subject themselves to the health problems which were rampant in the 2,4,5-T factory. In the '60's as production increased, worker health problems became even more frightening. As a matter of fact, James Springgate, who became Plant Manger of Nitro in '64 was required, as part of his job, to review Monsanto worker health complaints and estimated that over 100 workers complained of chloracne during the period from '64 to '68. Significantly, the Plant Manager estimated that there were more 2,4,5-T Monsanto employees who complained of health problems in the period of '60 to '64 than the 100 he estimated in the next four years.

In 1964, Monsanto sent to Dow for analysis, Monsanto's 2,4,5-T. The dioxin content of the sample showed three to ten ppm's. (As high as this amount was, it was nowhere near the huge amount of toxic contamination of the Monsanto product that further analysis was about to reveal.). On the 24th day of February, 1965, the Medical Director, Kelly, spoke to his Dow counterpart, V.K. Rowe. Rowe acknowledged that Dow had 20 cases of chloracne and admitted that he was sure that dioxin was the cause. (Exhibit 11a). The Memorandum clearly reveals that Dow's motivation for its secret March meeting was hardly salutory; since Dow suggested a "crash meeting with all the producers" in

an attempt to eliminate the contamination before the "PHS got into the act." Of course, the Public Health Service couldn't get into the act unless they found out about the toxic contaminant, a discovery that the conspiring chemical companies mightily tried to avoid. It was only one month later that V.K. Rowe wrote the infamous March 19 secret communication to certain 2,4,5-T manufacturers in which he alluded to the dioxin content of 2,4,5-T as "certain highly toxic impurities". (Exhibit 2 ).

In February of 1965 Monsanto and Dow shared information concerning their mutual problems. By that time, it was known by both companies that dioxin was the contaminant in their product. Therefore, as supported by the sworn admission of Monsanto employees as well as the annexed documentary evidence, Monsanto knew:

a) of the continuing acute health problems to which their 2,4,5-T employees had been subjected for the past 17 years,

b) that other chemical companies, both here and abroad had similar pblems, and

c) that the health problems to which Monsanto had personal knowledge not only included chloracne, but also involved:

1. fatigue
2. vertigo
3. loss of libido
4. painful joints

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Monsanto's 2,4,5-T was enormously toxic. In a September 14, 1965 interdepartmental memo which was then filed in the "Confidential Folder," Monsanto admitted that "during April, 1965, production of TDD rose to an all-time high and remained much higher than its previous norm-current - 50 ppm normal - 10 ppm". (Exhibit 11b).That amount was 50 times greater than the one ppm dioxin which Dow claimed was safe (although plaintiff's evidence establishes that even 1 ppm is toxic).

Monsanto did not remove this acknowledged enormously toxic contaminant from its 2,4,5-T. In a confidential communication dated almost four years later, Monsanto acknowledged that their 1968 experience showed a content of 40 ppm and that even in 1969, their contamination ranged from 5 to 7 ppm. (Ex.11c).

So serious was the problem that in 1968, after the medical director was informed that there had been no new chloracne cases since October of the previous year, he responded to that information by asking, "I don't want to be cynical, but are there any employees in the department who don't have chloracne already?" (Ex.11d).

As was reported in the confidential Monsanto final report on 2,4,5-T terminating January of 1969:

> "The incidence of chloracne has been almost universal among personnel engaged in the manufacture of 2,4,5-trichlorophenol (TCP) and 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T). The most severe cases have occurred in individuals involved in the clean up of uncontrolled autoclave batches (hydrolysis of tetrachlorobenzene). However, cases of varying severity have occurred consistently among operators primarily employed around the 2,4,5-T work up equipment - filteration, acidification, drying, etc."

Monsanto was able to isolate dioxin as the toxic ingredient when it first began to produce Agent Orange, and Monsanto knew for 20 years before 1969 that the 2,4,5-T that they produced contained toxic impurities that were clearly and dramatically hazardous to humans. Their knowledge emanated from their own personal experiences, from the reports of industrial problems from other chemical companies producing the same product and from confidential exchanges from the manufacturers.

There is no question that Dioxin was viewed by Monsanto and all other defendants as highly toxic. They knew that the dioxin contaminated 2,4,5-T sold by them to the Government was being mixed together and used in Vietnam. But Monsanto never informed any governmental officer with regard to the risks of dioxin contamination associated with Agent Orange or the methods of dioxin control; nor did Monsanto ever warn the Government with regard to the causal relationship between 2,4,5-T exposure and serious injury. In their Verified Answer to the Plaintiffs' Interrogatories, Monsanto has admitted that they were not responsible for, participated in, or familiar with any warnings to the United States Government with regard to the risks of dioxin contamination associated with Agent Orange, or with the methods of dioxin control.

R.Emmet Kelly, M.D., for many years the Director of the Monsanto Medical Department and the person whose responsibility it was to investigate and supervise Nitro workers' complaints, in his deposition, acknowledged the causal relationship between 2,4,5-T exposure and claims of peripheral neuropathy, nerve demyelination, chloracne, and even "the possibility of liver involvement"



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Thus, Monsanto's conduct clearly marks it as a prime participant with the other defendants in their efforts to conceal and misrepresent the hazards associated with the herbicides they were selling to the Government.

E. DEFENDANT DIAMOND SHAMROCK CORPORATION'S KNOWLEDGE ABOUT MANUFACTURING PROCESS DIOXIN AS CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN.

1. Documents submitted by Diamond Shamrock Corporation and testimony of the Defendant's own witnesses graphically demonstrate that there was an enormous amount of information exchanged relating to the contaminant involved herein, its manufacture, its means of analysis, methods of elimination, and last, and perhaps most importantly, knowledge by the defendants of the extent of contamination in the product sold to the government by Diamond.

2. The historical experience of Diamond Shamrock Corporation with 2,4,5-T is encapsulated in communication from Richard W. McBurney, M.D., dated March 27, 1963, addressed to Mr. Frank W. Jarvis, Vice-President of Diamond Shamrock Corporation, labeled Chloracne--Confidential. (Diamond Shamrock, Exhibit 12 This letter refers to a building of ancient vintage where 2,4,5-T acid processing actually takes place and advises that it is in this building that the workers are easily contaminated by vapors in the air. Paragraph 4, page 1, admits:

> "As long as this plant has been in operation, there has been a chronic problem in the employees hired--of a condition referred to as chloracne."

At one time, approximately 40 of the 72 workers in the plant were affected by chloracne. Paragraph 5 of page 1 states, "It is my impression and the impression of the management (Newark plant), that these byproducts are those of a chlorinated ether and are a result of the reaction of caustic soda on 1,2,4,5-tetrachloro benzene as used in the making of the 2,4,5-T."

3. This concern expressed by Dr. McBurney, however, does not begin and end with the problem of chloracne in the production workers. Rather, as may be seen on page 2 of his letter, there was a growing concern about a medical condition known as porphyria cutanea tarda. This is a disease of the blood forming elements of the body in which the hemoglobin of the red blood cells is broken down and, essentially, the spleen, liver, and kidneys are effected to a greater or lesser extent, depending upon the ingestion of such a chlorinated benzene. One of the physicians working on behalf of Diamond Shamrock at the Newark plant, Dr. Bleiberg, conducted a test on four men who had suffered the longest from chloracne only to find that two of these men had positive porphyn reactions in their urine.

4. Eugene Bak in the mid 1960's became production manager of the Diamond Shamrock Newark plant (page 27, lines 17-25). Bak testified at his deposition on January 27, 1983 that he was advised of health problems with the workers in the Newark plant when he first came to Newark and reported to Francis Kennedy, Plant Manager (page 39, lines 16-23; page 21, lines 2-10). He testified that he felt chloracne was a serious health problem when he became production manager (page 40, lines 19-23). He admitted that certainly half the workers in Acid and T-Ester Building were effected by chloracne (page 59, lines 11-25; page 60, lines 1-17). He conceded that the management suspected that the health hazard also included porphyria among the workers at Newark and that there was some positive findings in the urine specimens of these workers (page 66, lines 10-25; page 67, lines 1-25; page 68, lines 1-3). He testified that chloracne and liver problems existed in the Newark plant and he was concerned about it (page 68, lines 4-23). The plant manager for Diamond Shamrock at Newark considered chloracne to be a serious health problem while functioning in that capacity (Deposition of Francis Kennedy, page 48, lines 16-24; page 50, lines 3-8). Mr. Bak admitted that the same products were sold to the public that were suspected to cause chloracne in workers (page 74, lines 15-25; page 75, lines 1-4).

5. Mr. Bak also admitted that these same products were sent overseas as Agent Orange (page 75, lines 5-9). Given the admitted knowledge of Diamond Shamrock's production manager, it is shocking to consider the complete lack of disclosure to the Government of the information possessed by Diamond Shamrock (page 105, line 2):

"Q: At any time during those years 1965 through 1968, did you personally ever advise the United States Army of the contaminant in the TCP process stream?"

A: I have not personally.

Q: Did anyone to your personal knowledge on the part of Diamond Shamrock ever advise the Army of that?

A: I don't know."

6. Having established the existence of and knowledge of health hazards, not only in the production stages of the product, but in the final product itself, consider the interchange of this information between Diamond Shamrock and the other defendants in this law suit. The deposition testimony of Edward Lee Chandler, taken on February 8, 1983, indicates that in 1957, Chandler became manager of the technical service department of Diamond Shamrock which was a liaison between the technical development of products and the sales of same. (pg. 30, lines 19-25; pg. 31, lines 1-2). Diamond Shamrock Exhibit 13 is an interoffice memorandum addressed to Mr. R. A. Guidi, dated July 9, 1962, from Mr. Edward Lee Chandler. At that time, Mr. Guidi was the manager of the Newark plant. The letter clearly illustrates Diamond Shamrock's concern with the loss of two sizeable customers, Riverdale Chemical and Quaker City Tree, both of whom complained of chloracne problems with the use of the final products sold to them by Diamond Shamrock. The dermatological problem was so severe to the employees of these companies that Diamond lost them as customers.

Diamond's knowledge of the health hazards associated with the use of its products was unquestionably established by a serious outbreak of chloracne among users of their 2,4-D and 2,4,5-T in Columbia, South America. This problem was described by Lex Creamer, Diamond's representative, who forwarded a report to Diamond's New York office on March 18, 1965 (Exhibit 13a). As his report indicates, in one area alone twenty people were affected with most of them being hospitalized for months. He also indicated that the horses were badly affected with loss of hair, skin lesions and in one case death.

7. Considering Diamond Shamrock's concern over the loss of customers because of health hazards and the use of their esters, it is not surprising that we see Francis Kennedy and Edward Lee Chandler on a list of invitees to the now infamous Dow-Midland Conference of March 24, 1965, by letter from V.K. Rowe of Dow Chemical dated March 19, 1965. In that invitation Rowe directly addresses the toxicological problems caused by the presence of certain highly toxic impurities in certain samples of 2,4,5-T. He does not confine these problems to any single company, but rather admits that the problem was industry-wide and that the

purpose of the meeting itself was to deal with the toxicological and analytical aspects of this problem. It is indisputable that as of that date, Dow had possessed a method of analysis which it was willing to share with the invitees throughout the industry, but not with the military. Dr. Chandler never denied receiving this letter from Rowe, or in fact speaking to Rowe prior to his attendance at the meeting. He readily admitted attending this meeting. He did, however, deny any accurate recollection of what took place at the meeting in Midland (Chandler deposition, p. 96). In interoffice correspondence from E.L. Chandler to John Cort, Jr. dated March 25, 1965 with carbon copies to Francis R. Kennedy, Manager of the Newark Plant, and others (Exhibit 14 ), it is obvious first, that Dow Chemical was sharing with the rest of the industry the severe health hazards; secondly, Dow advised the industry that they had identified the causative agent as dioxin; thirdly, Dow had developed a new analytical method with a sensitivity level of 1 ppm; fourthly, Dow advised the industry of its intention to set a limit at that time of 1 ppm dioxin on this material; fifthly, Chandler admits that Dow had analyzed materials from other companies including Diamond Shamrock and found amounts as high as 10 ppm of dioxin in the 2,4,5-T acid. The last paragraph in this exhibit reconfirms the purpose, industry-wide, of the Midland meeting of March 24, 1965, where Mr. Chandler concludes "the purpose of this meeting was designed to help us solve this problem before outsiders confuse the issue and cause us no end of grief. Dow is sending the test results of our material to us incidentally and this will further check our techniques, etc." Having considered the

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universiality of the health problem of 2,4,5-T esters and the need throughout the industry to cooperate to some extent to alleviate this problem, what steps if any, did Diamond Shamrock take to eliminate the contaminant dioxin from the T ester which comprised half of the Agent Orange product? Kennedy returned to the Newark Plant after attending the Dow conference at Midland on March 24, 1965 with the knowledge that there was a problem involving dioxin that had to be solved (Kennedy deposition, p. 135, line 1-17).

8. The dioxin contamination of Diamond's herbicides caused it to lose customers, in particular, Dow.

On April 6, 1966 the following memorandum was sent from J.C. Kelly, Diamond's sales shipping coordinator in Division headquarters of its Ag-Chem Division in Cleveland, to J.O. King, sales manager in that division, regarding Dow's refusal to purchase Diamond's production:

April 6, 1966

"Mr. J.O. King Mr. J.C. Kelly

Dow Chemical Company

On March 21, we directed a sample of our Technical 2,4,5-T Acid to subject account. In talking with Ken Hanson on April 4, he advised that they would not be in a market for our material. Apparently, they feel that our material could conceivably re-create a chlor-acne problem at Midland and, as such,

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would not entertain the purchase of our present production.

J. C. KELLY

JCK/im

cc. Mr. F.R. Kennedy - Newark
Mr. R.A. Guidi"

9. There is no doubt that Diamond had considerable knowledge of dioxin risk reduction techniques. An interim report, January 9, 1967 of experimental work for TCP purification, reveals their awareness of Dow's studies regarding identification of the compounds causing chloracne and analytical procedures used to quantitatively identify the dioxin contamination. Diamond also knew what needed to be done to eliminate or reduce dioxin, and that this could be accomplished in several ways including alteration of the TCP condensation reaction or utilizing engineering techniques to remove dioxin from process streams after they have been reduced.

10. It is significant that from the time Dow gave Diamond Shamrock the means of analyzing its product in March of 1965, it was not until September of 1967 that a purification column was installed on the production floor and put into use. Despite such installation, and perhaps most significantly, by Diamond Shamrock's own analysis from January to March of 1968, it was running 3.8 ppm dioxin and related compounds in its 2,4,5-TCP. In October through December

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1968, it ran 9 ppm. Nevertheless, production continued, a. product was sold to the government. In the affidavit of Franc R. Kennedy, sworn to March 27, 1980, he speaks eloquently of the government's need for Agent Orange, but is absolutely silent on Diamond Shamrock's need for purification of a contaminated product that it knew that it was selling to the government without disclosure of the contamination problems. What effect, if any, did the performance of Diamond Shamrock corporation have on the defendants? Did the concern expressed by Dow in the Midland meeting in March of 1965 terminate its concern regarding the contaminant which it knew at that time was industry wide? Or in fact did the purported concern for this serious health problem continue among the various defendants well beyond the Dow conference? An answer to that can clearly be seen in a confidential memorandum of J.P. Frawley, dated July 12, 1965, of the Hercules Powder Company which relates to a telephone conversation dated July 9, 1965 with Mr. Earl Farnhan of Dow Chemical Company . Mr. Farnhan was convinced that no one else in the industry had done anything to remove the contaminant from their 2,4,5-T. Mr. Farnhan further stated that Dow was extremely frightened that this situation might explode. Mr. Frawley quotes Mr. Farnhan as stating that Dow "aware that their competitors are marketing 2,4,5-T which contains alarming amounts of acnegen and that if the government learns of this the whole industry will suffer. They are particularly fearful of a congressional investigation and excessive restrictive legislation on the manufacture of pesticides which might result."

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Obviously, it was not the intention of Hercules, Dow and others to disclose a problem of health to its customer, the United States Government, but rather to try and induce the industry at large to "clean-up" ("cover-up?") its product before the government found out about the health hazard. It is hard to conceive of greater evidence of the conspiracy of silence where, as here, the industry admittedly knew of a serious health problem, unknown to the government, than Mr. Farnhan's own words of precaution that Dow is fearful if the government learned of the alarming amounts of acnegen, the entire industry would suffer.

F. T.H. Agriculture and Nutrition Company, Inc. Knew About Dioxin as a Contaminant in 2,4,5-T and Knew About Concomitant Health Hazards and Failed to Warn the Military.

Much of what is known about the defendant T.H. Agriculture and Nutrition Company, Inc., formerly known as Thompson-Hayward Chemical Company, Inc., (hereafter "T.H.") is the result of a deposition of Edwin T. Upton and a review of T.H.'s produced documents. Mr. Upton was deposed on April 7 and 8, 1983 and T.H. produced documents totaling approximately 18,000 pages. Counsel for T.H. represented to counsel for plaintiffs that no confidential or proprietary documents were withheld. Mr. Upton's deposition, in conjunction with the documents, clearly shows that T.H. knew about dioxin in its end product (hereafter variously 2,4,5-T, 2,4,5-T ester and isooctyl ester 2,4,5-trichlorophenoxyacetic acetate) and knew about concomitant health hazards. Mr. Upton's deposition and T.H.'s documents further establish that neither Mr. Upton nor anyone at T.H. warned the military.

Edwin T. Upton first worked for T.H. on a full-time basis as a chemist beginning in 1946. (Upton Tr. at 27.) From Chemist, Mr. Upton progressed to Chief of the Quality Control Laboratory, Chief Chemist, and finally Laboratory Administrator. Id. at 27, 44. From 1946 to 1947 Mr. Upton worked on formulating usable forms of 2,4,5-T. Id. at 29. In experimenting with formulations, Mr. Upton made an informal literature search resulting in a paper which was presented at a regional American Chemical Society meeting in 1946 or 1947. Id. at 29. In preparing that paper he reviewed a number of patents on the use of phenoxy herbicides. Id. at 30. Those patents were reviewed prior to 1955. Id. at 31. In 1946 or 1947, Mr. Upton developed for T.H., a successful formulation of 2,4,5-T. Id. at 32-33. Between 1946 and 1947, Mr. Upton also worked on products containing a mixture of 2,4,5-T and 2,4-D. Id. at 35.

Through Mr. Upton's efforts, T.H. developed, in the early '50's, a herbicide which was a 50/50 mixture of 2,4-D and 2,4,5-T. That product was called DED WEED 50-50 BRUSH KIL. (Upton Tr. at 36). T.H. also manufactured 3-3 BRUSH KIL. That product was a 50/50 mixture of 2,4,5-T and 2,4-D. (Upton at 41).

T.H. established specifications for 2,4,5-T. Id. at 49. Those specifications were established in the late '40s. Id. Beginning in 1950 or 1951, T.H. began manufacturing 2,4,5-T according to those specifications. Id. at 51. 2,4,5-T was manufactured from approximately 1950 to some time before 1960 at a plant in Kansas City, Kansas. Some time after 1960, a new plant was opened in Turner, Kansas. In manufacturing the end product, isooctyl 2,4,5-trichlorophenoxyacetic acetate, T.H. began with trichlorophenol purchased from the Dow Chemical Company. The 2,4,5-trichlorophenol was converted to sodium 2,4,5-trichlorophenate. In a separate process, monochloroacetic acid was esterified with isooctyl alcohol to make isooctyl monochloroacetate. The two intermediates, sodium 2,4,5-trichlorophenate and isooctyl monochloroacetate were coupled to make the end product, isooctyl 2,4,5-trichlorophenoxyacetic acetate. Id. at 76.

From 1947 when he was a chemist until 1974 when he was the Laboratory Administrator, Mr. Upton remained responsible in a "hands on" or supervisory capacity for the analytical testing of raw materials, intermediaries and finished products. Id. at 44, 81. From 1947 to approximately 1965, T.H. utilized the official Agricultural Chemist Association method (Parr Bomb) for determining gross amounts of chlorine in the 2,4,5-T. Upton Tr. at 82. Beginning in 1964 or '65, T.H. began using an infrared spectrometer for determining the gross composition of its 2,4,5-T. Id. at 84. The infrared spectrometer continued to be used until Mr. Upton left T.H. in 1974. Id. at 85. In 1962 or 1963, T.H. obtained a gas chromatograph. Id. at 87.

From 1963 when T.H. obtained its gas chromatograph until the middle of 1964 that gas chromatograph was not used to determine impurities in 2,4,5-T. Id. at 88,89. From 1963 until the middle of 1964, T.H.'s gas chromatograph was not utilized to determine the amount of inert ingredients in the 2,4,5-T being manufactured by T.H. Id. at 89, 90.

On December 3, 1964, Dr. David Groth of the Regional Health Reserach and Training Facility in Cincinnati, Ohio, wrote to Mr. Upton. In that letter, Dr. Groth indicated that he was interested in the "determination of the toxic compound present in the commercially available 2,4,5-trichlorophenoxy-acetic acid which is sold as the iso-octyl ester." David Groth further indicated that Kimmig and Schultz had published a paper "which gave evidence that the skin and liver toxicity were not (emphasis in original) due to the 2,4,5-trichlorophenoxyacetic acid, but probably from some by-product which is present in very small quanities." From his reading of Kimmig and Schultz, Dr. Groth stated that he thought to be the responsible compound and drew a schematic of that compound. Of greatest importance, he noted as a result of his lack of knowledge, "however, there is no conclusive evidence that this, or any other specific compound, is responsible since no one has yet separated the various compounds present in commercial 2,4,5-T." Apparently, in the hope of being able to separate those compounds, David Groth requested E. T. Upton of T.H. to send him samples of isooctyl ester 2,4,5-T manufactured by T.H.

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After letters and conversations with employees of the Dow Chemical Company - which were the direct result of David Groth's letter - E.T. Upton sent samples of T.H.'s 2,4,5-T and Dow's trichlorophenol to David Groth. In a letter of January 14, 1965 which accompanied the T.H. samples, Mr. Upton wrote "we would appreciate very much receiving a copy of your analytical method, which I assume is based on gas chromatography for determining the 2,3,7,8-tetrachlorodibenzo-p-dioxin."

Apparently, Mr. Upton was aware that gas chromatography could be utilized to determine the existence of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the 2,4,5-T.

To assure himself that he would be advised if Dr. Groth discovered anything, Mr. Upton wrote a second letter dated February 17, 1965 in which he stated: "We are very much interested in your study of the toxicity of the by-products present in commercially available 2,4,5-trichlorophenoxyacetic acid esters. For our information, please send us a copy of your analytical method for the determination of the 2,3,7,8-tetrachlorodibenzo-p-dioxin in technical 2,4,5-T esters." See, Exhibit 4 (emphasis added).

Unfortunately, David Groth was never able to determine that, in fact, 2,3,7,8-tetrachlorodibenzo-p-dioxin was the substance in commercially available 2,4,5-T causing liver damage and chloracne. As explained by David Groth in his letter to Mr. Upton of February 26, 1965:

> I had hoped by this time I would have been able to give you some results on our technique. However, due to a shortage of funds we have not yet purchased the thin-layer chromatography apparatus that we plan on using for the separation.
>
> In previous correspondence I mentioned some articles which referred to the toxicity of 2,4,5 trichlorophenoxyacetic acid and possible toxic contaminants. The principal (sic) article is by Kimmig in Dermatologica 115:540-546. 1957. So far, that is the present state of our knowledge on the subject.

Like Kimmig and Schultz in 1957, David Groth was only able to speculate that 2,3,7,8-tetrachlorodibenzo-p-dioxin was the possible toxic contaminant. However, Mr. Upton, others at T.H. and others at Dow Chemical Company were keenly aware that David Groth was groping for answers to a serious industrial and end user helath problem. Representatives of Dow, T.H. and of the other defendant chemical companies had the answers Dr. Groth was seeking. Those answers were never provided to him.

Mr. Upton never wrote to Dr. Groth after David Groth's letter of February 26, 1965. Mr. Upton never informed Dr. Groth of information Mr. Upton had concerning 2,3,7,8-tetrachlorodibenzo-p-dioxin, its relationship to 2,4,5-T and intermediaries, and analytical techniques for determining the presence of dioxin. Upton Tr. 225, 226. While David Groth was never able to determine whether dioxin was a contaminant in 2,4,5-T, the same cannot be said for Mr. Upton and others at T.H.

David Groth's initial letter of December 3, 1964 was the catalyst for a number of events. After receiving David Groth's letter, Mr. Upton discussed the contents of that letter with Lindley S. DeAtley, Vice-President of Research and Development for T.H. Upton Tr. 102. Within a matter of days, Mr. DeAtley wrote a letter dated, December 11, 1964 to Dr. R.C. Dosser, Laboratory Director for the Dow Chemical Company. In that letter, Mr. DeAtley stated: "As we have corresponded and talked about the purity of trichlorophenol and related compounds on several occasions, I thought you would be interested in the attached letter of December 3, from Dr. David H. Groth of the Public Health Service." (Emphasis added.) When Mr. Dosser failed to respond, Mr. DeAtley wrote another letter of December 28, 1964 stating: "... we feel we must reply to the letter of December 3 from David H. Groth ..." (Emphasis added).

Mr. DeAtley never received a written response from Dow. Rather, Dr. R.C. Dosser of Dow called Mr. DeAtley on January 12, 1965 and "pointed out" that:

> "[I]f a compound, found in 2,4,5-T acid or its esters, proved to be damaging that this might lead to a flurry of successful claims by users of the herbicide who allegedly had been injured by it. Also, he said that although he did not know our method of processing Dow's tricholophenol, his chemist suspected that by some procedures, the toxic compound might be formed in processing through the sodium salt of the phenol to the sodium salt of the acid.

Dr. Dosser, of Dow, was clearly aware of alleged "user" injuries. T.H. was advised of those end user injuries at this time, if it did not have previous knowledge. Dr. Dosser, of Dow, also informed Mr. DeAtley of T.H., that Dow had developed an analytical technique for detecting dioxin and had been utilizing animal tests (the rabbit ear test) which had a sensitivity of about one part per million. Id. None of this information was conveyed to Dr. Groth at the Public Health Service though he had clearly expressed his interest. Upton Tr. 225, 226. Representatives of Dow and the representatives of T.H. were well aware of his interest.

When Mr. Upton responded to David Groth's letter on January 14, 1965-two or more days after Dosser's conversation with DeAtley - Mr. Upton failed to inform Dr. Groth of the information provided by Dr. Dosser, of Dow, to Mr. DeAtley, of T.H. Upton Tr. 225, 226. As noted earlier, Dr. Groth wrote to Mr. Upton on the 26th of February, 1965 and advised him that due to budgetary constraints, Dr. Groth would not be able to pursue his research. Upon receiving Dr. Groth's letter, E.T. Upton or others at T.H. clearly could and should have imparted to Dr. Groth all of the information they independently possessed and learned from the Dow Chemical Company.

As a result of the February 19, 1965 meeting, Dr. Charles E. Lewis, who worked for T.H. as its Industrial Hygiene Advisor, visited Dow. In his alleged Report on the Chloracne Problem, Dr. Lewis noted:

> Because of the past experience at Thompson-Hayward it would seem that two general approaches need to be made to the problem. First, because of the use of some material which was probably heavily contaminated with dioxin and other C.A. (chloracne) producting agents, it would seem important to sample (using the wipe sample method) the environment of the synthesis area to make sure that there is no residual contamination with these agents....It would seem highly desirable to go to the use of coveralls and showers as mandatory, as well as monthly inspection of these individuals for skin lesions and on an occasional, perhaps 2 to 3 months, check on blood tests for their liver function.
>
> . . . .
>
> In discussing this with Mr. Rowe (Chief Toxicologist at Dow) it was also thought that it might be wise to do an occasional sample of the final product of the operation here with V.P.C. (believed to stand for Vapor Chromatography) for dioxin and maybe(?) occasional rabbit test.

(emphasis added except the last; parentheticals added except the last). If the cover letter is an indication, Dr. Lewis' alleged report was written prior to April 26, 1965. Dow and T.H. were clearly concerned about end product contamination and hazards to users.

By February 19, 1965, and certainly by April 26, 1965 T.H. had a store of information concerning dioxin and analytical methodology. Nonetheless, neither E.T. Upton nor any other

representative of Thompson-Hayward Chemical Company wrote to Dr. Groth after his letter of February 26, 1965 in which he indicated an inability to obtain answers to his questions. Upton Tr. 225, 226.

### G. The Military Was Uninformed of T.H.'s Manufacturing Process And Its Capability For Risk Reduction.

In his first letter to Mr. Upton, Dr. Groth requested "any information you can give us concerning the manufacturing process, ie. starting compounds, reactions and possible by-products." In responding to Dr. Groth's request, Mr. Upton directed Dr. Groth to open literature on 2,4-D manufacturing processes. Mr. Upton did not direct Dr. Groth to open literature on 2,4,5-T manufacturing processes. The inference of conspiratorial silence again arises. In addition, Mr. Upton was undoubtedly reluctant to divulge trade secrets. When Dr. Dosser of Dow requested information on T.H.'s manufacturing process, T.H. again was willing only to direct the inquirer to published literature. From the published literature, neither Dow nor the military could have known T.H.'s manufacturing process.

The military's lack of knowledge as to the manufacturing process is important because "the type of manufacturing process used affected the level of dioxin contamination and that by exercising discretion as to the process, the defendants

controlled the extent of the dioxin hazard." See, In Re Agent Orange, 534 F.Supp. 1046, 1957 (E.D.N.Y., 1982).

By admission, some of the material used in the manufacture of T.H.'s 2,4,5-T was "heavily contaminated" in the mid-'60s. According to Mr. Upton, by 1970 or '71 tests of T.H.'s 2,4,5-T esters showed a lower level of contamination of up to two parts per million (hereafter "ppm"). Upton Tr. at 143. Samples taken from excess stocks of T.H.'s "Agent Orange" in 1973 from an inventory at Gulfport, Mississippi may belie those low 1970 or '71 figures.

The Gulfport samples showed a contamination level of from 0.7 to 4.1 ppm. Unfortunately, the date upon which T.H. manufactured the Agent Orange samples taken at Gulfport has not yet been determined. From the rate at which Agent Orange was being used, however, the Agent Orange sampled was probably manufactured by T.H. in the late '60s or early '70s.

From the mid-'60s when T.H.'s isooctyl ester 2,4,5-tricholorophenoxyacetic acetate was "heavily contaminated" to the late '60s or early '70s when T.H.'s Agent Orange contained lower but still hazardous levels of up to (and perhaps higher than) 4.1 ppm, Gene Douglas, a T.H. chemist under Mr. Upton, attempted to discover where dioxin was being produced in T.H.'s plant and to remove the dioxin with activated carbon.

Whether an activated carbon clean up process was instituted and the levels of dioxin in this herbicide during 1960-1969, will only be known after plaintiffs have had the opportunity to complete their discovery of T.H..

In addition to looking at an activated carbon clean up process, Gene Douglas conducted experiments in 1967 to determine the relationship between pressure/temperature and the production and amount of dioxin. From those experiments, Mr. Douglas clearly learned that over a certain temperature, dioxin formed and that the higher the temperature the more dioxin was produced.[7/] With that knowledge, Gene Douglas would have been remiss if he had not suggested that the sodium trichlorophenate be dried at a lower temperature. He might also have suggested that the wet ester be dried at a lower temperature and that the excess unreacted phenol be driven off with steam instead of heat. Whether those suggestions were made and implemented will also not be known until plaintiffs complete their discovery.

Clearly, T.H. knew of methods for reducing the level of dioxin in its end product. T.H. also knew from 1965 and perhaps before 1965 of the dangerousness of dioxin and T.H. knew that the level of hazard increased with the level of dioxin. There has been no proof, on the other hand, that the military knew about T.H.'s original manufacturing process. There has been no proof that the military experimented with a pressure/temperature dioxin relationship. There has been no proof that the military experimented with an activated carbon clean up process. Nor has there been any proof by T.H. or any of the defendants that the military was told about the foregoing.

7/ Whenever production is increased it is usually done by increasing the temperature of the synthesis run." The higher temperature resulted in increased dioxin in the waste and in the end product.

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Finally, neither T.H. nor the other defendants has put in any proof that "the government had knowledge equal to theirs (about the above discussed risk reducing techniques) and that even with that knowledge the government imposed no requirement or restriction with respect to the manufacturing process or the level of dioxin contamination." The evidence points instead to T.H.'s failure to disclose these techniques to the military, just as it failed to warn them of the hazards associated with the dioxin contaminated herbicides it was selling to the Government.

## H. T.H. Knew of Means For Detecting Dioxin And Failed To Disclose Those Methods to the Military.

T.H. clearly learned from the Dow Chemical Company (if they did not already know) how to use gas chromatography for the detection of dioxin in trichlorophenol, sodium trichlorophenate and later 2,4,5-trichlorophenoxyacetic acetate. From discussions with H. Gill of Dow, Mr. DeAtley and Mr. Fuhlhage clearly knew about the use of gas chromatography for detecting dioxin. Mr. DeAtley and Mr. Fuhlhage learned about Dow's detection method prior to February 23, 1965. T.H. never informed Dr. Groth of their knowledge concerning the use of gas chromatography even after Dr. Groth's letter of February 26, 1965 wherein he alerted T.H. that he had not been able to purchase a gas chromatograph and devise a method for separating the compounds. Whether or not T.H. and the other defendants had a duty to test their

products using gas chromatography, they had a clear duty to advise the military of its availability.[8/]

Use of a gas chromatograph to identify dioxin and determine the levels of contamination is a risk reduction technique. Knowledge of gas chromatography (and the rabbit ear test) before and after 1965 is important. Under the contracts for the procurement of "Agent Orange," the defendant chemical companies were required to utilize the Parr Bomb method and when it became available, mass spectrometry. Upton Tr. 222. Neither of these methods is capable of detecting trace amounts of impurities. Neither of those methods can detect dioxins. Id. at 223,224.

A government inspector was frequently present when T.H. conducted its Parr Bomb and later, mass spectrometry tests. Though present, that inspector could not learn about the presence of dioxin in the 2,4,5-T esters through either the Parr Bomb or mass spectrometry tests. T.H. and the other defendants in similar situations had a clear duty to divulge to those government inspectors the availability of a better method for the detection of dioxin and determination of levels of contamination. That did not occur in T.H.'s case.

During Mr. Upton's deposition, he stated that during the testing of the final 2,4,5-T product, a Mr. Block, who he believed to be a government inspector, was present. Upton Tr.

8/ Defendants also had a duty to tell the military about the rabbit ear test which had been in existence since at least 1941 for detecting acnegens to 1 ppm.

at 221. The test method employed was the Parr Bomb. Gas chromatography was not utilized. Though Mr. Block was present during numerous tests of the 2,4,5-T end product, Mr. Upton never told Mr. Block about gas chromatography or the existence of dioxin as a contaminant in 2,4,5-T. Upton at 224, 225. Nor is there any evidence that anyone at T.H. informed the military of gas chromatography as a method for detecting dioxin.

## I. T.H.'s Participation In The Conspiracy

The evidence indicates that T.H. entered that conspiracy, as early as December 11, 1965 with Mr. DeAtley's letter to Dow, two years before T.H. produced its first Agent Orange for the military.

Dr. David Groth's letter of December 3, 1964 was the catalyst for a series of meetings and conversations between January and March of 1965 involving most of the defendants in this litigation on the subjects of dioxin and hazards to workers and end users.

T.H. clearly participated in those conversations and meetings. Out of those conversations and meetigs came a conspiracy of silence.

Though Mr. Upton had the ability to inform Dr. Groth, of the Public Health Service, of dioxin, gas chromatography, risk reducing manufacturing procedures and health hazards associated with dioxin, he did not do so. Upton at 225, 226.

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Though Mr. Upton had the opportunity on numerous occasions to inform the government inspector, Mr. Block, of dioxin, its hazards and of availability of gas chromatography and alternative manufacturing processes, Mr. Upton did not do so. Id. at 224, 225. Furthermore, the Court should note that T.H. has not produced evidence indicating that anyone at T.H. informed the military of the foregoing. A conspiracy of silence reigned.

J. THOMPSON CHEMICAL WAS KNOWLEDGEABLE ABOUT THE MANUFACTURING PROCESS, DIOXIN AS A CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS, AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN.

Thompson Chemical Company also had far more knowledge about the manufacturing process than military decision makers.

There can be no question that over numerous years as a manufacturer of TCP and 2,4,5-T, T.C. was fully aware of the manufacturing process for those compounds. T.C. knew that in the synthesis of tetrachlorobenze to TCP, heat and pressure were utilized. T.C. knew that in the distillation of water, alcohol and anisole, heat was employed in the production of 2,4,5-T, the end product. T.C. was thoroughly familiar with the manufacturing process for 2,4,5-TCP and 2,4,5-T.

K. T.C. Knew That A Highly Toxic Impurity Was In Its TCP and 2,4,5-T

As a manufacturer of TCP, T.C. may have been informed in 1956 by C.H. Boehringer Sohn that a TCP or 2,4,5-T process that used heat or pressure above a certain maximum resulted in a contamination of the TCP and 2,4,5-T with a highly toxic impurity.

C.H. Boehringer Sohn had experienced horrendous outbreaks of chloracne with liver damage in some cases in two separate plants. To assure that other manufacturers of TCP and 2,4,5-T did not experience similar incidences, C.H. Boehringer Sohn sent in 1957, "Information of the reaction conditions under which no chloracne results to all known producers of chlorophenol." Plaintiffs have established that The Dow Chemical Company, as a manufacturer of TCP, received such information from C.H. Boehringer Sohn. As a manufacturer of TCP (a chlorophenol), T.C. probably received the same information in 1957 from C.H. Boehringer Sohn, as to a toxic impurity arising under certain conditions in the manufacture of TCP and 2,4,5-T.

Dr. K.H. Schulz of the University Skin Clinic in Hamburg reported in "Die Naturwissenshaften" 44: 337-338(1957), what he believed to be the contaminant in the TCP and 2,4,5-T being manufactured by C.H. Boehringer Sohn. Had anyone at T.C. read that article, he or she would have been alerted to the possible presence of dioxin in T.C.'s 2,4,5-T and TCP. Though he did not start with T.C. until approximately 1965, Mr. M.S. Buckley may have read Dr. Schulz's article. Thompson Tr. p.43, 50.

Regardless of whether T.C. received information from Boehringer, or the Naturwissenshaften article, T.C. was undoubtedly aware o a number of industrial exposure incidents in which workers manufacturin TCP and 2,4,5-T experienced chloracne, liver damage in some instances, and maladies involving the nervous system. See, generally, tetrachlorodibenzo-para-dioxin in the Environment, Robert W. Baughman (unpublished dissertation for the Harvard Department of

Chemistry, 1975). An awareness of those incidents would have alerted T.C. to the presence of a highly toxic impurity in TCP and 2,4,5-T.

If T.C. had not learned of the existence of a highly toxic contaminant in TCP and 2,4,5-T through C.H. Boehringer Sohn, Dr. Schulz' article in 1957 or through knowledge of industrial worker exposures, T.C. clearly came to learn about dioxin from its own experiences with employee injury. Some time prior to February 3, 1967, employees at T.C. experienced cases of severe chloracne. For an unexplained reason, Mr. M.S. Buckley of T.C. was sufficiently well informed to call The Dow Chemical Company to inquire of recommended treatment for the exposed. Mr. W.J. McCoy of Dow recorded in a memo to file his conversation with Mr. Buckley of T.C.:

> Mr. M.S. Buckley of Thompson Chemical phoned Howard Sheldon February 2, indicating that he believed they have a severe chloracne problem with some of their employees. He indicated that they already have two men affected and believe that they may have two more employees that appear to be affected as well. They are using Hooker's tetrachlorobenzene to make their trichlorophenol.
>
> Buckley was asking if Dow would have any recommendations for medical treatment for their employees.

Thompson Tr. 31. Thus, T.C. knew about dioxin as a contaminant in TCP and 2,4,5-T as early as 1956 and certainly no later than the end of 1966.

The military placed no restrictions on T.C. with respect to its manufacturing processes. T.C. had clear discretion in the choice of processes to use. See, Thompson, TR. 38. T.C. well understood that the process used determined the amount of dioxin in the 2,4,5-T. When M.E. Buckley of T.C. called Dow to discuss T.C.'s chloracne problem, Mr. Buckley "started talking about the chemistry of this material. Apparently, Mr. Buckley knew the chemical origins of dioxin and knowing that, knew that alternative manufacturing processes existed.

T.C. was fully aware of process alternatives. T.C. had absolute freedom to select the manufacturing process. Had the military known that different temperatures, pressures, alcohols, and phenolate water content resulted in different levels of dioxin contamination, there can be no doubt, the military would have required the safest method.

As previously shown, different manufacturing processes resulted in different levels of dioxin contamination and while T.C. and the other defendants were clearly aware of that fact, the military was ignorant of this matter because T.C. did not warn the military of the relationship between process selected and level of dioxin. Thus, T.H. also was part of the conspiracy of silence to conceal from the military. The facts of presence of dioxin, associated health hazards, and risk reduction processes.

L. HERCULES INCORPORATED WAS KNOWLEDGEABLE ABOUT THE MANUFACTURING PROCESS, DIOXIN AS A CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS, AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN.

Hercules sold the product known as "Agent Orange" to the military beginning sometime in July, 1965.

The "orange" was a mixture composed of equal volumes of 2,4-D and 2,4,5-T.

Sometime in February, 1965, Hercules learned from another defendant, Dow Chemical Company, that a previously identified acnegen (chloracnegen) was a contaminant in 2,4,5-T (Frawley dep. 35)

That beginning sometime in June, 1965, Hercules knew that the 2,4,5-T which it was selling to the military was contaminated with dioxin (Frawley depo. 24; 67).

Hercules learned from Dow in March, 1965 that the acnegen was dioxin (Frawley depo. 37), and that dioxin had the capacity to produce physiologic and systemic injury at a very low dosage (Frawley depo. 47).

Hercules knew that unless dioxin was removed from intermediates such as trichlorophenol it would carry though to the finished product. (Frawley depo. 65, 70).

Hercules produced dioxin contaminated herbicides which were ultimately sold to the military for use in Vietnam. Although the evidence as to the dioxin content of Hercules' herbicides is disputed by Hercules, it was sufficient to persuade this Court to recently reconsider and deny Hercules' Motion for Summary Judgment. The evidence included:

1. The Hercules internal memorandum (Ex.14a), reporting that Dow's sampling showed an excess of 2 ppm. dioxin in Hercules product as late as 1966;

2. The fact known to Hercules that Dow was purchasing Hercules' contaminated 2,4,5-T for sale to the military in order to fulfill Dow's contracts for delivery of Agent Orange;

3. The Gulfport, Mississippi sampling which revealed that 5 - 10% of the Hercules samples tested contained dioxin in the range of 14 - 16 parts per million;

4. Hercules knowledge since the 1950's of dioxin formation in its 2,4,5-T and 2,4-D manufacturing process;

5. Hercules knowledge of chloracne problems experienced by its plant employees during the period 1950 - 1959.



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Hercules never informed any agency or department of Government, particularly the United States military to whom it sold "orange", that the product it was selling to the military was contaminated with dioxin.

That Hercules never disclosed to any agency, or any department of Government much less did it notify the military to whom it was selling the dioxin-contaminated "orange" the information it had obtained both from industry and independent sources concerning the toxic effects of exposure to dioxin and its potential hazard to human health including disfiguring skin diseases, liver damage and systemic diseases. (Frawley depo. 78-79; 87-88; 90-91; 93-94; 95; 104-107; 110-111; 113-114; 115; 130-133; 138).

Hercules processes for manufacturing 2,4,5-T were at all times proprietary. (Frawley depo. 71-72).

Hercules never disclosed the details of its manufacturing process to the military or to any agency of government at any of the times relevant to this litigation. (Frawley depo. 28).

## II. DEFENDANTS' MISREPRESENTATIONS OF THE SAFETY OF THEIR HERBICIDES TO OTHER GOVERNMENT AGENCIES

Concurrently with their conspiracy of concealment and failure to warn the military, defendants also attempted to silence any criticism of dioxin contaminated 2,4,5-T and to obtain the United States Governments' approval of the contaminated herbicides whech they were selling to the military. Defendants formed what came to be known as a "joint industry task force on phenoxy herbicide tolerances" whose sole purpose was to persuade the pesticide regulation division (PRD) of the United States Department of Agriculture (USDA) to declare various phenoxy herbicides, including 2,4,5-T, as toxicologically safe. The technical term used was "negligible residue tolerance."

On or about August 23, 1966, the Task Force held its first meeting at the Madison Hotel in Washington, D.C.

Members of the Task Force included representatives of Defendants Diamond-Shamrock, Hercules, Inc., Monsanto Co., Dow Chemical Co., and Thompson-Hayward, later to be joined by Thompson Chemical Corporation and Uniroyal, Inc.

The Task Force was convened under the aegis of the National Agricultural Chemicals Association, a chemical industry activist organization owned, operated, managed and controlled by the chemical industry.

Mr. George E. Lynn, an executive of Dow Chemical Company was elected Chairman while Mr. C.L. Dunn, an executive of Hercules, was elected Vice-Chairman.

The minutes of the August 23, 1966 meeting revealed that the National Agricultural Chemicals Association had called the meeting at the request of an unidentified member company. The purpose of the meeting as set forth in the minutes was to ascertain if the companies present wished to form a Task Force and work jointly in an effort to secure negligible residue tolerances for phenoxy herbicides. Put another way, its purpose was to persuade the United States Department of Agriculture to declare phenoxy herbicides such as 2,4,5-T safe (nontoxic to humans and animals), notwithstanding the mass of information which each other concerning the toxicity of 2,4,5-T to humans.

The member companies meeting decided that the task force would be foremd,

> "...to work with the Food and Drug Administration and the United States Department of Agriculture for the purpose of securing the establishment of tolerances for existing no-residue registrations of phenoxy herbicides (--2,4,5-T--)."

One of the activities delineated in the minutes is as follows:

> "--2 Each member of the task force will compare and submit to the Chairman a listing of the toxicological and residue information which his company has on each of the herbicide chemicals involved..."

The next meeting of the task force which occurred on September 27, 1966 at the Jefferson Hotel in Washington, D.C. was attended for the first time by a representative of Thompson Chemical Corp. Consequently by September 27, 1966, defendants Dow Chemical Co., Thompson Chemical Corp., Diamond-Shamrock, Monsanto Co., Thompson-Hayward, and Hercules, Inc.

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were now members of the industry Task Force. Significantly, by this time, all defendants were aware of dioxin contamination of 2,4,5-T and the fact that it carried through to the end product posing a hazard to consumers. Hercules Chief Toxicologist, Dr. John P. Frawley, had by this time not only received information from Dow, but also from Monsanto and Badische in Europe concerning their problems with dioxin contamination arising out of the manufacture of trichlorophenol.

They were also aware of potential hazards to human health based upon the March 24, 1965 dioxin conference (supra) as well as the subsequent contacts by Dow with other companies to inform them of the frightening implications of their continued manufacture of dioxin contaminated 2,4,5-T as per the Frawley memorandum dated July 12, 1965.

At the September 26, 1966 meeting, the subject of "toxicological and residue data" arose and it was decided

> "--that each member of the task force is to send to Dr. Popham, any and all toxicological and residue data which he may have relative to phenoxy herbicides. . ."

The Task Force engaged a Dr. Popham whom later minutes would describe as formerly with the Agricultural Research Service of the United States Department of Agriculture. He was, in effect, to become the Task Force's point man for purposes of deceiving the government concerning the nature and extent of the toxicological data which was locked within the phenoxy herbicides industries' confidential files.

On October 25, 1966, the Task Force again met, this time at the offices of the National Agricultural Chemicals Association in Washington, D. C. The minutes reflect that the

Agricultural Research Service of the United States Department of Agriculture, appointed Dr. L.L. Danielson of the Crops Research Division "--to work with the Task Force --" The minutes further describe that Dr. Danielson

> "--is going to search the USDA files for any residue data that is available and Dr. Popham will work with him to collate it with what the Task Force already has. --"

Dr. Danielson was to search the USDA files to determine whether those files had any information on the toxicity of the herbicides under consideration including 2,4,5-T. What Dr. Danielson and his superiors at the USDA did not know was that current toxicological data on the toxicity of 2,4,5-T was safely reposing within the Task Force companies who had solicited the USDA's "assistance." As will be seen (infra) the USDA had not an inkling of the problem of dioxin contamination of 2,4,5-T as the Task Force conspirators well knew.

The minutes of the January 18, 1967 meeting of the Task Force reveal that Dr. L.L. Danielson of the Agricultural Department had, by that time, been apparently retained as a part-time "consultant." How this squared with his duties at the US Department of Agriculture and a possible conflict of interest is unclear. It seems not to have presented any problem to the task force.

At that meeting the committee "discussed" the fact that a point needs to be made with both the FDA and PRD/USDA that there is considerable public interest involved in the continued use of 2,4-D, etc., (including 2,4,5-T) and that in view of all the data now available, the agencies should extend themselves to consider and act favorably on the Task Force's proposition that the negligible residue tolerances should be established for all current registered uses.

None of the data obtained by Hercules or any of the other producers from Dow concerning the toxicological hazards associated with the use of the product and the adverse impact upon laboratory animals as reported by Dow at the March 24, 1965 conference

and in the other communications between the defendants ever found its way into the petition.

On March 28 of 1967, Mr. George E. Lynn, an executive of Dow Chemical then Chairman of the industry Task Force composed a report detailing the activities of the Task Force including the individuals who would be cooperating with it in establishing a negligible residue tolerance. The report shows that several representatives of the USDA including the Administrator of the Agricultural Research Service were invited to cooperate with the Task Force.

The report further indicates that Dr. George W. Irving, Jr., administrator of the Agricultural Research Service of the USDA and Dr. James L. Goddard, Commissioner of Food and Drugs, were invited to "cooperate" with the Task Force in this project "by supplying such technical assistance and data as would be appropriate with the public interest."

The report further shows that the committee in the presence of representatives of the USDA and the Food and Drug Administration made it a point to stress:

> "that in view of the wide use of these herbicides by the American farmer for food production, the Task Force felt the USDA and the FDA also had a vital interest in the continued availability of these essential herbicides.. ."

One of the objectives of the Task Force as described in the memorandum was to:

. "collect all available data from private and published sources with respect to toxicity . . . pertinent to the use of any and all phenoxy herbicides--"

"--The probable sources of such data being

(a) Agricultural Research Service, USDA;

(b) industry (data used in support of no residue registrations);

(c) state experiment stations;

(d) scientific literature;

(e) Food and Drug Administration, USDHEW.

Significantly, the kind of "industry" data to be supplied was not left to speculation. It was to be only that data which could be "--used in support of no residue registrations --" As will be seen, any belief that the U. S. Department of Agriculture or the Department of Health, Education and Welfare might have had about industry supplying its current data or directing USDA to its scientific literature would at the time of submission of the petition turn out to be a sham. As will be further seen (infra), not only did industry not report the state of its current knowledge about dioxin contamination of 2,4,5-T, but deliberately submitted antiquated literature none of which was critical of 2,4,5-T much less containing any mention of an acnegen or a chloracnegen and certainly not dioxin.

By the time of the April 20, 1967 meeting, as reflected in the minutes, the Task Force learned that

". . . the FDA's concept of a negligible tolerance is in a range of 0.1 ppm but 0.2-0.3 ppm is not out of line if data justifies it. . ."

Of course, the 0.1 ppm etc., has no reference to dioxin contamination since the USDA at that juncture has absolutely no knowledge from the Task Force about the problem of dioxin contamination of 2,4,5-T. One would expect that, given defendants claimed knowledge by USDA, FDA and HEW of the dioxin contamination problem and its potential to human health, at least one of these

minutes would have shown some discussion and perhaps even a disclosure to these agencies or their representatives at the meeting about the potential hazards. The minutes contain no such reference.

The minutes contain a schedule of the different phenoxy herbicides and opposite 2,4,5-T all defendants,except Uniroyal appear to have contributed towards the fee for putting the petition together and the filing. They each appear to have been assessed the sum of $1,100.00.

On May 11, 1967, the National Agricultural Chemicals Association on behalf of the task force informed Hazelton laboratories by letter, that it had been selected to prepare the petition to have 2,4,5-T declared safe to humans, animals and crops. The fraud and deception continued with the following empty promise described in the third paragraph of the letter to Hazelton:

> "The industry Task Force will turn over to Hazelton all of the information on the above mentioned phenoxy herbicides which it has gathered from various sources with respect to animal toxicity and crop residues..."

An examination of the studies concerning animal toxicity submitted with the petition reveals in substance that 2,4,5-T is as safe as drinking water. Of course, the V.K. Rowe studies of 1950 were included, showing 2,4,5-T to be safe while the V.K. Rowe studies of 1965 showing toxicity to humans and animals as discussed at the secret March 1965 dioxin conference were conspicuously absent.

The Task Force minutes of October 17, 1967 report

> "considerable discussion was given to possible handling of the use of these herbicides on rangeland. The high application rates involved, up to 6 pounds per acre, could result in high residues on the treated forage immediately after application. . ."

Significantly, the military only used 3 pounds per acre in Viet Nam. The Committee then had to consider the problems associated with application of 6 pounds per acre of 2,4,5-T. The minutes reflect that there was discussion of possible approaches such as

> ". . .requesting a sufficiently high numerical tolerance, requesting that the use be declared a "non-food use," and using label statements specifying a minimal time interval for grazing the treated range and/or for slaughtering cattle which have grazed the land. . ."

The Committee then decided as a better solution

> ". . . to list this use under a new heading "Forest Grass, Pasture, Range. . ."

It was also decided to include in the

> . . . petition the notation which appears in the 2,4-D entry in the USDA summary of registered agricultural pesticide chemical uses under the "Pasture: Clover, Grass" item to the effect: "Do not graze dairy animals on treated areas within seven days after application."

Nothing appears to have been beyond the imagination and ability of this resourceful group of conspirators. With a spray rate of 6 pounds per acre the only way to overcome the toxic residue was to have the USDA increase the tolerance level. Of course, at this point there is still no mention by industry of dioxin contamination to the product and its potential hazard to human health. The fact that the Task Force did not wish to permit the dairy animals to graze on treated areas for at least seven days after application demonstrates some consideration for animals when weighed against the fact that no one told the military to keep the soldiers out of the sprayed areas for at least one week.

The minutes further reflect that at 12:00 noon, Drs. L.L. Danielson and D.L. Klingman of the Agricultural Research Service of the USDA joined the group. Dr. Klingman is quoted as discussing the spraying of range lands with herbicides and that many more acres would

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be benifited if they were sprayed. He is further quoted as urging

> ". . . that the task force seeked to obtain clearance for this use so that farmers and ranchers could continue to utilize these valuable tools. ."

However, his associate from the USDA, the occasional part-time consultant to the task force, Dr. Danielson, went even further when he

> "promised to assist the task force in every way possible and proper in obtaining regulatory clearance for these materials so as to keep them available. Specifically, he and Dr. Klingman promised to consult their files in an effort to locate any pertinent data which would be helpful to the task force in its efforts to obtain tolerances."

It is clear that the minutes do not reflect any knowledge by the USDA, FDA, HEW that any of these phenoxy herbicides, including 2,4,5-T are toxic.

Significantly, for the first time, Uniroyal Chemical joined the Task Force by E.A. Hafner in attendance.

On November 27, 1967 on the stationery of Hercules, Inc., C.L. Dunn, Chairman of the industry Task Force wrote to Dr. Harry A. Hayes, Director of the Pesticide Regulation Division of the United States Department of Agriculture. In substance, he stated that the National Agricultural Chemicals Association Industry Task Force on phenoxy herbicide tolerances had assembled petitions requesting tolerances to cover uses previously registered on a "no-residue" basis. What this means is that previously, the phenoxy herbicides had been registered with the USDA as having a no residue toxicity. Now, the industry was seeking by its petition, to establish a toxicity tolerance for these very same herbicides.

Mr. Dunn went on to misrepresent on page 1 of the letter:

"There is no hazard to animals as evidenced by the extensive use of these materials for more than a decade, nor is the presence of residues in meat or milk a regulatory problem..."

Nothing was said in that letter about the animal studies conducted by Dow; nor that Dow had determined that dioxin was a contaminant in 2,4,5-T which carried through unless extracted, carried through to tne end product, nor that Dow had alerted all producers of 2,4,5-T to the potential hazards associated to humans exposed to dioxin contaminated 2,4,5-T; nor that Dow had set an internal specification of 1 ppm of dioxin contamination based upon their experience with laboratory animals; nor that Dow had expressed to the producers at the March 24, 1965 meeting that their analysis of their competitors 2,4,5-T showed what fate described as "surprisingly high amounts of the acnegen" which they identified as dioxin; nor was there any mention of the telephone call of the substance of knowledge gained by Dr. Frawley from the telephone call received from Earl Farnham of Dow Chemical Company on July 9 of 1965 alerting Dr. Frawley to the fact that Dow was frightened that the whole industry might explode and that there might be governmental intervention by way of a Congressional investigation and a banning of pesticides because of what Dow perceived as "alarming amounts of acnegen" in their competitors' 2,4,5-T; nor any disclosures by Mr. C.L. Dunn who attended the secret dioxin conference with Dr. John Frawley on behalf of Hercules and was copied on the memo Dr. Frawley wrote recounting his conversation with Farnham of Dow. At no time did the so-called industry Task Force on phenoxy herbicides

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ake disclosure to the USDA or FDA people in attendance at heir meetings of the common knowledge which they had all cquired beginning in November, 1964 when Dow had devised a eans for the identification of dioxin in 2,4,5-T.

On November 27, 1967 on the stationery of Hercules, Inc. r. C.L. Dunn, acting in his capacity of Chairman of the Task orce wrote to Dr. Harry Hayes, Director of the Pesticide egulation Division of the United States Department of Agriculture nforming him that the industry Task Force had assembled petitions equesting tolerances on the phenoxy herbicides. The fourth aragraph of Mr. Dunn's letter continues the misrepresentation nd fraud when he states:

> "there is no hazard to animals as evidenced by the extensive use of these materials for more than a decade --"

On that same date, November 27, 1967, Mr. Dunn wrote to the Force informing them that both he and Don McCollister (Dow) were ouraged by the apparent unconcern of the USDA

> "for the farmer users of phenoxy herbicides. In addition, Dr. Anderson seemed quite opposed to a cooperative program. He expressed sensitivity to criticism by G.A.O. Investigators who recently complained about USDA developing data subsequently used by a manufacturer for registration purposes. --"

On December 8, 1967, the conspirators submitted to the etition control branch of the Food and Drug Administration of he Department of Health, Education and Welfare a petition to a 2,4,5-T declared safe. The cover letter is on the station- ry of National Agricultural Chemicals Association, signed by . L. Dunn, Chairman. The petition consists of seven sections,

a-g. Section C reads as follows:

> "full reports of investigations made with respect to the safety of the pesticide chemical. --"

An examination of the bibliography in support of the Task Force claims a lack of toxicity shows that not one study critical of 2,4,5-T was cited.

Instead, these defendants submitted to the unsuspecting, gullible and ingenuous USDA, Food & Drug Administration, and HEW, studies by V. K. Rowe, McCollister and Spencer of Dow Chemical Company dated 1950, all of which had been negated by Dr. Rowe's "startling" confirmation of dioxin as the toxic chloracnegen in November, 1964 and Dow's subsequent experimentation with dioxin contaminated 2,4,5-T upon laboratory animals, none of which work found its way into the open scientific literature much less into the FDA petition.

Subsequently, the Task Force received a letter dated April 8, 1968 from the Department of Health, Education and Welfare to Mr. C. L. Dunn, Chairman of the Task Force, informing Mr. Dunn that the toxicology data submitted by the industry was insufficient especially with respect to the fact that there would be a carry over into meat and milk.

The petition was subsequently withdrawn along with the petition which sought to have 2,4-D declared safe also.

Defendants' efforts to disparage any claims of the toxicity of dioxin did not cease, however. When the National Cancer Institute which commissioned the so-called "Bionetics Report" released its findings concerning the potential health hazards of dioxin contaminated 2,4,5-T, Dr. John Frawley, Chief Toxicologist of Hercules, sought to belittle the ignorance of the National Cancer

Institute about the toxicity of dioxin. In a letter dated November 25, 1970 responding to a letter from his counterpart in England, Dr. John C. Higgins, of the Hercules Powder Company of England, Dr. Frawley made the following caustic and critical disparagement of the National Cancer Institute's knowledge of dioxin and its toxicity:

> "--- the Government Agency sponsoring the study (NCI) was not familiar with the toxicity of the dioxin and allowed publicity on the results without consultation with better informed government or industrial scientists. ---"

He reserved his most severe criticism for the surgeon general when, in that same letter to Dr. Higgins, he wrote:

> "---on the basis of this single observation in mice, the Surgeon General (who has never in the past gotten involved in safety evaluations) declared before a Congressional Committee that even pure 2,4,5-T presented an imminent hazard to the health of the public. This triggered the banning of 2,4,5-T for all household and several industrial uses ..."

It was not until 1979 that the Environmental Protection Agency (hereinafter "EPA"), although knowing that some manufacturers produced 2,4,5-T with less than 1PPM, instituted deregistration proceedings against 2,4,5-T. The EPA's Prehearing Brief on The Risk Associated with the Registered Uses of 2,4,5-T and Silvex concludes:

> "In sum, the data on toxic effects in animals and humans together with the data on exposure potential establish that the continued use of 2,4,5-T and Silvex contaminated with TCDD (dioxin) pose risks of adverse effects on human health. (parenthetical added).

Though the EPA is undoubtedly concerned with the health hazard dioxin in 2,4,5-T presents to those who manufacture it, the focus of EPA's concern is the user, the innocent bystander and the environment. Since EPA apparently believes that less than 1PPM is unsafe. The inescapable inference is that defendants' conspiratorial conduct, misrepresentations and failure to warn were responsible in substantial measure for the EPA's delay in commencing deregistration proceedings.

## III. THE DEFENDANTS SUPPLIED DIOXIN CONTAMINATED HERBICIDES WHICH WERE MIXED TOGETHER BEFORE BEING SPRAYED IN VIETNAM MAKING IMPOSSIBLE IDENTIFICATION OF WHICH DEFENDANT'S HERBICIDE CAUSED INJURIES TO PLAINTIFFS.

The defendants' dioxin contaminated herbicides were supplied in drums not bearing the defendants' corporate name. They were mixed together before spraying. A description of "standard operating procedures" is contained in an official U.S. Air Force Technical Report[9/], (pp. I-15, 15).

Each of the 11 different companies that manufactured military herbicides packed them in new 1CC 17C 55-gal 18 gauge steel drums for shipment to Southeast Asia.

Each herbicide drum was marked with a three-inch color-coded band around the center to identify the specific military herbicide. This marking was initially a 12-inch band, but was changed to a 3-inch band in March 1966.

About 10 out of every 10,000 drums shipped were received in a damaged or defective state. This represented a damage rate of 0.1 percent. About 50 percent of these damaged drums leaked as a result of punctures or split seams. There were caused by improper loading and defective drums. Forklifts operated by Stevedores also caused punctures. Redrumming was accomplished at the ports.

About 65 percent of the herbicide was shipped to the 20th Ordnance Storage Depot, Saigon, and 35 percent was shipped to

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9/ "The Toxicology, Environmental Fate and Human Risk of Herbicide Orange and its Associated Dioxin" Alvin L. Young, et al., October 1978.

the 511th Ordnance Storage Depot, Da Nang. Under the normal handling procedures, drums were unloaded at Da Nang and Saigon from the cargo vessel directly into semi-trailers and were placed in an upright position. The trailers were driven to the various units of the 12th Air Commando Squadron (primarily at the bases of Da Nang, Phu Cat, or Bien Hoa) for disposition. Normally the contents of the drums were transferred into blocked F-6 trailer tanks through a suction tube without removing the full drums from the semi-trailers. Each F-6 trailer held 4,298 gal or about 78 drums of herbicide.

When the herbicide was pumped from the drums into the F-6 trailers about 0.5 to 1.5 gal remained in the drum. Hence the drum was placed on a drain rack and the "drippings" were collected from many drums in a pan-type receptacle and used for spraying base perimeter areas.

## IV. DEFENDANTS' JOINT ACTION TO PREVENT GOVERNMENT PRODUCTION OF 2,4,5-T AND 2,4-D

The defendants together comprised virtually the entire 2,4-D and 2,4,5-T industry. As we have demonstrated, they acted conspiratorially or in concert to conceal from or misrepresent to the government the hazards associated with their products. In addition, to guard their dominant market position, they acted jointly to prevent the government from constructing and placing in operation at Weldon Springs, a plant for the production of 2,4,-D and 2,4,5-T. This is evidenced by a document authored by M. F. Wilkerson, Diamond's Marketing Manager, reflecting the industry decision taken by the defendants at a meeting October 4, 1968 of the Task Force created by the National Agricultural Chemical Association (NACA), attended in person or by representation by defendants, Monsanto, Hercules, Diamond, Dow & Thompson-Hayward.

The document reviewed the industry capacity "as secretly submitted", to produce both 2,4-D and 2,4,5-T as opposed to the purchase patterns of the military.

Although the production data submitted by each defendant was coded to preserve secrecy, Mr. Wilkerson estimated their respective capacities:

"A bit of upside-down reading gave the following breakdown of the participating members' capacities. These were coded but are exact. I have attached Company names which may or may not be, with the exception of Diamond, associated correctly with the capacity number.

| 2,4-D | | 2,4,5-T | |
|---|---|---|---|
| 5.0 MM | - Hercules | 5.5 MM | - Hercules |
| 12.0 MM | - Diamond | 3.0 MM | - Diamond |
| 40.0 MM | - Dow | 12.0 MM | - Dow |
| 24.0 MM | - Monsanto | 7.2 MM | - Monsanto |
| 14.0 MM | - Chipman | 4.5 MM | - T-Hayward |
| TOTALS 95.0 MM | | 32.2 MM | |

T-Hayward acknowledged they produced no 2,4-D as did Chipman for 2,4,5-T.

This group's best estimates for total annual domestic requirements of D and T were:

2,4-D - 55 MM lbs.
2,4,5-T - 18 MM lbs.

Hooker acknowledged they now have TCB capacity to supply all producers, on the basis of these estimates, except for Dow (who produce their own) and T-Hayward (who are presently being supplied TCP by Dow.)"

The task force then adopted the following position:

"SUMMARY OF POSITION

The group of phenoxy herbicide producers at their meeting of October 4, 1968 after estimating the capacity of the domestic industry to produce 2,4-D and 2,4,5-T; after estimating as accurately as possible the domestic civilian consumption of these products and the military requirement based upon the stated needs and current delivery schedules, concluded that there is sufficient domestic production of 2,4-D to fully meet both the civilian and military requirements, and that the production of 2,4,5-T would meet a substantial part of both the civilian and military need. It was concluded that the questions which prompted the Government Officials to make the decision to construct and place in operation a plant at Weldon Springs to produce both 2,4-D and 2,4,5-T have changed, and that the industry should request an opportunity to explore these data with the Government.

It was further concluded that even if it is assumed that the military will require the full amount of its needs as heretofore estimated, that there would be a very substantial over-production of both 2,4-D and 2,4,5-T if the Weldon Springs plant is operated at full capacity. This raised questions of serious import to the domestic industry which should be thoroughly explored with the Government.

## V. THE MILITARY WAS NOT AS KNOWLEDGEABLE AS THE DEFENDANTS ABOUT THE MANUFACTURING PROCESS, DIOXIN AS A CONTAMINANT, DETECTION METHODS, RISK REDUCTION METHODS AND HEALTH HAZARDS ASSOCIATED WITH EXPOSURE TO DIOXIN

The disparity of knowledge between the defendants and the military was enormous. It is a significant factor giving rise to the defendants' duty to warn the military of the hazards accompanying use of their herbicides known to the defendants, and the duty to inform the military of the means of risk elimination or reduction as this Court noted in 534 F. Supp. 1046, 1055:

> "A supplier should not be insulated from liability for damages that would never have occurred if the military had been apprised of hazards known to the supplier. A supplier, therefore, has a duty to inform the military of known risks attendant to a particular weapon that it supplies, so as to provide the military with at least an opportunity fairly to balance the weapon's risks and benefits."

The good sense of imposing a duty to inform is readily apparent. Such a duty does not interfere with the military's prerogatives by requiring suppliers and courts to second-guess the military's decisions. Indeed, it enhances those prerogatives by helping to ensure that suppliers will share their knowledge and expertise with governmental decisionmakers. Nor does such a duty cause delays in supplying needed ordnance - the suppliers are obligated merely to share knowledge and expertise already in hand.

In order for knowledge about hazards to have helped the military "fairly to balance a weapon's risks and benefits," it must have been possessed by individuals who were in positions of sufficient authority and responsibility to act on that knowledge. If the decisions in question were those regarding whether and how to deploy Agent Orange in Southeast Asia and which of the various forms of the Agent to employ, knowledge about hazards must have been possessed by a decisionmaker relatively high up in the chains of command and authority. Moreover, for the knowledge to have informed that relevant decisionmaker, it must have been possessed by him in a cohesive manner so that he would be in a position to integrate it into a meaningful whole.

It is not sufficient for military contractors to share information with anyone at all or with individuals so far down the relevant chains of command and authority as to render the information useless as a means of increasing the rationality of the policy decisions being reached by the appropriate decisionmaker at the appropriate level in the chain of authority.

Nor is it sufficient if the information consists of isolated bits and pieces of knowledge, scattered both vertically and horizontally throughout the governmental bureaucracies and shared in piecemeal fashion, with one person in government being informed as to another aspect. The first of these threats to rational decisionmaking might be termed the threat of vertical nonintegration. Both defeat the objective of rational

decisionmaking by preventing knowledge about hazards from being available to those attempting, in the Court's words, "fairly to balance the risks and benefits."

In their prior submission, "Plaintiffs' Memorandum Concerning the Government Contract Defense Phase of the 'Agent Orange' Products Liability Litigation: A Management Plan for the Discovery Phase", June 8, 1982, plaintiffs addressed the legal implications of the question of who in the government must have known, and noted that under the relevant case law, including that of the product liability field, the following rules apply in determining the issue of knowledge imputation or information transference:

1. Inter-Agency imputation of knowledge is wholly impermissible and intra-agency imputation use narrowly limited (pp. 22-68).

2. Information transference must be targeted to the appropriate decisionmaker and focused to alert to danger (pp. 22-31).

It is clear from the record that judged by these standards, the defendants have breached their duty to warn and inform the responsible governmental decisionmakers.

Apart from the question of who (ie. the high level rational decisionmaker) in the government should have possessed the information defendants had and withheld, is the issue of what information would rational governmental decisionmakers have wanted the chemical companies to share with them in order to be "fairly to balance the risks and benefits," given the

levels, and the third focusing on risk avoidance. The fourth type of information is more judgmental than factual, consisting of the conclusions, however, that the chemical companies had reached regarding the risks presented by Agent Orange.

Finally, there is the question of "when?" -- ie., the relevant time frame within which the government must have had knowledge about the hazards associated with Agent Orange?

Consistent with the concept of informed and rational decisionmaking, the crucial time for the government to have had knowledge of the hazards was the time during which decisions were made regarding the purchase and deployment of Agent Orange in southeast Asia. The key to understanding the relevant time frame is the objective that the military not be forced unnecessarily to act on inadequate information. Thus, suppliers of the chemical herbicides were obligated to share whatever relevant information they possessed at the time of sale and were obligated to share additional information as it became available to them throughout the period during which those herbicides were being used by the government.

The discovery to date establishes that these chemical companies were in a position, at little or no cost, and indeed had the duty, to draw the hazard and risk avoidance pieces together and timely warn and share them with the responsible government authority who made the decisions that directly and drastically affected the welfare of the plaintiffs. The defendant companies

failed to do this. Defendants' elaborate discovery of hundreds of officials have at most produced bits and pieces of information about the hazards of dioxin in general scattered uselessly across the length and breadth of various federal bureaucracies. Thus, defendants have also failed in their duty to warn and inform the responsible governmental decisionmaker as to the specific facts the military needed to know in order to make an informed decision.

VI. UNDER THE PRECEDING FACTS AND CIRCUMSTANCES, EACH DEFENDANT'S BREACH OF ITS SEPARATE DUTY TO WARN MAY BE CONSIDERED THE "CAUSE IN FACT" OF PLAINTIFFS' INJURIES, AND THE PROBLEM OF SEPARATE DEFENDANT IDENTIFICATION THEREFORE DOES NOT EXIST; BUT IN ANY EVENT, THE DEFENDANTS MAY BE HELD JOINTLY AND SEVERALLY LIABLE UNDER THE THEORIES OF CONCERTED ACTION, ENTERPRISE LIABILITY AND ALTERNATIVE LIABILITY

Because of the manner in which the defendants sold Agent Orange to the Government, and the manner in which the Government then utilized it so as to expose the plaintiffs to its effects, it is unlikely, no matter how firmly it is established that Agent Orange in fact caused the plaintiffs' injuries, that any plaintiff will be able to identify with certainty which one or more of the defendants actually produced the specific batch of Agent Orange to which he was exposed, to his detriment. Rather, because the defendants put no company-identifying marks on the barrels of Agent Orange they sold to the Government, and the Government treated the product generically, the most that plaintiffs will be able to prove is that they were all injured by Agent Orange, virtually all of which was produced by the defendants. To go further than this, and to require each plaintiff to identify the specific defendant or defendants whose Agent Orange caused his injury, would present impossible problems of proof.

At one time in the law, perhaps, such problems of proof might have been fatal to a plaintiff's case. The demands of modern society, however, have brought change to the law of causation and liability. The courts have clearly recognized

that if they are to continue to serve the ends of justice in an evolving society, the rules of law they apply must also evolve. As the Supreme Court of California put it, in considering the similar problems of proof of causation and liability facing a plaintiff in a products liability action involving the drug DES:

> "In our contemporary complex industrialized society, advances in science and technology create fungible goods which may harm consumers and which cannot be traced to any specific producer. The response of the courts can be either to adhere rigidly to prior doctrine, denying recovery to these injured by such products, or to fashion remedies to meet these changing needs. Just as Justice Traynor in his landmark concurring opinion in Escola v. Coca Cola Bottling Company (1944) 24 Cal. 2d 453, 467-468, 150 P.2d 436, recognized that in an era of mass production and complex marketing methods the traditional standard of negligence was insufficient to govern the obligations of manufacturer to consumer, so should we acknowledge that some adaptation of the rules of causation and liability may be appropriate in these recurring circumstances ... "

Sindell v. Abbott Laboratories, 607 P.2d 924, 926 (Cal. 1980). Or, as Judge Meyer of the New York Court of Appeals more succinctly put it in another products liability action involving DES, "Products liability law cannot be expected to stand still where innocent victims face 'inordinately difficult problems of proof.'" Bichler v. Eli Lilly & Co., 55 NY2d 576, 580; 450 NYS2d 776,779 (N.Y. 1982).

Thus, Court as well as commentators have proposed means which permit recovery by plaintiffs under circumstances such as these, where the conduct or product of a specific defendant out of a group of potentially liable defendants cannot be identified as the "cause in fact" of the plaintiffs' injuries. Such proposals involve application of principles of "concerted action", "enterprise liability", "alternative liability", and, more recently, "market share liability".10/

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10/ The Court in Sindell v. Abbott Laboratories, 607 P.2d 924 (Cal. 1980) developed the market share liability theory as a specific modification of the alternative liability theory to surmount the rational difficulties in applying the alternative liability theory in cases where not all or substantially all potentially liable parties are named as defendants. Since, as Exhibit 1 to this Memorandum clearly demonstrates, virtually all potentially liable parties are named as defendants here, the problems presented in Sindell, and the specific solution of market share liability devised by the Sindell Court to overcome them, do not apply. Plaintiffs, therefore, do not discuss the market share liability in this memorandum.

Plaintiffs believe that the lengthy factual statement fully supports the theories of concerted action, enterprise liability and alternative liability. These arguments will be addressed seriatum. However, there is good reason to examine at the outset the implications of the failure to warn theory as it has developed in this case. On its own it is dispositive of the problem of defendant identification.

The plaintiffs have presented facts in this case establishing that the defendant chemical companies failed to warn the government about a broad range of risks related to the use of Agent Orange. Plaintiffs submit that the very special nature of the breach of the duty to warn issue as it arises in this case moots the issue of causation as it relates to the identification of which defendant should be deemed responsible for which plaintiff's harm. As we shall demonstrate, each defendant individually in the truest sense of the word was a "cause in fact" of the entirety of the harm.

It will be helpful to focus on the nature of the failure to warn claim. Plaintiffs contend that each of the defendants failed to warn of risks which they either knew or should have known about. These break down into various categories. First, plaintiffs contend that the defendant failed to share with the

United States Government information concerning the possible hazards attendant to the use of dioxin contaminated Agent Orange. What suspicions did they harbor or should they have had that the herbicide caused a broad range of diseases? The defoliation project subjected soldiers to doses and exposure to the herbicide heretofore unknown to mankind. This was not spraying a bush in one's backyard. Thousands of gallons of the defoliant were to be sprayed from the air to defoliate jungles. Thus, any test results, experiments, suspicions and conclusions however tentative should have been shared with the government with total candor. Plaintiffs have shown that this did not occur. Second, there was a long history of industrial accidents that indicated that problems of dioxin contamination were related to the manufacturing process. These accidents took place over a rather long period of time. Some were of considerable severity. They have been noted in the factual introduction to this memorandum.

The disastrous results of these industrial accidents caused the defendants to discuss the need for extraordinary precautions in the cleanup to assure that dioxin was avoided or removed from the workplace and to protect the workers in the cleanup process. There was no assurance that the dioxin which was the cause of these industrial catastrophes was avoided or removed from the final product. Plaintiffs have demonstrated

that defendants failed to fully inform the government of these industrial accidents, the precautions and methods discussed or used to avoid the formation of or rid the plants of dioxin and most important of the terrible consequences to those injured as a result of exposure to the dioxin.

Finally, plaintiffs have shown that defendants had information concerning their ability and non-ability to determine the level of dioxin contamination in the final Agent Orange product. Some defendants knew much about their ability to test for dioxin and their ability to control its presence. Others knew that they were unable to test for the presence of the dioxin contaminant and that their quality control techniques were erratic at very best. The evidence establishes that the defendants failed to inform the government about their analytical and testing capabilities and the methods available to them to control the risk by instituting alternate methods of manufacture that would significantly reduce or eliminate the dioxins or their inability to control the risk in that their quality control techniques were such that they did not know how to evaluate or control the dioxin level that was in their product.

At first blush, it would appear that plaintiffs are presenting a classic failure to warn case that would require conformance to normal causation principles. However, on reflection it is clear that there is something very different about this failure to warn case. Warnings serve two purposes. The standard failure to warn case serves the purpose of risk reduction. Most products raise the spectre of some element of danger if the products are not used properly. A warning can reduce the probability of harm (thus effecting the risk-utility balance) by alerting the user to risks that may eventuate should the user not follow the prescribed instructions. Alternately, a warning may inform a user that he belongs to a special class of persons who should not utilize a product at all or utilize it with special precautions. This form of warning is very common in drug cases. Both forms of warnings are designed to achieve a reduction of risk since they permit the user to intelligently respond to risks that attend the use of the suspect product.

There is, however, another category of failure to warn cases. In that type case, the contention is not that the defendant failed to warn so that risk could be reduced, but that the risk level is constant and there is little that can be done by the user to reduce the probability of harm. The function of the warning in this second genre of product cases is to inform

the user of risks attendant to the use of a product so that the user can decide whether he/she wishes to expose himself/herself to an irreducible risk. This class of failure to warn cases is very closely analogous to the informed choice medical malpractice case. The issue in those cases is not the conduct of the defendant per se, but rather the failure to give the patient sufficient information so that the patient can make an informed and knowledgeable choice as to whether to expose himself to a given therapeutic procedure. See e.g. Canterbury v. Spence, 464 F. 2d 772 (DC Cir) cert denied 409 US 1064 (1972); Cobb v. Grant, 8 ___ Cal 3d 229, 104 Cal Rptr. 505, 502 P. 2d 1 (1972).

The product liability analogue to these informed choice medical malpractice cases is exemplified by such well known cases as Davis v. Wyeth Laboratories, 339 F. 2d 121 (9th Cir. 1968); Reyes v. Wyeth Laboratories, 498 F. 2d 1264 (5th Cir. 1974) cert denied 419 US 1096. Cunningham v. Charles Pfizer & Co. Inc., 532 P. 2d 1377 (Okla. 1974). In these cases use of polio vaccine was attended with a small but irreducible risk-level which could not be affected by production. In Davis v. Wyeth Laboratories, Judge Merril recognized that he was faced with this problem:

> "There are many cases, however, particularly in the area of new drugs, where the risk, although known to exist, cannot be ... narrowly limited and where knowledge does not yet explain the reason for the risk or specify those to whom it applies. It thus

> applies in some degree to all, or at lease a significant portion, of those who take the drug. This is our case; there seems to be no certain method of isolating those adults who may be affected adversely by taking Type III Sabin vaccine.
>
> In such cases, then, the drug is fit and its danger is reasonable only if the balance is struck in favor of its use. Where the risk is otherwise known to the consumer, no problem is presented, since choice is available. Where not known, however, the drug can properly be marketed only in such fashion as to permit the striking of the balance; that is, by full disclosure of the existence and extent of the risk involved." 399 F. 2d 121, at 129.

The function of the warning in this case the court concluded was not to reduce the risk but instead to provide the plaintiff with the opportunity to decide whether to expose himself to a risk which could not be further reduced by any action on his part. The Court noted:

> "When, in a particular case, the risk qualitatively (e.g., of death or major disability) as well as quantitatively, on balance with the end sought to be achieved, is such as to call for a true choice judgment, medical or personal, the warning must be given." Id. 399 F. 2d at 129-130 (emphasis added)

Also see Model Uniform Product Liability Act. Sec. 104 (c)(3), Twerski, Old Wine in a New Flask-Restructuring Assumption of Risk in the Products Liability Era, 60 Iowa L. Rev. 1, 44-46 and Twerski, Weinstein, Donaher and Peehler, The Use and Abuse of Warnings in Products Liability - Design Defect Litigation Comes of Age, 61 Cornell L. Rev 495, 517-521 (1976).

The importance of the stated distinction is that it affects the causation issue in a most interesting fashion. If

the question is asked how responsible is each defendant for not sharing the totality of all the risk information which it knew or should have known about, the asnwer is clear. The failure of each defendant to warn the government was responsible for the ignorance of the government and contributed, not only to the use of each defendant's product, but to the very decision to use Agent Orange as a defoliant at all. That decision was not a divisible one. There is thus joint and several liability in the most classic and traditional sense. The reason that this informed choice argument resolves the identification problem is that the focus has switched from the nuance of each defendant's product to the defendants' collective and individual responsibility for failing to inform the government so that it could make a decision with all the information before it. Since the decision was non-divisible and was contributed to by everyone's failure to warn, the liability ought to be joint and several as well. As long as the failure to deliver the requisite information was a substantial factor leading to the decision to deploy Agent Orange, the plaintiffs have fully discharged their burden on causation. Concurrent tortfeasors do not have the luxury of the but-for argument in this context. See, Anderson v. Minneapolis St. P. & St.

M.R.R. Co., 146 Minn. 430, 179 N.W. 45 (1920), Kingston v. Chicago & N.W.R. Co., 191 Wis. 610, 211 N.W. 913 (1927).

The facts of this case support the conclusion that the failure to discharge one's own duty to warn must be viewed in the context of the government's decision to utilize Agent Orange as a defoliant. The defendants were not lone rangers in this case, totally unaware of each others activities. The facts point to a heavily concentrated industry with a high degree of special expertise with regard to the manufacture and use of herbicides. This highly concentrated industry dealt with a dizzying array of government agencies. From time to time bits and pieces of knowledge were in the possession of one person or another in one government agency or another. The information that was available to the defendants was or should have been put together by the defendants in a coherent fashion so that the responsible persons in the responsible government agencies were delivered the total risk picture. We shall demonstrate at trial that this was never accomplished. The defendants had full knowledge that the Agent Orange that went to Vietnam was to be loaded in planes to be mixed and sprayed without discrimination as to which defendant's product was being utilized. The consequences of the dangers if the suspicions and fears about dioxin turned out to be true were staggering. Hundreds of thousands of soldiers would be exposed to the risk. If we hypothesize that a government well aware of the risk would have or well might have decided against the defoliation then it would seem clear that the aforementioned

facts, if proven, strengthen the argument that each bears some responsibility for that final decision. The relationships between the manufacturers and their knowledge of how the product was to be deployed add to the strength of the argument that they cannot easily separate themselves into fragments for the purpose of causation. Whether or not the aforementioned facts do or do not amount to concerted action they are clearly a predicate for the proposition that the breach of the duty to warn cannot be isolated.

Finally, and as a separate argument, plaintiffs note that several defendants had specific knowledge not only of the dioxin contamination of their own product but of the rather substantial problems that other defendants had with the dioxin content in their product. So much so that defendants were called together to discuss the problem. The government was the conspicuous uninvited guest to that meeting. Once the defendants became aware of the problems that existed with regard to the manufacture of dioxin contaminated Agent Orange the question is did they have a duty to warn the government not only about their own product but the problems that were being faced industry wide. An argument could be made, given the long standing relationships between such defendants as Dow and Hercules with the government, that even if they had decided not to manufacture and sell Agent Orange to the government they would have had a duty to disclose to the government the information that they had

discovered about the products of other chemical companies were manufacturing the product at a highly toxic level. The relationships between these defendants and the government was not that of pure strangers. This is not the classic case of a stranger who refuses to come forward and rescue another. Long standing relationships in which the parties have come to trust each other's judgment may be a predicate for the imposition of an affirmative duty to act. See, e.g. Prosser, Wade and Schwartz, Cases and Material on the Law of Tort, pp. 440-442 (Seventh Ed. 1982). Relationships having far less moment have been held to trigger a duty to act affirmatively. See, Connelly v. Kaufmann & Baer Co., 349 Pa. 261, 37 A. 2d 125, (1944); Parvi v. City of Kingston, 41 NY2d 553, 344 NYS2d 161, 362 NE2d 553 (1977); Hutchinson v. Dickie, 162 F. 2d 103 (6th Cir. 1947).

However, this case is not one where defendants were uninvolved in the manufacture and sale of Agent Orange. They were selling to the government and were looked to by the government as the most important source of information with regard to herbicides. Dean Prosser has noted that the imposition of a duty is a matter of good common sense:

> "It should be understood at the outset that there is no magic in 'duty'. It is merely a word with which the court states its conclusion that there is no liability; and it means whatever the court wants it to mean in the particular case. No general formula ever has been devised to state when there is, and when there is not, a duty in negligence cases; and it is very likely that none will ever be. This is because consideration of social policy vary depending on the precise issue

before the court and social policy questions always underlie the duty issue." Prosser, Wade and Schwartz p. 404 (Sixth Ed. 1976)

The court thus must determine whether the conditions in this case support the imposition of such a duty. We believe that given the relationship between the government and the defendants, the high foreseeability that danger to hundreds of thousands of soldiers would result if the information was not shared, the common use of the Agent Orange in Vietnam through indiscriminate mixing, and the highly specialized knowledge that existed within the chemical industry that a duty to inform the government of the other defendant's problems is established beyond peradventure. When one adds to this the "take charge" aspect of Dow and other defendants with regard to the information that was to be disseminated and the attempt to jealously guard it from public view, the duty issue simply disappears. Once a defendant has decided not to stand aside but to act affirmatively, the duty to act reasonably under the circumstances is firmly established. Restatement (Second) of Torts Sec. 32; Parvi v. City of Kingston, 41 NY2d 553, 362 NE2d 960 (1977).

The implications for the causation issue once a duty has been established to warn the government of the dioxin contamination that existed in other defendants' products is obvious. If the duty to warn is as we have set forth, then there can be no argument that responsibility should be limited to the individual defendant. By hypothesis the breach of the

duty to inform the government was specifically directed to the highly toxic product of a co-defendant. It was that very product which was deployed in Vietnam. There is thus no causation issue left to decide. The very product which caused the harm was allowed to be deployed because the defendants not only failed to warn of the dangers which were indigenous to their product but that which the entire industry was selling. Once the duty issue is resolved causation is resolved as well. Each defendant who did not reveal that which it should have revealed bears direct responsibility for the harm caused by the product of the other defendants which they knew to be more highly toxic then their own.

Should the Court require still further grounds for holding the defendants jointly and severally liable, however, ample such grounds exist under any or all of the theories of concerted action, enterprise liability and alternative liability, discussed seriatim below.

A. The ~~Facts and Circumstances Warrant Application of~~ the Concerted Action Theory as a Basis for Defendants' Joint and Several Liability

Concerted action among two or more defendants resulting in injury to a plaintiff is a fact situation under which joint and several liability has historically been imposed. Hall v. E.I. DuPont de Nemours & Co., Inc., 345 F.Supp. 353, 371 (E.D.N.Y. 1972);

1 Harper & James, The Law of Torts §10.1 at 697-98 (1956); Prosser, Joint Torts and Several Liability, 25 Calif. L.Rev. 413, 429 et seq. (1937); See also In re Beverly Hills Fire Lititgation, Civil Action No. 77-79, Order 215, p.8 (S.D. Ohio, filed November 14, 1979) (Order attached as Exhibit 16 ; hereinafter referred to as "Beverly Hills"). The elements of the concerted action theory are prescribed in Section 876 of The Restatement of Torts, which provides in part as follows:

> For harm resulting to a third person from the tortious conduct of another, a person is liable if he . . . (b) knows that the other's conduct constitutes a breach of duty and gives substantial assistance or encouragement to the other so to conduct himself, or (c) gives substantial assistance to the other in accomplishing a tortious result and his own conduct, separately considered, constitutes a breach of duty to the third person.

With respect to this theory, Prosser states that:

> "(T)hose who, in pursuance of a common plan or design to commit a tortious act, actively take part in it, or further it by cooperation or request, or who lend aid or encouragement to the wrongdoer, or ratify and adopt his acts done for their benefit are equally liable with him. (P) Express agreement is not necessary, and all that is required is that there be a tacit understanding . . ."

Prosser, Law of Torts §46, p.292 (4th Ed. 1971); See also Sindell v. Abbott Laboratories, 607 P.2d at 932 (Quoting Prosser);

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and Hall v. DuPont, 345 F.Supp. at 371 (Quoting Prosser).

Three elements are necessary to prove a case of joint and several liability for concerted action in a products liability case:

First, plaintiffs must establish a causal relation between the plaintiffs' harm and the targeted defendants.

Second, the plaintiffs must prove that defendants in the group participated by cooperative or concerted activities to cause this harm.

Third, plaintiffs must show that the defendants in the group have by their actions or omissions contravened a legal standard of care. See Hall v. DuPont, 345 F.Supp. at 371; Beverly Hills, Order at pp. 8-9.

Expanding upon these elements somewhat, and considering them each in turn, it is clear from the Sindell and Hall cases that plaintiffs are not required as part of their proof of causation to identify the injury-producing party. In Hall v. DuPont, for example, the Court noted that "the issue of who 'caused' the injury is distinctly secondary to the fact that the group engaged in joint hazardous conduct." 345 F.Supp at 372.

Of course, the plaintiffs must still identify the injury-producing product, but under the concerted action theory, the tortious event is considered to be the express or tacit agreement among the defendants to commit a culpable act. Beyond identifying the injury-producing product, plaintiffs must only

show that each defendant was a substantially contributing factor in producing, promoting and placing the defective product into the stream of commerce. Sheiner, DES and a Proposed Theory of Enterprise Liability, 46 Fordham L.Rev. 963, 983 (1978). This proof links the harm done to a particular defendant. Thus, the fact that a specific injury-causing party is unknown does not prevent a plaintiff's recovery. Beverly Hills, Order at pp. 10-11.

To establish that defendants are a substantial factor in plaintiffs' injuries, therefore, it is necessary for plaintiffs to show that all defendants in the group manufactured and promoted similar defective products. Id., at p. 11; Hall v. DuPont, 345 F.Supp. at 374.

By placing a defective product into the stream of commerce and promoting it, the manufacturer increases the public usage of the product. This, in turn, compounds the chance of injury caused by the product. Thus, each defendant who produced and promoted the defective product in concert with others shares in the responsbility for plaintiffs' injuries. Id.

Under the facts and circumstances of the present case, it is evident that if plaintiffs can identify Agent Orange as the defective and injury-producing product, and further establish concerted action among the defendants with respect to its production and promotion and to failure to warn the government

of the risks attending its production and use, then there will be little if any remaining question regarding causation. No defendant disputes, for example, that it supplied Agent Orange to the government during the relevant period. We will turn our discussion, therefore, to the more substantial matter of concerted activities.

In addition to satisfying the causation requirement, plaintiffs must also establish that the targeted defendants acted by cooperative or concerted activities before the theory of concerted action will be imposed. Hall v. DuPont, 345 F.Supp. at 371; Beverly Hills, Order, p. 11.

Generally, all this means is that there must be at least some tacit agreement or understanding among the defendants. Prosser, Law of Torts, §46 at 292. In the products liability arena, and in this case, the tacit agreement or understanding among the defendants must be to market and promote a defective product, or to fail to warn of undue risks or dangers known to or foreseeable by them. Beverly Hills, Order at p. 13; Hall v. DuPont, 345 F.Supp. at 372.

The preceding factual materials, together with the Exhibits attached to this Memorandum, clearly establish the existence, not just of concerted activity or tacit agreement, but of an actual, ongoing and pervasive conspiracy among the defendants to market and promote Agent Orange, a product known

by them to be dangerous and defective, and to actively conceal such dangers and defects from both the government and the general public. The evidence further discloses substantial sharing among the defendants of information relating to the risks and dangers attending the production of and exposure to Agent Orange.

To briefly recapitulate some of this substantial evidence of conspiracy and cover up, the plaintiffs would direct the Court especially to the long history of industrial accidents involving Agent Orange-related materials; Dow's 1963 misrepresentation to the military that it was unaware of any problems associated with the production or use of Agent Orange; the March 24, 1965 conference among the defendants at Dow headquarters in Midland, Michigan, at which the defendants were all in attendance or upon which they were briefed; the N.A.C.A. task force formed by the defendants to study the production methods and effects of exposure to Agent Orange-related products; the Ad Hoc Committee formed by Dow and Hercules to, in effect, lobby the government in favor of Agent Orange-related products; the Boehringer agreement; the sharing among the defendants of analytical and dioxin detection knowledge; Dow's sampling and testing of other defendants' products, and reporting to them of its results; the withholding from the government of effective analytic techniques for testing for toxic contamination of Agent Orange, despite the knowledge that the government's techniques were insufficient; the successful drive by the defendants to

claims, this element will not be discussed at length here. Plaintiffs would only refer the court here to the somewhat novel aspects of their failure to warn claims, discussed more fully in Section VI of this Memorandum above. In other respects, their product liability claims parallel those in the more typical products liability case. Suffice it to say that, for present purposes, the matter of the defendants' breach of some applicable standard care, whether that standard be of strict liability, negligence, or conduct warranting imposition of punitive damages, will not be a stumbling block to imposing liability upon the defendants under the theory of concerted activity.

The plaintiffs have therefore alleged and substantiated an ample basis for invoking the concerted activity liability doctrine against the defendants, and for holding them jointly and severally liable to the plaintiffs.

B. The Facts and Circumstances of this Case also Warrant the Imposition of Liability Upon the Defendants Under the Theory of Enterprise Liability

The facts and circumstances of the present case also warrants application of the theory of enterprise liability as a means of bridging the gap of causation between the injury-causing product and the particular defendants.

Enterprise liability blends the theories of concerted activity, discussed supra, and alternative liability, discussed infra, although it is based primarily on the latter of these. Sheiner, supra, 46 Fordham L.Rev. at 974:

> "Under enterprise liability, the plaintiff must prove there is a high probability that (his) injury was caused by the tortious behaviour of some one of the defendants—a modification of alternative liability. In addition, (the plaintiff) must show that defendants concertedly adhered to a dangerous, industrywide safety standard in their manufacture of the injury-producing product. Evidence of these two elements will shift the burden of proof on causation to the defendants.
>
> Enterprise liability would impose joint and several liability in a situation which occurs with increasing frequency in our highly industrialized society. Fungible products with delayed and dangerous effects cause injury, but the instrmentality and agent producing the specific injury are unidentifiable.[36]" Id.

The theory of enterprise liability was suggested by the Court in Hall v. DuPont, 451 F.Supp. 353.

The theory of enterprise liability proceeds from a determination of fairness: as between an innocent victim and members of an industry who are negligent or who have joint control of the risks, the latter should bear the cost of the injury. Enterprise liability is proposed as an equitable method of allocating these risks in a manner both affording the plaintiffs an opportunity to recover and protecting the defendants against unjust loss.



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In the Fordham Law Review article, Schiener suggests seven requirements for imposition of enterprise liability. These requirements are as follows:

1. There existed an insufficient, industry-wide standard of safety as to the manufacture of the product.

2. Plaintiff is not at fault for the absence of evidence identifying the causative agent, but rather, this absence of proof is due to defendant's conduct.

3. A generically similar defective product was manufactured by all the defendants.

4. Plaintiff's injury was caused by this defect.

5. Defendants owed a duty to the class of which plaintiff was a member.

6. There is clear and convincing evidence that plaintiff's injury was caused by a product made by one of the defendants. For example, the joined defendants accounted for a high percentage of such defective products on the market at the time of plaintiff's injury.

7. All defendants were tortfeasors.

Scheiner, supra, 46 Fordham L.Rev. at 995. Once plaintiffs prove these things, the burden of proof as to causation shifts to defendants, each of which can exonerate itself only by showing that its product could not have been the one which injured the particular plaintiff. Id.



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Plaintiffs submit that each of these seven requirements are met here, and ~~that imposition of enterprise liability upon the defendants is therefore proper~~.

First, there was no real industry standard of safety for the manufacture, testing and use of Agent Orange-related products. Certainly, knowledge of the danger of dioxin contamination was there, as was the technological ability to detect and reduce the magnitude of its incidence. But these cannot be considered "standards" in any real sense, for the reason that the defendants largely ignored them. Even those defendants who apparently did make some efforts to monitor and reduce the incidence of dioxin contamination in their products cannot be considered to have formulated or adhered to an adequate standard of safety, for the evidence suggests that any level of dioxin contamination can have serious effects when exposure is prolonged or repeated. And for the infantry in Viet Nam, prolonged, repeated exposure was probably the norm. No ~~adequate standard of safety therefore existed~~.

Second, the plaintiffs are not at fault for their inability to pinpoint which defendant, or defendants caused their specific injuries. This inability is due, rather, to the manner in which Agent Orange was distributed to and utilized by the government. Whether or not the defendants are at fault in this regard, as between plaintiffs and defendants, the latter should bear this risk. See, e.g., Sindell v. Abbott Laboratories, 607 P.2d at 936.

Third, the requirement that a generically similar defective product be manufactured by all the defendants is met in this case. All the defendants manufactured generically similar Agent Orange-related products; all of their products suffered from dioxin contamination to one degree or another; none of the defendants labeled their containers, making it impossible to tell one defendants' product from another's once delivered into the government's possession; and the government in fact treated the products generically, mixing the products indiscriminately. ~~The requirement of a generically similar defective product is therefore met.~~

Fourth, there is substantial evidence both that plaintiffs' injuries were caused by the dioxin contaminated Agent Orange, and that the government utilized this contaminated product in consequence of the ~~defendants'~~ failure to warn. ~~The fourth requirement is therefore met.~~

Fifth, as discussed more fully above, the defendants both owed and breached their duty of care to the plaintiffs, those ultimately and foreseeably exposed to Agent Orange, in failing to remedy or warn of the known dangers of dioxin contamination. The fifth requirement of enterprise liability is therefore satisfied.

Sixth, there is clear and convincing evidence that the plaintiffs' injuries were caused by a product made by one of the defendants. Exhibit 1 to ~~this Memorandum~~ establishes that

defendants accounted for over 99% of the Agent Orange market, both in terms of gallons and dollars sold. This case is therefore distinguishable from Sindell, in which the Court declined to apply either enterprise or alternative liability theories because of the absence as parties of significant members of the affected industry, and the sixth requirement of enterprise liability is easily met,

Seventh, all defendants are tortfeasors in the present case. All of them manufactured defective products; all of them knew the others' products were similarly defective; all of them knew the government and the public were unaware of the existence of the defects; all of them knew the government relied upon their collective and individual representations as to the product's safety; yet none of them effectively eliminated or warned of the known defects, as a consequence of which the plaintiffs were injured.

Thus, all of the requirements for imposition of enterprise liability outlined by Scheiner have been met in the present case. Considerations of fundamental fairness require that the culpable defendants, having control of the risks, and not the innocent plaintiffs, bear the consequences of plaintiffs' inability to identify with specificity the defendants which caused their respective injuries. Imposition of enterprise liability upon the defendants fulfills such considerations of fundamental fairness, and application of enterprise liability in this case is therefore warranted.

C. THE FACTS AND CIRCUMSTANCES OF THIS CASE ALSO WARRANT THE IMPOSITION LIABILITY UPON THE DEFENDANTS UNDER THE THEORY OF ALTERNATIVE LIABILITY.

One final theory of liability advanced by the plaintiffs is that of alternative liability. The theory of alternative liability applies "where negligence on the part of [several] defendants is clear, and it is only the issue of causation which is in doubt, so that the choice must be made between letting the loss due to failure of proof fall upon the innocent plaintiff or the culpable defendants." Prosser, Law of Torts, §41, p. 243 (4th Ed. 1971). The theory of alternative liability is adopted in Section 433 B(3) of the Restatement of Torts, which provides that:

> Where the conduct of two or more actors is tortious, and it is proved that harm has been caused to the plaintiff by only one [or more] of them, but there is uncertainty as to which one [or more] has caused it, the burden is upon each such actor to prove that he has not caused the harm.

Thus, as under the enterprise liability theory, where the alternative liability theory is applicable, the burden of proving causation shifts to the independently acting defendants.

The classic case applying the alternative liability theory is Summers v. Tice, 33 Cal. 2d 80, 199 P. 2d 1 (1948). In Summers, the plaintiff was injured when two hunters negligently shot in his direction. It could not be determined which of them had fired the shot which actually caused the injury

to the plaintiff's eye, but both defendants were nevertheless held jointly and severally liable for the whole of the damages. The California Court reasoned that both were wrongdoers, both were negligent toward the plaintiff, and that it would be unfair to require plaintiff to isolate the defendant responsible, because if the one pointed out were to escape liability, the other might also, and the plaintiff-victim would be shorn of any remedy. In these circumstances, the Court held, the burden of proof shifted to the defendants, "each to absolve himself if he can." Id., p. 86, 199 P.2d p. 4. The Court stated that under these or similar circumstances a defendant is ordinarily in a "far better position" to offer evidence to determine whether he or another defendant caused the injury, or, if not, then as between the defendants and the innocent plaintiff, it is the former who should bear the consequences of any lack of evidence concerning causation.

Relying principally upon the ruling in Summers, the Plaintiffs in Sindell v. Abbott Laboratories likewise sought to impose alternative liability upon the defendants for their manufacture of the defective product DES. The District Court, however, rejected plaintiffs' claims in this regard and refused to apply the theory of alternative liability upon the facts before it, distinguishing the holding in Summers from the case before it as follows. In Summers, all the parties who were or could have been responsible for the harm to the plaintiff were joined as defendants. In contrast, the Plaintiffs in Sindell,

named only five of the approximately two hundred manufacturers of DES as defendants. Thus, while on the one hand, there was certainty in Summers that the defendant who actually caused plaintiff's injury was among those to be held jointly liable, and a fifty percent probability that either of the defendants was responsible for plaintiff's injuries, on the other hand, there was no rational basis in Sindell upon which to infer that any of the five named defendants caused plaintiff's injuries, since any one of the two hundred companies which manufactured DES might have made the product which injured the plaintiff. Accordingly, the Court in Sindell refused to apply the theory of alternative liability.

The clear implication of the Court's analysis in Sindell is that if the market in that case had been smaller and more cohesive, and if all or practically all potentially liable manufacturers had been joined as defendants, the case would have fallen squarely within the holding in Summers v. Tice and the theory of alternative liability would have applied. In this regard, the present case is far more analogous to the situation in Summers than in Sindell, for here, virtually all potentially liable manufacturers are named as defendants. As in Summers, the question in this case is simply which of the named defendants caused plaintiff's injuries. Unlike the situation in Sindell, the possibility that the named defendants will be held liable for the acts of those outside the group and not named as defendants

is remote to non-existent. For the foregoing reasons, therefore, application of the theory of alternative liability is warranted and the defendants may be held jointly and severally liable on such grounds.

At the least, the factual ~~matter~~ issues relevant to the alternative liability theory are in dispute in the instant case. Thus, whether it is joint and several liability (Hall) or ~~a~~ enterprise liability (Sindell) or ~~joint~~ alternative liability (Summers), the existence of seriously disputed issues of material fact precludes the granting of the defendants' demurrer and summary judgment motions.

is remote to non-existent. For the foregoing reasons, therefore, application of the theory of alternative liability is warranted and the defendants may be held jointly and severally liable on such grounds.

At the least the factual issues relevant to the alternative liability theory are in dispute in the case. Thus, whether it is joint and several liability (Hall) or enterprise liability (Sindell) or alternative liability (Summers), the existence of genuinely disputed issues of material fact precluded the granting of the defendants' demurrer and summary judgment motion.

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## CONCLUSION

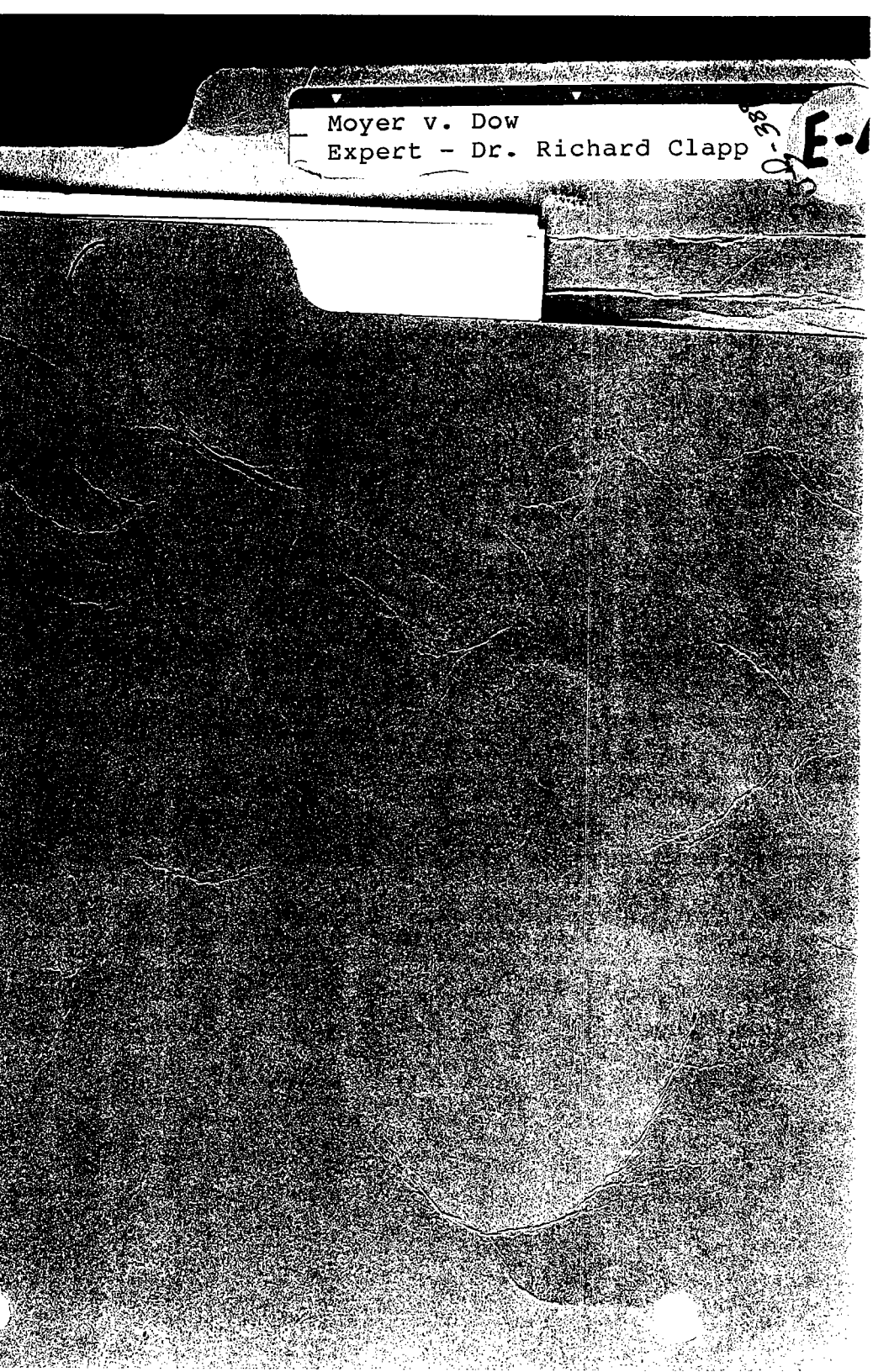
The reasons for defendants' conduct are not yet fully clear. Was their failure to act as they should have due to a desire to maximize profits?

What additional costs, if any, were necessary to eliminate the dioxin contaminant from their product? Why didn't defendants who had cost plus contracts with the military, spend whatever sums were necessary to eliminate the dioxin from their products?

The discovery that remains to be completed may answer these questions. What is clear, however, is the "cover up" mentality that pervaded defendants' activities during the Vietnam era, and well beyond.

We append hereto as Exhibit 15 , a letter dated September 15, 1977 from the President of Dow Chemical to all Dow U.S.A. supervisors. The letter speaks for itself and provides further evidence of the continuing conspiracy of silence. That letter states the fundamental corporate position with respect to its responsibility to outsiders, to a great portion of whom that company sells products for profit.




Moyer v. Dow
Expert - Dr. Richard Clapp
E-1

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Recorded Statement of Dr. Richard Clapp

Schuler: This is Richard Schuler, it's August 27th, 1993, I'm on the telephone with Dr. Richard Clapp. Dr. Clapp, do I have your permission to to record this?

Clapp: Yes you do.

Schuler: Okay, now, uh you were going to tell me about some comments with regard to the recent material I sent to you.

Clapp: That's right. It was a Federal Express package dated August 18th but it was the transcript of Kenny Crump's deposition that was in Moyer v. Dow and I don't see the date here on the deposition but I think you know which one I'm talking about.

Schuler: Right. It's the only one.

Clapp: Okay. Um, the first thing is this question about the potency factor calculating on page uh thirty-six, line twelve. You asked him about a calculation of a cancer potency factor.

Schuler: Okay.

Clapp: Which he had done. Um, and let's see if I can get the little page earlier if he says what it's for. Um, well in any case, I think it's important when he uses his cancer

potency factor which isn't here in the deposition, uh to know exactly which it is and how it differs from the potency factors used both by the EPA and by the Agency for Toxic Substances and Disease Registry for Dioxin. Here, I think we're talking about Dioxin. And uh,

Schuler: Okay.

Clapp: Those agencies both have cancer potency factors that they've used and have been peer reviewed and have become, you know, part of the um the database on which prudent findus would rely, I would say.

Schuler: Okay.

Clapp: And so, uh, that I think you might ask does he know what the EPA and the ATSDR potency factors are and why his is different.

Schuler: Okay, that's the EPA...

Clapp: Yeah,

Schuler: What was the other agency again?

Clapp: It's, the initials are A-T-S-D-R.

Schuler: A-T-S-D-R.

Clapp: Right. I think they actually just incorporate the EPA's but they both put out statements about the toxicity of or the carcinogenicity of uh Dioxins that I think are different from Dr. Crump's.

Schuler: Okay.

Clapp: I mean this is just my suggestion, you may not need to bring this up.

Schuler: No, I think that's a good suggestion.

Clapp: Okay, and then on page forty-one, there's a reference to somebody that he had worked for or reported to at the Council of Environmental Quality and he gives the name David Bermaster, spelled, B ..line eleven, B-E-R-M-A-S-T-E-R. I think that's actually David Bermaster spelled B-U-R-M-A-S-T-E-R, who's a friend and colleague here in Boston.

Schuler: Okay.

Clapp: So if there's anything that, um, you needed to know about Dr. Crump's work for David Burmaster,

Schuler: Okay.

Clapp: I could find it out or you could find it out.

Schuler: Okay, that's good to know.

Clapp: Um, and that's also on this question of carcinogenicity.

Schuler: Carcinogenicity, okay.

Clapp: Um, let's see, this case in Colombia, South Carolina I believe if I'm working for the plaintiff's firm, you should know in that same case, this is on page forty-three,

Schuler: Okay.

Clapp: Uh, and he's working for the defendant's, in Colombia, South Carolina, their issues are trichloroethane in water.

Schuler: Okay.

Clapp: Um, let's see what else I found here. I think we talked earlier about Dr. Schultz. He refers several times to Dr. Carl Schultz who is another industry guy that I run across.

Schuler: Right, well I've taken his deposition in this case,

Clapp: Oh, you have, I see.

Schuler: yeah, and I think you should have that. I feel virtually certain I sent it to you.

Clapp: Maybe you did. Yeah, I didn't bother go back to look through that stuff but probably you did.

Schuler: Yeah.

Clapp: There's a couple of references to a Dr. Squire and one of them is on page fifty-one.

Schuler: Okay.

Clapp: And then later I think it actually comes up again. I'm not going to be able to find the second reference, but Dr. Squire, this actually is a key thing I think, Dr. Squire re-analyzed slides from an animal test done by a man named Kociba, K-O-C-

I-B-A.

Schuler: Right.

Clapp: And it's a real serious question about what was done in that re-analysis and I think that certainly the the pathologist that I know, and there is a guy I know who is a pathologist,

Schuler: Okay.

Clapp: who's looked at Squire's re-analysis..and he thinks it was improperly done. And that for one thing it included uh re-designating some slides as um non-tumors that were first designated as tumors and the re-analysis was suppose to only include designating things that were considered sort of premeoplastic lesions as non-tumors.

Schuler: Okay.

Clapp: So it went beyond the scope of the re-analysis as it was laid out and it raises the question as to why the did that. They weren't even suppose to be looking at that second group of slides, um and I think that, itself, has not really been accepted the Kociba, uh sorry, excuse me the Squire re-analysis has not been accepted broadly as an appropriate re-analysis of the Kociba, um findings...

Schuler: Okay.

Clapp: by the general scientific community, it's only the industry side that says that uh Squire re-analysis is what you should rely on.

Schuler: Oh, I see.

Clapp: I certainly wouldn't and I don't not that you're asking me to. I'm not a toxicologist, but I think that if there I were a toxicologist in this case that you had gotten, they would probably say the same thing. So I think it's, maybe again it's worth your knowing that Squire's re-analysis is not the all and end-all on this question of how toxic uh TCDE is to animals.

Schuler: Okay. Yeah, that is important.

Clapp: Crump seems to rely on that heavily.

Schuler: Okay.

Clapp: Uh, let's see what else I have here this is not the way you wanted to spend the last hour or two of your work day, but.

Schuler: Oh, no, no. no, that's quite all right. I'm going to be here for a while longer, so uh. I like to get things done.

Clapp: All right.

Schuler: No, I'd rather be fishing, but uh [laugh], or playing golf I guess.

Clapp: Yeah, there you go. I think it's probably hotter

here than it is where you are I think it's ninety-five in Boston today.

Schuler: Yeah it's hotter [laugh] than here, it's about eighty-eight here I think...it's still pretty warm though [laugh].

Clapp: Yeah, that's true. So we'll wait till the sun get's a little lower before we go out to the golf

Schuler: That's right [laugh].

Clapp: Uh let's see, there was some back and forth on page eighty-four. You were sort of, it looked like, about to nail down where he got his exposure as to whether it was a sprayer or as a driver and he finally said he received all of that exposure while they were spraying and I think there's something inconsistent in there and I urge you to, um, have Mike Ellenbecker look at that. I think there's something, if it's through what he says in there I think there making some inconsistent assumptions, either he or Nick, one of the two.

Schuler: Okay, I going to, um, I think I've already sent or it's in the process of being sent that same package to Ellenbecker, yeah, this exposure.

Clapp: And also on page, this is a very small point but on page one hundred five, he said he thinks anastrosarcoma is a soft tissue sarcoma but he's

not a hundred percent sure,

Schuler: Un, hun.

Clapp: It's not. He's a hundred percent wrong actually about that.

Schuler: Okay.

Clapp: Um, and that's probably not a major point on his side either itjust happens to be a factual error.

Schuler: Okay.

Clapp: This stuff about his risk assessments and the parts you know the uh, the uh risk assigned ten to the eighteen or whatever the heck he comes up with

Schuler: Yeah.

Clapp: It's all, in the deposition it's all impenetrable to me, I'm sure the pages where he lays it out are where the numbers are, but, uh at some point somebody should look at those numbers because I think they're absurdly low ... the risks that he estimates are absurdly low.

Schuler: Well the, wasn't there attached to what I sent you a copy of um of his numbers?

Clapp: No.

Schuler: Okay, well let me, I will send you, send a copy of Crump analysis exhibits to Dr. Clapp, okay. You did have some papers there, preliminary though,

supposedly they were that lay these numbers out...

Clapp: Right.

Schuler: that I can send to you.

Clapp: I'd be curious to see them because it's, you know, amazing to me that he's making such statements.

Schuler: Yeah.

Clapp: Um, yeah here's the second reference to the Kociba studies it's on page one twenty-two, and um, again their using these life-time risks of cancer based on the Kociba studies...

Schuler: Right.

Clapp: and I assume that means the re-analysis of this Kociba study by Squire, which I think is faulty.

Schuler: Okay.

Clapp: So if his risk assessment these life-time risk calculations are resting on that on Squire's re-analysis of the Kociba studies as he seems to be saying on page one twenty-two at the bottom, then I think he's on a house of cards or whatever foundation I'm saying cause I think that the Squire re-analysis has been picked apart as not valid.

Schuler: Okay.

Clapp: Um, and also the assumptions about numbers of stages of the carcinogenic process I think also

there there would be plenty of room for argument about that the way he lays it out.

Schuler: The wah he analyzes it.

Clapp: Yeah. Uh, I guess I think those are the main things that I really say the sort of key point is this Kociba stuff and the degree in which he relies on it, I think is very vulnerable there.

Schuler: Okay. Well I'll go back and when I do my own adaptation and when I get ready for his remaining part, his deposition I'll load up in that area...

Clapp: Yeah.

Schuler: and see what I can get at 'em.

Clapp: Yeah, I can send you some, by then, whenever it is I think even if it's now or when..

Schuler: It's not going to be until, you know, either mid-September or October so it's a ways off.

Clapp: By then there may be a new report out from the EPA on their reanalysis of Dioxins that that deals with this question of Kociba and uh re-analysis of Squire by Squire. If that's available I'll send it to you. You can use it.

Schuler: Oh, I would love it.

Clapp: .. let you even use it. It's in draft now, I have the draft you know the EPA stamps it not for situation or quotation but if it's in final form

you could read it right into the record cause it will be, I think, a contradiction to what um Crump was saying.

Schuler: Yeah, oh I'd love to see that.

Clapp: Okay.

Schuer: Uh, maybe you could even send me a copy of the draft.

Clapp: Yeah, I will.

Schuler: I've got, I actually do have the draft of that EPA that nine-volume or ten-volume assessment, is it in there?

Clapp: Yeah, it would be in the "Dose Response" chapter.

Schuler: Okay, all right. When did you say they're going to come out with the final one?

Clapp: The final version of the Chapter Seven of that is being reviewed on September 7th, and I think, you know, whatever the Federal Register says thirty days after that their suppose to have the final.

Schuler: Okay.

Clapp: Of that chapter and then these other chapters are coming in different times but the whole thing is all delayed but it's due to be done by the end of this year.

Schuler: Okay.

Clapp: And that's going to help our side.

Schuler: Yeah, I noticed that the, what is it, the uh National Science Foundation, was that it?

Clapp: National Academy of Sciences.

Schuler: National Academy of Sciences, yeah.

Clapp: They come out strongly on soft-tissue sarcoma.

Schuler: Yeah, they really did.

Clapp: That's their number one cancer actually for the Agent Orange and Dioxin contamination. Um and the guy who wrote that chapter said that you know even since we had done our Vietnam Veteran's report in 1990 a lot of new stuff has come in that just strengthens the case, so it gets stronger all the time actually on soft-tissue sarcoma. That's what he said and that's what the report reflects I think.

Schuler: Yeah I think it does too and it seems to me what this case is boiling down to and I anticipate getting a trial date, I thought we were going to get one in September but they switched judges on us at the last minute and uh so this judge is telling me that we got to move to set it and I have moved to set it and now he's telling us we'll probably get a trial date in the spring so I anticipate a trial date this spring and I'm sticking to this as hard as I can because I need

to get this case tried.

Clapp: Right.

Schuler: You know it's just been around too long, Bob's passed away and his widow, you know, really could use the help so.

Clapp: Yeah.

Schuler: I'm um, I'm really leaning on trying to get this case wrapped up and uh you know Dow has taken the position .. they wrote me a letter or I guess or solicited a demand from me of some months ago, I sent them a demand I sent them demands earlier so I renewed my demand and I got the recent medicals in which were like seven or eight hundred-thousand dollars in medical expenses and sent them up their and they asked me if I wanted to mediate this case and I said fine if you're willing to do it and then they know I've never heard from them so they... I don't know whether it's a communication problem with... I don't know if this is the way they usually are in cases cause they seem to, they seem to say one thing in one moment and then they change their mind or they go the other direction in another moment.

Clapp: No.

Schuler: Uh, you probably had more experience in cases with

them then I've had but..

Clapp: Right, well it always seems like there's different law firms involved at the local level and then perhaps Dow Corporate law office gets involved and changes things that the local people are trying to set up.

Schuler: Yeah. That -- that's one of my impressions. That may be happening.

Clapp: Yeah.

Schuler: Cause I knew, I know they do have some kind of guy inside, some kind of house counsel that's monitoring this..

Clapp: Yeah.

Schuler: but, uh, it just makes it tough to you know to take the for their worth..

Clapp: Right.

Schuler: And they probably do that by design I guess, like to..

Clapp: Yeah, that's my impression of these guys. The Dow people and then [inaudible] is even worse. Their involved with another set of pesticides.

Schuler: Yeah,

Clapp: They're completely un-trustworthy.

Schuler: Yeah. And I noticed that...were you involved in that case up in Canada with the soda, the Sprayers

of Dioxin Association?

Clapp: No. I know about it, but I wasn't personally involved in it.

Schuler: Yeah.

Clapp: I met Jerry White for example and ..

Schuler: Oh did ya?

Clapp: Yea.

Schuler: Cause I had conference with Jerry. I went up there and went through a lot of their documents and everything.

Clapp: Yeah.

Schuler: They settled that case I understand..

Clapp: Right..that's my understanding too.

Schuler: Did you hear anything about the settlement or what their..

Clapp: I didn't, I think what and woman who told me was Jane Saganoff, do you know her? She's a uh, she works with Barron and Bud and I think I might have given you her name because of some other expert that she had deposed a juror facing [inaudible]

Schuler: Yeah, I don't recall talking with her, but uh..

Clapp: She had hear about the settlement and she I think said that it was a substantial settlement. I can't remember the dollar she mentioned the dollar amount. Uh, but Jerry White, you know, he wanted

more. He wanted people to go to jail or something.

Schuler: Oh, yeah, yeah. He wanted New Brunswick Power Corporation. They were funding the case because they reached a preliminary settlement with them and part of the settlement was that they would fund the case against Dow.

Clapp: Yeah.

Schuler: and the manufacturer. So they had like ah, an unlimited pocket there. Their lawyer, they apparently can't have contingency fees in Canada so their lawyer was charging by the hour and had burned up an incredible amount of legal fees I know that, I remember I was really surprised and uh, but he wanted, even though New Brunswick was funding this thing, he really had an ax to grind with the power corporation.

Clapp: Yeah.

Schuler: I guess because that was the local target and

Clapp: That was, I guess his disappointment was that he didn't get somebody behind bars as a result of all this.

Schuler: Yeah, yeah.

Clapp: But, uh, I don't know. Personally I think some of these families got some help and that's a pretty

good settlement.

Schuler: Yeah, that's enough. All right.

Clapp: So that's all I could... **THE END**

MOYER v. DOW

ANNOTATION OF DEPOSITION OF RICHARD W. CLAPP
TAKEN ON APRIL 17, 1992

4/12 My profession is epidemiology with emphasis on community environmental exposures and diseases.

4/17 Epidemiology is the study of the patterns of diseases and the causes of diseases, usually in humans.

5/2 Maybe the term is "environmental epidemiology" and the source of exposure would be from something in the air or in the water, or in some cases it would be the workplace or where people live.

5/7 C.V. marked as Exhibit No. 1.

7/6 I'm employed by John P. Snow, Incorporated which is a public health consulting company; primarily government contracts in the area of child health, family planning, AIDS prevention; and in my group, environmental health.

7/20 About a third of my personal work is involved with litigation support.

8/2 My work is primarily for plaintiffs and occasionally for government agencies.

8/16 I was contacted by Mr. Schuler, I'm guessing it was a year ago last fall.

8/19 I was asked to review the epidemiologic literature about exposure to herbicides and their contaminants and this cancer, soft tissue sarcoma.

9/3 I have been asked to render an opinion as to scientific causation. I am not a medical doctor, so I will not be rendering an opinion about the cause of Mr. Moyer's disease.

9/15 There is significant evidence in the literature. The weight of the evidence in the literature supports the association between specific herbicides and their contaminants and soft tissue sarcoma.

10/5 I am not in a position to say that as a result of being exposed to herbicides while working for Orange County, that Mr. Moyer now suffers from soft tissue sarcoma and the resulting complications of having that disease. I think that is a medical opinion.

10/16 I recognize the list of articles that was attached to answers to interrogatories dated 1/3/92. I prepared that

list.

11/3 Other than the articles on that list, there is an exchange between Dr. Fingerhut and Dr. Collins that was in a journal called "Epidemiology" in 1992. It doesn't change my opinion. It buttresses it.

12/5 In my view, the articles on this list are the most reliable in making the determination of whether there is an association between exposure to 2,4-D or 2,4,5-T or any of its contaminants and soft tissue sarcoma.

12/8 Ranking or weighing a publication in terms of its reliability is a judgment process that involves consideration of the design of the studies, who it was they were studying, the information about the disease and the exposure, the degree they have been carefully characterized, the size of the study, how many cases were involved, and the methods of statistical analysis, whether they seem appropriate to the data.

12/22 The interpretation that the authors gave the data are of less importance, but is something that I take into consideration.

13/5 The size of the population studied is one of the important criteria.

13/13 You would tend to give more weight to the larger study that has more precision.

14/9 I think a study of sufficient size can determine scientifically an increase of as little as ten or twenty percent over an expected number of disease end points in a population.

14/16 If it is a rare disease, you might need a very large, hundred-thousand size population to show up a ten or twenty percent increase. A more common disease, say heart disease, you might be able to detect a ten or twenty percent increase in half that or less.

15/1 I was asked to pay particular attention to 2,4-D, 2,4,5-T and 2,4,5-TP, which is sometimes called Silvex, and their contaminants.

15/5 Initially, I think Diquat was on the list to consider, but that's not anything that I have been paying attention to recently.

15/12 I did not reach any conclusions with respect to the health effects of exposure to Diquat, hydrothol, Hydeout,

Roundup or Rodeo.

15/22 I believe some chlorinated dioxins have been found as contaminants of 2,4-D, and this is getting into an area that is not an area of my expertise: toxicology.

16/10 A dioxin is a chemical that has a particular structure, where it's made up of two benzene rings connected with oxygen bridges and then a number of chlorine atoms attached.

16/16 Contaminants of 2,4,5-T: in particular, an isomer of dioxin that's called 2,3,7,8-TCDD.

16/23 I don't have the specific dioxin, but there are dioxin contaminants of 2,4,5-TP as well.

17/8 Risk assessment is not within my field of expertise.

17/12 With respect to the 2,4-D specifically, I believe the literature supports the assertion that people who are exposed to 2,4-D in the context of work or other ways are at an increased risk of cancer.

18/22 My opinion assumes that there is an increased risk of cancer for those people who are exposed to 2,4-D and that there is no threshold for exposure to carcinogens.

19/2 I always assume in my work that exposure to a carcinogen always results in some increased risk of cancer.

20/6 It's basically the question of whether the studies of the human populations exposed to 2,4,5-T and other herbicides show they are at increased risks of cancer, in particular, soft tissue sarcoma. My conclusion is that there is evidence in the scientific literature that persons so exposed are at increased risks for that cancer.

20/20 I am not in a position to say how much increased risk someone has by being exposed to any particular level of 2,4,5-T.

21/2 The opinion that I have been asked to express about 2,4,5-TP is basically the same as with respect to 2,4,5-T.

21/10 When I mentioned 2,4,5-T I said soft tissue sarcoma, but I deliberately did not say soft tissue sarcoma when I talked about 2,4-D.

21/15 I think the literature suggests most strongly with 2,4-D

there is an increase for cases of non-Hodgkin's lymphoma. There is almost no situation where there is pure 2,4-D exposure without other chemicals. It's very hard to sort.

22/12 I have no opinion about cases other than non-Hodgkin's lymphoma with respect to 2,4-D.

22/16 Non-Hodgkins lymphoma and soft tissue sarcoma are two different types of cancer, but they have some important similarities. Both seem to be related to a patient's immune status.

22/22 If their immune status is suppressed in some way because of the drugs they have been taking, there is an increased risk for those patients of both of those cancers.

23/3 The epidemiological definition of "confounder" is the substance or the exposure that is associated with a disease and also with the other exposure that you are interested in.

23/13 The AIDS Virus, HIV is associated with one particular soft tissue sarcoma called "Kaposi's sarcoma."

23/18 I think immunosuppressive drugs, the types of drugs that are given to patients who have gone through a kidney transplant, for example, are at increased risk of soft tissue carcinoma.

24/1 Soft tissue sarcoma is very rare. It represents about one percent of the cancer deaths.

24/7 I think the highest rate is in children.

24/19 Currently, if you include the Kaposi's sarcoma, the highest rates of occurrence are from San Francisco. If you exclude San Francisco, there is no other area that is high.

25/17 The risks to the general population of cancer death are one out of three, roughly. That is a lifetime risk.

25/23 The risk of cancer, not cancer death, is somewhat higher than that, perhaps one out of two and a half, now. These numbers are going up. Cancer is a more frequent disease and more common cause of death.

26/7 About half a million people in the U.S. die of cancer a year. I would expect roughly one percent, or 5,000 of those to be by virtue of soft tissue sarcoma.

27/24 I would expect some portion of these 5,000 deaths to be the result of exposure to herbicides, but I couldn't tell you what that portion might be.

31/20 Say it is three per hundred thousand. Then you will need 33,000 people of our age to look at in order to expect to see one soft tissue sarcoma.

32/3 If it turned out that there were two soft tissue sarcomas out of those 33,000, you would compute what is called a relative risk of that 33,000, and it would be 2.0 So the number would be twice as many as you actually expect in that population.

32/13 There is a formula to determine whether or not that increased relative risk is simply the result of chance.

32/20 You look at the number of people and the size of the excess, and you put those into mathematical terms, and it's called a chi square result, and you see whether the chi square exceeds the level of statistical data. If it does, the probability is that the finding was a result of chance.

33/9 Before you can conclude that the increase is due to something other than chance, there are other considerations that an epidemiologist would take into account. The biological plausibility of the association, whether it is consistent with the findings from other studies, that kind of thing.

33/17 Those are the most important ones. Whether the study was properly done, and for example, the exposure preceded the disease.

33/21 The simplest definition of relative risk is the incidence of disease in an exposed population divided by the incidence of the disease in an unexposed population.

34/3 If that ratio produced a one, that would tell us that there is no difference between the incidence in the exposed and the unexposed.

34/14 I don't think there is an answer to how big the relative risk has to get before you would say there is more likely than not an association between the substance and the disease.

35/22 In order to conclude from a 1.1 an association between the substance and the disease, you would normally need a very large population.

36/2 10,000 or more I would say.

37/6 There may be studies that conclude that there is no increased risk of cancer as a result of exposure to 2,4,5-T for a particular study population. I don't believe any make that as a global conclusion.

37/12 For the particular study population in New Zealand, there may be studies that conclude no association between 2,4-D and soft tissue sarcoma.

37/15 No, I don't believe any make that particular conclusion about 2,4,5-TP.

37/19 There are a couple of articles where 2,4,5-TP is mentioned as part of the mix, but not specifically focusing on 2,4,5-TP.

37/24 The difference chemically between 2,4,5-T and 2,4,5-TP is beyond my area of expertise, but in general, there is propinic acid added to the 2,4,5-TP. It is the P molecule.

38/7 So far as I know, there are no studies on specifically whether 2,4,5-TP causes cancer.

38/14 There are studies where humans are exposed to a mix of chemicals and 2,4,5-TP is part of that mix. There are studies of 2,4,5-TP that is also contaminated with chlorinated dioxin. There are numerous studies where people are exposed to substances that include chlorinated dioxin.

39/4 The common thread with TP is dioxin contaminants which are common to other chemicals as well.

39/24 I really don't have an opinion on whether it is the dioxin that finds itself in the 2,4,5-T and not the 2,4,5-T itself that causes the increased risk of cancer. I think the two in combination, the dioxin in combination with the 2,4,5-T, and the dioxin with the contaminants.

40/4 Beyond that I don't have an opinion as to which is more important. They may be important together or they might be important individually, and I can't sort that out in my area of expertise.

41/2 My literature review leads me to conclude there is an increased risk of cancer, and specifically non-Hodgkin's lymphoma, as a result of exposure to 2,4-D. I am not in a position to say whether or not there is an increased risk of soft tissue sarcoma as a result of the exposure

to 2,4-D, or any other specific cancer.

41/14 It depends on which list you use as to how many types of cancer there are. My list is about ninety. I think that is a middle-of-the-road number.

42/3 If you are talking specifically about questions of observation or investigator bias or recall bias, I do not share those concerns or criticisms of the early works of Dr. Lennart Hardell.

42/17 My understanding of those criticisms are that they center on possible investigator bias on the patients' part, recall bias, inability to remember certain things. I believe Dr. Hardell and his colleagues adequately address those in the initial studies and in subsequent studies. I do not agree with the blanket statement that those early studies are agreed to be flawed.

43/8 In the area of the study of 2,4-D or TCDD or 2,4,5-T I wouldn't say there is any one person particularly persuasive in the epidemiological field. I definitely would include Dr. Hardell, Dr. Eriksson and Dr. Fingerhut now as three very persuasive epidemiologists.

44/4 The precise meaning of a negative relative risk is that the risk or the incidence of disease in the exposed people is lower than in the unexposed people.

45/2 I see that the largest study on this table that I am reading from, the paper "Scientific Solutions," is by Wickland and Holm. It's 3,054,620 and exposure is to a mixture, but I'd have to go back to the article to see what the mixture was.

45/10 I don't have a specific number in mind for the expected relative risk that is associated with exposure to 2,4-D. It's different for different studies. It's greater than one in the aggregate.

45/14 It's based on combining several studies where they have technically focused on 2,4-D. One in particular by Sheila Zahm. It's a 1990 article, but it was relative risk of 1.5 for non-Hodgkin's lymphoma.

46/2 I don't have a reference for the specific chemicals, 2,4-D, 2,4,5-T or TP. They are always mixed with other chemicals.

46/10 A meta-study or meta-analysis is where you combine the data of a bunch of separate studies. You effectively increase the size of the study by looking at groups of

numbers aggregated together; you get the larger numbers.

46/20 I have not tried to do that in determining the association between 2,4,5-T, 2,4,5-TP or 2,4-D and soft tissue sarcoma.

47/3 The basic problem is that the different studies are not entirely comparable to one another. So it is an apples/oranges type of problem. You can't throw them all into one mix and get a believable or credible result.

47/10 Some are called "case control studies" and the others are what are called "cohort studies". They have given assumptions in how you do those studies, and you can't take the numbers from one study and simply add them to the numbers from another.

47/24 A cohort study is where you look at a group of people who work in some occupation or in some industry, and then follow them through time and see how many diseases and what type of diseases the people in that cohort got.

48/23 In a case control study, instead of starting out with some sort of workers, you start out with patients with a specific disease, and then you select people who are like the patients but don't have the disease.

49/22 The advantage of a cohort study is so you can get a better understanding of exposure at the outset. You define the exposed group by some agreed upon criteria at the outset of the study, and then follow them through time.

50/5 The weakness of the cohort study is if you are looking at a rare disease, it may take a long time for enough of those diseases to show up, and sometimes cohort studies go on longer than the investigators do.

50/12 The principal advantage of a case control study is that you can study a rare disease by going someplace a lot of those patients are diagnosed and assemble a sufficient number of cases to do the study rather quickly.

50/17 Its weakness is that you are depending on people's recall or recollection of what their exposures were, because they had it prior to their getting the disease.

51/8 When I say that people exposed to 2,4-D from my review of the literature have an increased risk of cancer, that assumes that 2,4-D is a cancer causing agent, it is a carcinogen.

51/18 A carcinogen is some substance that causes cancer in exposed humans.

53/6 When I say that 2,4-D is a carcinogen what I mean is that exposure to 2,4-D increases the risk that someone will get cancer as a result of that exposure.

53/16 I think I take all of the articles into consideration in forming my view, but I don't have a particular ranking in mind.

54/3 I was asked to render an opinion in a case that never went to trial about 2,4-D.

54/23 This was a person who sprayed 2,4-D on his farm in Kansas and was diagnosed with and actually died of non-Hodgkin's lymphoma.

55/3 I worked for the Plaintiff. His name was Mr. Sloan.

55/19 I think it was about a year ago.

56/1 No other cases where I have testified specifically about 2,4-D. I have testified about Agent Orange, a component of 2,4-D.

56/7 I have never testified about 2,4,5-T, excluding Agent Orange, or about TP. I have testified about 2,3,7,8-TCDD.

56/17 The first time was in Times Beach, Missouri -- the soil was contaminated with dioxin, 2,3,7,8-TCDD.

57/6 The second TCDD case was a patient who died of soft tissue sarcoma and was exposed at a trucking terminal where he worked in St. Louis to dioxin in the soil -- TCDD contaminated soil.

58/3 None of the Times Beach people contracted the disease. My testimony was simply that they were at an increased level of getting the disease.

60/7 No. I don't believe that the association between the increased risk of cancer and exposure to Agent Orange is by virtue of the T component. I think it's the mixture.

60/9 The contaminant is TCDD and varieties of dioxins.

60/12 I testified about Agent Orange at Congressional Hearings. I think the first one was in June of 1990 and a year later, perhaps August of 1991.

62/3 We have a separate transcript file.

63/11 I have testified in two cases involving exposure to herbicides or pesticides. One was a group of workers at a pesticides plant that made a chemical called DBCP, and I testified at a San Francisco state court regarding the exposure to DBCP and particular cancers.

63/17 The second one was people or children in a school district whose water was contaminated, and that they would be at an increased risk of cancer as a result of that exposure.

64/10 Other substances I have been concerned with in my testimonial experience: electromagnetic radiation, diesel exhaust fumes, a substance called ethyl acrylate and trichloroethylene.

64/24 I have not testified for a defendant in these cases.

65/5 I testified about TCE just once. It was in Denver, and it was, I believe, called Renoid vs. Martin Marietta. Dr. Teitelbaum was on the other side.

65/15 I testified in one diesel case. That was a man in Florida who actually had lung cancer, was a non-smoker, and had worked in a railroad yard where he was exposed to diesel emissions from the railroad -- from the engines.

66/1 It was Smith v. Amtrak.

66/14 I testified in one plexiglas case. That's a man who was exposed to a spill of the chemical ethyl acrylate coming out of a tanker truck in his front yard, and it was in Louisiana.

66/20 The man's name was Washington and the defendant was a trucking company, but I forget the name of the trucking company.

67/18 I am not aware of any association between EMF and soft tissue sarcoma.

67/21 I have testified just once on EMF. I was working for the New Jersey Department of the Public Advocate. The were objecting to an electric utility company's plan to put a power line through three residential neighborhoods.

69/2 My correspondence with Mr. Schuler contained letters transmitting documents. A letter from me transmitting the literature lists. Fax Sheets, that type of thing, and a couple of bills.

69/16 I received Mr. Moyer's medical records from Mr. Schuler.

70/5 I reviewed them to verify the diagnosis of soft tissue sarcoma.

70/11 I thought it would be important to know in general whether this was a case about soft tissue sarcoma.

70/16 I just glanced at the depositions and statements. I didn't read them carefully.

71/5 The document we did for the Agent Orange Task Force for the veterans groups definitely talks about the cancers which we believe are caused by certain exposures and soft tissue sarcoma.

72/5 I don't believe the epidemiological studies associate the length of exposure or the overall dose with the risk of increased likelihood of cancer.

72/11 Some of the studies do talk about exposure of two years or less. I believe in particular Dr. Hardell's and Dr. Zahm's.

72/18 Some of Hardell and Zahm's studies concern exposure for a total of one year or less. It is usually a group that's exposed one to six years, and whatever it is.

73/4 When you say "one year or less" in general that means covering some number of days, but certainly not five days a week all year long.

73/8 Dr. Fingerhut and I are colleagues. We discuss scientific things over the phone, at conferences. She works at the National Institute for Occupational Safety and Health in Cincinnati.

73/23 To evaluate these publications, I think it's the generally accepted method in the epidemiological field to consider the study design, the size of the study, the definitions of exposure and disease as they are described in the study, the statistical analysis, and any other knowledge that I might have about the plausibility of the exposure that they are talking about being related to the disease. Then forming an opinion based on what I consider the aggregate strength of the evidence.

74/24 I gave the Fingerhut studies a lot of consideration because it was a carefully defined group who were known to have been exposed to TCDD.

75/10 I think I gave relatively little weight to a small study

by Cook and others where they looked at one particular plant.

75/20 I think the series of studies by Dr. Hardell and Dr. Eriksson I gave a lot of consideration to. I think they are, in the aggregate, very persuasive.

76/1 And in a sort of obvious way, my own work, two of which studies are on the list, looking at veterans in particular.

76/13 One text I used in teaching is Epidemiology in Medicine by Hennekens and Buring, but I wouldn't call it the single authoritative text.

76/19 There is one by Checkeway, and I believe it is called Research Methods in Occupational Epidemiology.

77/19 There is one other text, Environmental Epidemiology, and it's a committee of authors of the National Academy of Sciences that wrote it, but I don't know if it's good, bad or indifferent.

78/7 In the general field of epidemiology, Hennekens and Buring are authoritative.

78/11 I think Dr. Hardell is an authority in cancer epidemiology.

78/14 Dr. Fred Li, who works in Boston at the Dana Farber Cancer Institute, I consider an authority in cancer epidemiology.

80/17 To consider how much weight to give a study when looking at whether the exposure to TCDD would cause an increased risk of cancer, it depends how intense the exposure is, and how long you are going to follow them.

81/13 In instances where people who worked in a plant where there were very few controls on exposure and people who were wet from exposure to some chemical, or where there had been an accident and people got very large doses, even if it were for a very short period of time, I think a cohort study of 500 would be worth studying.

82/9 The size of a group for a study would depend on the particular circumstances.

82/11 There was a cohort study in Massachusetts, I believe it was something like thirty people in this one plant had very high exposure to asbestos.

82/17 I was part of that study, and there were very significant findings in cancers related to asbestos exposure.

83/13 The list of confounders that should be considered when determining whether or not there is an association between an exposure to 2,4-D, TCDD, or 2,4,5-T and an increased risk of cancer are: immunosuppressive drugs; family history of those cancers or other diseases; radiation, by which I mean the ionizing kind, the x-ray type radiation; possibly dietary history.

84/4 I think ionizing radiation, particularly, can cause almost any cancer.

84/20 Some people are exposed at work to ionizing radiation, either because they work in an x-ray department, administer radioactive drugs, or they work in a nuclear power plant or in a nuclear submarine.

85/6 There is radon and potassium 40 that comes from the soil. There is also ionizing radiation that comes from the sun or elsewhere in space, so-called cosmic radiation.

86/13 I think people who live in Florida and Boston are at increased risk of cancer more than the rest of the country. In Florida, it might well be because of sunlight exposure, in Boston, it might be because of the old industrial history, air pollution or ground or water.

89/21 As I sit here today, I do not have an opinion one way or the other as to whether any of these subject chemicals listed in my subpoena increase the risk of cancer.

91/17 I have had discussions with Drs. Hardell and Eriksson about their work.

92/3 I have talked with Dr. Zahm about her work in Kansas and Nebraska and other places. She also testified at some Congressional hearings that I testified at.

92/13 I talked to Dr. Teitelbaum at those same hearings.

93/4 I have not had any of these conversations specifically with reference to this case.

93/11 Dr. Hardell and I usually send faxes and articles back and forth. I don't believe I kept those cover sheets.

94/21 I only know Mr. Nesbet by reputation and he certainly has a good reputation.

95/12 John Graham directs a center at Harvard School of Public

Health. It's called the Center for Risk Analysis.

95/23 I don't agree with his work. I don't agree with his conclusions.

96/11 I think that the weight of Dr. Graham's evidentiary review process undervalued Dr. Zahm's work. Her work is convincing.

96/15 Dr. Zahm was a member of Dr. Graham's task force and I know she disagrees with the conclusions of the task force as well.

97/16 Undoubtedly, there are experienced people in the field who disagree with the view that I have about 2,4-D, yes.

97/24 I can't think of anyone that I would consider my professional equal who disagrees with my conclusion that 2,4-D, 2,4,5-T, 2,4,5-TP or that 2,3,7,8-TCDD increases one's risk of cancer if exposed to it.

99/4 I am sure there is still disagreement, but I think that 2,4,5-T is pretty broadly accepted in the field to be carcinogenic in humans.

101/10 By identifying certain textbooks as authoritative in epidemiology, that does not mean that I agree with all the statements made therein.

101/16 And by identifying certain individuals as possible authorities in the field of cancer epidemiology, that does not mean that I agree with all the statements made by these individuals.

[10] professor of environmental health sciences at [11] the University of South Carolina.
[12] Q. You gave me or actually your [13] counsel for Dow and Occidental gave me what [14] appears to be a curriculum here. Let me show [15] it to you.
[16] A. Well, let me give you a new one [17] that's a little more updated from that.
[18] Q. That's what I was just going to ask [19] you. [20] Let's go ahead and have this new [21] curriculum marked as Plaintiff's 1 to his [22] deposition. [23] (PLF. EXH. 1, Resume for Carl O. [24] Schulz, was marked for [25] identification.)

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[1] BY MR. SCHULER:
[2] Q. Let me try and save some time. Do [3] you go by Dr. Schulz? Is that---
[4] A. Yes. That's fine.
[5] Q. Let me save some time and ask you [6] what differences there are between the resume [7] that I have and this new resume that you handed [8] me and we marked as Plaintiff's 1?
[9] A. I have added two new publications [10] on the top of page 3 and I think one new [11] presentation on the top of -- I don't know what [12] page that is, but two new presentations at the [13] top of the page that starts out presentations.
[14] Q. Okay.
[15] A. That's the only difference I'm [16] aware of.
[17] Q. My pages are unnumbered.
[18] A. Right.
[19] Q. So why don't you point out for me [20] the two publications, for example, that you [21] added?
[22] A. Okay. Right under the word [23] publications, Schulz, Lee and Mathews, [24] absorption and distribution of subcutaneously [25] implanted silicone gel P/H 3200 in female rats.

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[1] Q. What does the P/N stand for in [2] that?
[3] A. It's just part number.
[4] Q. All right. What is the other [5] publication you've added?
[6] A. Bates, Schulz and Lee, 1993, [7] developmental toxicity evaluation of the [8] mammary implant material, silicone gel P/N [9] 3200, implanted subcutaneously in rats.
[10] Q. And are those the two publications [11] you're referring to?
[12] A. Yes.
[13] Q. What presentations, now, have you [14] added in the resume?
[15] A. The first one is called "Stealth [16] Poisons: Chemicals That Damage the Central [17] Nervous System." Presentation to the Carolinas [18] Brain Injury Symposium. Charlotte, North [19] Carolina. April 29, 1993. [20] And the other is "Absorption and [21] Distribution of Subcutaneously Implanted [22] Silicone Gel P/N 3200 in Female Rats." The [23] Society of Toxicology 32nd Annual Meeting. New [24] Orleans, Louisiana. March 18, 1993.
[25] Q. All right. And, otherwise, the

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[1] resume is the same?
[2] A. I think so. I believe so, yes.
[3] Q. The publications that you have [4] added, the two that involve silicone gel, don't [5] have anything to do with herbicides or [6] pesticides; correct?
[7] A. That's correct.
[8] Q. And the same with the presentations [9] regarding stealth poisons and implanted [10] silicone gel; right?
[11] A. That's correct.
[12] Q. I noticed, in looking at your [13] resume initially, that you've testified before [14] the FDA regarding silicone gel; is that [15] correct?
[16] A. That's correct.
[17] Q. And were you hired to do that by [18] any particular trade or industry group or [19] individual or what?
[20] A. By a manufacturer of silicone [21] mammary implants.
[22] Q. Who was the manufacturer of that?
[23] A. McGhan Medical Corporation of Santa [24] Barbara, California.
[25] Q. Have you testified in silicone gel

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[1] cases before?
[2] A. No, I have not.
[3] Q. Have you reviewed individual cases [4] for any manufacturers?
[5] A. I have had preliminary interviews

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IN THE CIRCUIT COURT OF THE NINTH JUDICIAL CIRCUIT IN AND FOR ORANGE COUNTY, FLORIDA

KIMBERLY MOYER, AS PERSONAL REPRESENTATIVE OF THE ESTATE OF ROBERT W. MOYER, II, DECEASED,

Plaintiff,

vs.

CI 89-8657

DOW CHEMICAL COMPANY, OCCIDENTAL CHEMICAL CORPORATION, MONSANTO AGRICULTURAL PRODUCTS COMPANY, HELENA CHEMICAL COMPANY, AND SOUTHERN MILL CREEK PRODUCTS CO., INC.,

Defendants.

DEPOSITION OF: CARL O. SCHULZ, Ph.D.

DATE: March 5, 1993

TIME: 9:32 A.M.

LOCATION: Law Offices of Nexsen, Pruitt, Jacobs & Pollard 1441 Main Street Columbia, SC

TAKEN BY: Counsel for the Plaintiff

REPORTED BY: WANDA K. CECIL Court Reporter

Computer-Aided Transcription By: A. WILLIAM ROBERTS, JR., & ASSOCIATES Charleston, SC Columbia, SC (803) 722-8414 (803) 731-5224

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(INDEX AT REAR OF TRANSCRIPT)

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[1] STIPULATION [2] It is stipulated by and among [3] Counsel that this deposition is being taken in [4] accordance with the Rules of Civil Procedure; [5] that all objections as to Notice of this [6] deposition are hereby waived; that all [7] objections except as to form are reserved until [8] the time of trial; and that the witness does [9] not waive reading and signing of this [10] deposition. [11] * * * * * * * * * * * * [12] CARL O. SCHULZ, Ph.D., [13] being first duly sworn, testified as follows: [14] EXAMINATION [15] BY MR. SCHULER:

[16] Q. Would you state your name, please?

[17] A. Carl O. Schulz.

[18] Q. What is your address, Mr. Schulz?

[19] A. 2500 Hayward Street, Columbia, [20] South Carolina 29205.

[21] Q. By whom are you employed, sir?

[22] A. COSAR, Incorporated.

[23] Q. What is your position with COSAR, [24] Incorporated?

[25] A. I'm the president.

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[1] Q. What is COSAR, Incorporated?

[2] A. It's my own independent consulting [3] practice in toxicology.

[4] Q. Do the letters stand for anything? [5] COSAR, is it an acronym?

[6] A. No. Well, the C-O-S is my [7] initials, but it doesn't really stand for [8] anything. I just liked the sound of it.

[9] Q. Okay. How many employees does [10] COSAR have?

[11] A. Two of us.

[12] Q. Yourself and who else?

[13] A. An assistant.

[14] Q. What is his or her name?

[15] A. Junko Brown.

[16] Q. How do you spell that first name?

[17] A. J-u-n-k-o.

[18] Q. And is that a man or a woman?

[19] A. It's a woman.

[20] Q. When you say you have this [21] consulting business, do you operate this from [22] the address that you gave me or do you operate [23] the business from some other address?

[24] A. No. I gave you my home address. [25] My office is at 2231 Devine Street.

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[1] Q. And that's in Columbia?

[2] A. In Columbia. Yes.

[3] Q. And is that the offices of COSAR, [4] Incorporated?

[5] A. Yes.

[6] Q. Do you have any other businesses or [7] activities of an employment nature that you are [8] engaged in?

[9] A. Well, I'm also an adjunct associate

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[6] with defense attorneys preparing for potential [7] litigation in silicone mammary implant cases, [8] but that has never gotten to the point of [9] discussing specific cases and specific issues.
[10] Q. And the defense attorneys are [11] representing what manufacturers, if you know?
[12] A. One is---
[13] MR. WAGNER: Dr. Schulz, if you [14] have not -- if you have been retained only as a [15] consultant, as opposed to someone to testify as [16] an expert, I don't believe you're required to [17] reveal for whom you are consulting. [18] You can if you want to, and I don't [19] know if the lawyers that you're dealing with [20] would have an objection to it or not, but. . .
[21] THE WITNESS: I can't remember the [22] lawyers' names, frankly, who I've talked to.
[23] BY MR. SCHULER:
[24] Q. Okay. My question, though, was do [25] you know who the manufacturers were that they

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[1] were representing?
[2] A. Yes. One was McGhan Medical [3] Corporation and the other is [4] Bristol-Myers-Squibb.
[5] Q. All right. Let me just go through [6] your background a little bit here.
[7] A. Uh-huh.
[8] Q. I was a little bit confused by the [9] summary or the notation here regarding your [10] degree. Now, you got your Ph.D. in organic [11] chemistry; correct?
[12] A. That's correct.
[13] Q. Do you have a degree in toxicology, [14] too, as such?
[15] A. Not a degree, no.
[16] Q. Okay. If I understand your resume [17] correctly, though, you became a postdoctoral [18] fellow in environmental medicine at Johns [19] Hopkins School of Hygiene in 1971, 1972; [20] correct?
[21] A. Correct.
[22] Q. And you equate environmental [23] medicine to toxicology?
[24] A. Well, toxicology was an area of [25] specialization within the Department of

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[1] Environmental Medicine at the School of Public [2] Health at that time.
[3] Q. All right. And then from 1970 -- [4] actually, before 1971, when you had this [5] fellowship, after your postdoctoral time in [6] chemistry, you began employment in effect; [7] correct?
[8] A. That's correct.
[9] Q. As a research chemist?
[10] A. No. As a toxicologist. Well, [11] research chemist -- let's see. I got my [12] doctorate in chemistry and was a chemist and [13] then decided I wanted to become a [14] toxicologist. So in '71, I left Union Carbide [15] and went to Johns Hopkins and retrained in [16] toxicology, as a postdoctoral fellow.
[17] Q. I understand.
[18] A. Okay.
[19] Q. So you got your degree in [20] chemistry, you worked as a research chemist for [21] a couple of years?
[22] A. Right.
[23] Q. Went back and did postdoctoral work [24] in toxicology and then started out as a [25] research associate, I guess, at Johns Hopkins;

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[1] correct?
[2] A. Yes.
[3] Q. And that was for two years, and [4] then you worked for the Center for Occupational [5] Safety and Health, Stanford Research [6] Institute. Is that a private corporation?
[7] A. Yes, it is.
[8] Q. And what did you work on in your [9] two years at that institution?
[10] A. SRI had a contract from the [11] National Institute of Occupational Safety and [12] Health to develop what are called criteria [13] documents, which are the scientific bases for [14] establishing standards for occupational [15] exposure to chemicals in the work place. [16] And I was senior toxicologist on [17] that project, developing the toxicology [18] information that went into these criteria [19] documents for a number of compounds.

[20] Q. Did any of those compounds include [21] the herbicides that we're involved with in this [22] case?
[23] A. No.
[24] Q. What types of compounds are you [25] talking about in that---

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[1] A. A variety of industrial compounds. [2] Methanol, methyl parathion, malathion, [3] isopropyl alcohol, carbaryl. I can't [4] remember. Another dozen or so industrial [5] chemicals.
[6] Q. So that was a private company that [7] had a contract with the government?
[8] A. Correct.
[9] Q. And then you spent two years there [10] and moved to the Food and Drug Administration, [11] Bureau of Foods; correct?
[12] A. Correct.
[13] Q. And what were your duties there?
[14] A. I was a petition review [15] toxicologist. When individuals or companies [16] submit applications to the Food and Drug [17] Administration, in this case, it was new animal [18] drug applications. For drugs to be used in [19] food producing animals, I reviewed the [20] toxicology data that they submitted with their [21] petition to make a determination whether that [22] would be safe for human health to use that drug [23] or chemical in food animals.
[24] Q. Okay. Any of your work there [25] involve the herbicides we're concerned with in

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[1] this case?
[2] A. No.
[3] Q. And then you -- it looks like, and [4] correct me if I'm wrong, that you stayed with [5] the Food and Drug Administration, but were in a [6] different branch?
[7] A. That's correct.
[8] Q. Okay. You went to the Bureau of [9] Veterinary Medicine, biological program [10] specialist?
[11] A. Right.
[12] Q. Correct?
[13] A. Yes.
[14] Q. Was that a transfer at your request [15] or was that a promotion?
[16] A. It was a promotion at their [17] request. At this point in the history of the [18] Food and Drug Administration, we were [19] implementing something called the bioresearch [20] monitoring program, which involved a series of [21] standards and inspections to ensure the quality [22] and integrity of toxicology data submitted to [23] the Food and Drug Administration. [24] So the Bureau of Veterinary [25] Medicine asked me to head up their compliance

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[1] and enforcement program for the laboratory -- [2] toxicology laboratory part of that program.
[3] Q. What, essentially, were you dealing [4] with as far as the animals were concerned, [5] though?
[6] A. Well, we were conducting [7] inspections of toxicology laboratories that [8] were conducting tests that would be submitted [9] to the government in support of the safety of [10] food animals -- food additives in animal drugs [11] and to make sure that they were in compliance [12] with the regulations.
[13] Q. Did any of that work involve the [14] herbicides that we're concerned with in this [15] case?
[16] A. No.
[17] Q. All right. 1978, then, to '82, [18] still in the Food and Drug Administration. [19] Looks like now in the Bureau of Drugs. And it [20] says, chief, gastrointestinal and contraceptive [21] drug products branch. Was that another [22] promotion?
[23] A. Yes, it was.
[24] Q. And what was the reason for your [25] move there?

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[1] A. Well, the initial program had been [2] set up that I was administering in the Bureau [3] of Veterinary Medicine and an opportunity came [4] for me to advance and become a branch chief, [5] which is also an increase in grade and salary, [6] so I took it and went to the Bureau of Drugs [7] and was in charge of this branch of about 12 [8] people in the over-the-counter drug review.
[9] Q. Gastrointestinal

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and contraceptive [10] drug products, those types of things, you said [11] over-the-counter, antiacid type drugs and---
[12] A. Antiacids. Right.
[13] Q. ---oral contraceptives for women?
[14] A. No. Because that's a prescription [15] drug. The only non-prescription contraceptive [16] drug that we evaluated was spermicidal gels and [17] creams and sprays.
[18] Q. And you were there for [19] approximately four years?
[20] A. Yeah. There's a mistake there I [21] notice on -- now, that I see that, that would [22] have been until 1981, of course, because I left [23] there to go to Clement Associates. It was just [24] about three years.
[25] Q. And did any of your work there

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[1] involve the herbicides?
[2] A. No.
[3] Q. All right. '81, you went to [4] Clement Associates, Inc. What is Clement [5] Associates, Inc.?
[6] A. Clement Associates is a consulting [7] firm in Washington that does environmental [8] occupational toxicology and risk assessment.
[9] Q. A private corporation?
[10] A. Yes.
[11] Q. And, back in 1981, who was running [12] Clement Associates, Incorporated?
[13] A. Well, when I went to work there the [14] president was John Colojefski.
[15] Q. How big a company is Clement [16] Associates, Incorporated?
[17] A. Well, at that time, it probably had [18] about 60 employees, I would guess. Now, it's [19] been absorbed into a much larger corporation [20] and I've somewhat lost track of both their [21] exact corporate identity and their size.
[22] Q. Who was your boss at Clement [23] Associates?
[24] A. When I began there it was Joe [25] Rodricks.

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[1] Q. And you said you were in the [2] division of life sciences?
[3] A. That's correct.
[4] Q. What other divisions did they have?
[5] A. Well, there was an engineering [6] division; and I think those were the only two [7] essential program divisions. There might have [8] been a division of administration and [9] management or something like that, but [10] engineering and life sciences were the two main [11] program parts.
[12] Q. And what were your duties and [13] responsibilities as associate director of the [14] division of life sciences?
[15] A. Well, I supervised the staff of [16] about eight or a dozen staff scientists and [17] assistant staff scientists in a variety of [18] contract activities, primarily for the federal [19] government.
[20] Q. Was Clement Associates, Inc., [21] mostly a government contractor working on [22] different projects for the government?
[23] A. At that time, we were probably 95 [24] percent government contracts and about 5 [25] percent private.

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[1] Q. And in '81 to '82, as associate [2] director of the division of life sciences, did [3] you have occasion to work on any herbicide [4] projects?
[5] A. I think so. I don't know exactly [6] when, at that point, my involvement with [7] herbicides began. It began within the first [8] two years or so that I worked at Clement. [9] Probably -- I can't place it exactly. Probably [10] about 1982 when I began heavy involvement with [11] the phenoxy herbicides.
[12] Q. What was your first involvement [13] with phenoxy herbicides, as you recall it?
[14] A. We submitted a proposal to the [15] Veterans Administration in response to a [16] request for proposal to perform a literature [17] search and review on scientific literature and [18] the potential health effects of herbicides that [19] were used in Vietnam.
[20] Q. And did you get that contract?
[21] A. Yes, we were awarded that contract

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[22] in -- again, I'm thinking 1982. It was a [23] three-year contract. We re-competed it in 1985 [24] or so and won it for three more years and then [25] a one-year extension on that. So I believe

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[1] that we had the contract for seven years, is my [2] recollection.
[3] Q. Was the first work product that you [4] were involved in with regard to phenoxy [5] herbicides published around 1985?
[6] A. Well---
[7] Q. At the conclusion of this [8] three-year contract?
[9] A. No. We did it every year. We [10] published a two-volume summary every year once [11] we began the contract. And I think the first [12] one covered through 1981 or the middle of 1981, [13] so it would have been published in '82, I [14] think.
[15] Q. So the first publication of the [16] literature summary would have been around 1982?
[17] A. Yeah. It says back in here. I [18] think I've got them all listed. Okay. I'm [19] mis-remembering, as I tend to do. 1984 was the [20] first publication that I did. We completed it [21] in '83. That's right. I'm remembering now.
[22] Q. So the first publication that you [23] were associated with involving phenoxy [24] herbicides was in 1984?
[25] A. Correct.

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[1] Q. And that was the one listed here on [2] your resume that says Veterans Administration, [3] 1984. Synopsis of Scientific Literature on [4] Phenoxy Herbicides and Associated Dioxins, [5] Number 1, Volumes 1 through 4?
[6] A. Well, yes. The volume right above [7] it, too. The way these work is we published a [8] two-volume set, in that case in '84, it would [9] have been 3 and 4; 4 being an annotated [10] bibliography, 3 being a critical review of the [11] literature. And then we summarized those in [12] what we called a synopsis or a lay language [13] summary, which was published the same year. So [14] what you have, basically, is three volumes came [15] out every year, if you will. [16] Two, 8 1/2 by 11 books, one being [17] an annotated bibliography and one the critical [18] review. And then the smaller, little pamphlet [19] like that the VA produces, which were designed [20] to be a summary of those volumes, but written [21] in a way that educated lay people could read [22] them and understand them.
[23] Q. Okay. So if I understand you [24] correctly, the contract and the product of the [25] contract with the Veterans Administration over

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[1] the years has been essentially a three-volume [2] output, the annotated bibliography, the [3] critical review and the summary pamphlet I'll [4] call it for lack of a better word?
[5] A. Synopsis. Yes.
[6] Q. Synopsis?
[7] A. Yes. Right.
[8] Q. Okay.
[9] MR. WAGNER: Every year, not in [10] total. I don't know if there's a [11] miscommunication.
[12] MR. SCHULER: Pardon?
[13] MR. WAGNER: It's every year, not [14] in total.
[15] MR. SCHULER: Right.
[16] Q. You up date it from year to year?
[17] A. Yes. Well, it's a whole new [18] document each year. In that -- in the period [19] that we had this contract, approximately 300 [20] relevant articles were published every year. [21] We wouldn't up date -- in other words, each [22] volume is a new and separate document that [23] contains none of the literature of the previous [24] years, except if we referred back to it to make [25] a comparison, you know, or extension in the

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[1] critical review part.
[2] Q. Okay. So each year, you would [3] review the new articles that came out in the [4] prior year?
[5] A. That's correct.
[6] Q. So each installment of this would [7] be approximately 300 new articles to be [8] reviewed and

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synopsized?
[9] A. Correct.
[10] Q. Have you done any original research [11] on phenoxy herbicides that's been published?
[12] A. No.
[13] Q. As far as the bibliography that [14] you've done and the review of the articles and [15] research that has been published, just from [16] your experience now, 300 articles a year on [17] phenoxy herbicides, is that a relatively active [18] investigation based on the number of articles [19] or how would you describe it?
[20] A. I would say it's been one of the [21] major research efforts of the last ten years.
[22] Q. And the average has been around [23] 300, give or take, in each of the years that [24] you've been involved?
[25] A. Yes. That's pretty accurate, I



[1] think. 300 is a good number. It was higher [2] than that, dropped down a little bit, and came [3] back up again. In fact, in the middle of this [4] somewhere, I published a paper that had a graph [5] in it of papers per year and so forth.
[6] Q. Those are articles from the product [7] of research from all over the world; correct?
[8] A. Yes, yes. The nature of our [9] contract was that we review the world's [10] literature.
[11] Q. Did you ever go back and look back [12] beyond your initial engagement in 1982, [13] roughly, to determine and look back [14] retrospectively to see whether, say, in the [15] prior decade from 1972 to 1982, whether there [16] had been that much research activity regarding [17] the phenoxy herbicides or whether, at some [18] point, there was a dramatic increase in the [19] research?
[20] A. Well, I looked at that. What [21] you'll notice is that the first year that we [22] had the contract, the first publication was [23] Volumes 3 and 4. Volumes 1 and 2 were produced [24] by another contractor under an initial contract [25] from the Veterans Administration. And their



[1] mandate in their contract was to review all the [2] literature published up through 1981. See, [3] when we got it, it became a yearly up date; but [4] they were to go back as far as they could find [5] anything. And---
[6] Q. Could I stop you for one second?
[7] A. Yes.
[8] Q. Who was that company that did that?
[9] A. The name of that company was called [10] JRB Associates, and they were in Washington at [11] the time. I don't think they exist any more.
[12] Q. Who was the individual, if you [13] know, at JRB Associates who had the [14] responsibility for that?
[15] A. I don't have any idea. I don't [16] think I ever knew.
[17] Q. You ever talk with anyone of JRB?
[18] A. No. They were, of course, bitter [19] that they lost the contract to us, so. . .
[20] Q. So there was a---
[21] A. But I did have their Volumes 1 and [22] 2, which I still have. And, over the years, of [23] course, it's been incumbent on me to evaluate [24] the completeness and accuracy of the work they [25] did. And, in general, it was fairly complete.



[1] There's some omissions, which we [2] tried to pick up. And, actually, we included [3] in that first set of volumes we did, 3 and 4, [4] we included some earlier literature when we [5] identified it and saw that it wasn't in Volumes [6] 1 and 2 and we thought it was important. We [7] put it in 3 and 4 even though it was published [8] prior to the era of coverage of our review. [9] So I'm fairly confident that the [10] review, through the last year we did it, was [11] quite complete.
[12] Q. To go back to my original question, [13] though, since you've looked at Volumes 1 and 2, [14] that was the initial volumes 1 and 2 done by [15] JRB Associates, can you give me some kind


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of an [16] idea, looking backward from 1982 to whatever [17] year they went back to, what type of activity [18] in terms of number of articles per year or any [19] way you want express it?
[20] A. I'm sorry. Yes. I lost the track [21] on that. No. Clearly, there was not [22] significant research, published research [23] interest in this area much before the [24] late '70s. [25] I would say that Volume 1 and 2

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[1] bibliography covering everything before the [2] middle of '81, I would say probably there's -- [3] I'm just guessing, but approximately 500 [4] articles in that first volume bibliography. So [5] prior to the middle of '81, only 500 articles [6] total were published.
[7] Q. Going back all the way to the '40s [8] or---
[9] A. Well, it depends. I mean, probably [10] the earliest papers specifically on dioxins was [11] 1957. Health effects of phenoxy herbicides, I [12] can't remember the earliest paper, but probably [13] in the '60s or so, early '70s maybe.
[14] Q. Going back to the article that you [15] referenced in '57. That wasn't the [16] Kimmig-Schulz---
[17] A. Schulz. Yes.
[18] Q. I was going to ask you about that [19] today because I noticed---
[20] A. It's not me.
[21] Q. I figured it wasn't you. Either [22] that or you've discovered the---
[23] A. Foundation of youth.
[24] Q. ---Ponce de Leon foundation [25] somewhere. But is it anybody related to you?

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[1] A. No.
[2] Q. Spells the name the same.
[3] A. Yes. Well, Schulz, spelled the way [4] I spell it, it's is the most common surname in [5] Germany. So it's not surprising.
[6] Q. Smith?
[7] A. Yeah. It's the Smith of Germany. [8] But, no, I don't.
[9] Q. So you're not related to the Schulz [10] of Kimmig and Schulz?
[11] A. No.
[12] Q. Okay. And the 1950s article that [13] you're referring to, do you recall that [14] specifically?
[15] A. No. I'm just -- I'm hesitant even [16] there. I can't, now as I think back, remember [17] when articles relevant to the health effects of [18] phenoxy herbicides, per se, started to appear. [19] I didn't think about that in preparation for [20] today.
[21] Q. Okay. But in any event, the [22] articles that you're referring to, the '57 [23] article on dioxin and the '60s article on the [24] health effects -- early '60s, I think you [25] said -- health effects of phenoxy herbicides,

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[1] they're all in that Volume 1 and 2 that we've [2] been talking about?
[3] A. Yes.
[4] Q. Do you have copies of the JRB [5] Volumes 1 and 2 in your library?
[6] A. Yes, I do.
[7] Q. How big a tomes are we talking [8] about here?
[9] A. Well, they're -- probably each [10] volume is 300 to 400 pages.
[11] Q. Did they do just the bibliography [12] and annotation to the bibliography or did they [13] also do a---
[14] A. They did a critical summary, too.
[15] Q. Did they do a synopsis, also?
[16] A. No. The synopsis was a new thing [17] in our contract. And, if you look, the first [18] synopsis I did was Volumes 1 through 4. So I [19] went back, and for the lay language thing, [20] synopsized the two volumes that summarized the [21] two volumes that JRB did, as well as the first [22] two that we did.
[23] Q. Do you recall any published [24] research -- and if you don't recall just tell [25] me so. I realize that I'm probably testing

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[1] your memory here. But do you recall any [2] published research in the 1950s that originated [3] out of Dow Chemical Company that related to the [4] health effects of phenoxy herbicides?
[5] A. No, I don't re-

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call.
[6] Q. What about in the 1960s?
[7] A. I don't recall, but there could [8] have been. I just don't remember.
[9] Q. Would the summary volumes of the [10] scientific, published scientific literature in [11] this area investigate those published articles [12] that originated out of industrial research, as [13] well as independent scientific research?
[14] A. If they were published in the [15] publicly available domain. And not even [16] necessarily published, if they were -- I think [17] we did a pretty good job, at least after we [18] took over, of identifying documents not [19] published in normal scientific journals, so to [20] speak, that we could get our hands on.
[21] Q. Okay. When you first became [22] involved with this project in your association [23] with Clement Associates, was the search that [24] you did -- and I looked at, I think, one of the [25] versions of what you've done and I think it was



[1] a later version. But were the searches that [2] you did of the scientific literature both [3] manual, as well as computer?
[4] A. That's correct.
[5] Q. And just -- you don't have to get [6] into great detail, but how would you [7] essentially do the manual search? By going to [8] some library somewhere or how did you do that?
[9] A. Very typically, although the normal [10] approach was to start with the computer data [11] base search of the common data bases, Med-Line [12] and Tox-Line, specifically. [13] You would identify, from that, a [14] large number of relevant articles which you [15] would get the hard copies of. Then, typically, [16] you would look in the bibliographies of those [17] to find references to other articles that you [18] may have missed. So that was part of the [19] manual searching. [20] Part of the manual searching would [21] be looking at something called Current [22] Contents, which is just a compilation of the [23] tables of contents of all the scientific [24] journals in the field, and you'd have certain [25] journals that you'd screen the table of



[1] contents for, every month as they come out, [2] looking for it. [3] And then there were a few other [4] printed current literature things that you look [5] at. One that we used quite a bit in the early [6] days was something put out by the National [7] Cancer Institute. No. Chem Abstracts. [8] Chem Abstracts Service would put [9] out these monthly or weekly publications that [10] would just compile the abstracts relevant to a [11] certain area, like carcinogenesis or [12] reproductive effects, and we'd scan those, too, [13] for articles relevant to dioxins or phenoxy [14] herbicides.
[15] Q. I know you've described what you've [16] done, but what was the overall reason for the [17] contract, if you know, let by the Veterans [18] Administration?
[19] A. Well, it was mandated by public [20] law, and I can't remember what law that was [21] now, passed in about 1979 or something, that [22] had a number of provisions in it for the [23] Veterans Administration to investigate the [24] possible link between exposure to herbicides in [25] Vietnam and long-term health effects in Vietnam



[1] veterans. [2] And one of the specific [3] specifications that Congress put in that [4] legislation was that the VA review and -- I [5] don't know whether it the mandated publication, [6] but it said review and maintain and up date a [7] file of all literature relevant, scientific [8] literature, medical literature, relevant to the [9] health effects of the herbicides that were used [10] in Vietnam. So the contract grew out of a [11] congressional mandate.
[12] Q. And that mandate grew out of the

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[13] what, concern arising about the health effects [14] of Agent Orange on the Vietnam veterans?
[15] A. Correct.
[16] Q. Were you involved, during your time [17] with Clement Associates, with any other [18] projects, other than this one?
[19] A. Relevant to phenoxy herbicides or [20] just---
[21] Q. Any project.
[22] A. Oh, many projects. Many other [23] projects.
[24] Q. That did not involve phenoxy [25] herbicides?

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[1] A. That's correct.
[2] Q. Can you give me some examples of [3] some of the things you recall you were involved [4] with during that, I think, 1981 to 1985?
[5] A. Yes. We had a -- in the early [6] first two of those years or so, we had a [7] contract with the Office of Pesticide Programs [8] at EPA to review data that was submitted to it [9] in support of the safety of pesticide for [10] registration of pesticides or re-registration [11] of pesticides.
[12] Q. Pesticides referring to insect [13] killers?
[14] A. Everything. Insect killers, [15] fungicides, wood preservatives.
[16] Q. Okay.
[17] A. So forth. And, of course, that [18] will raise the question. Herbicides could have [19] been covered under that, but I don't recall [20] that while I was involved with that project, I, [21] or any of the people I supervised, reviewed any [22] data on a herbicide that was one that we used [23] in Vietnam or is relevant to this case.
[24] Q. Okay.
[25] A. So it's, I think, coincidental that

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[1] it didn't have that involvement.
[2] Q. Did you publish anything as a [3] result of that contract?
[4] A. No, no. That was, of course, all [5] confidential work for EPA.
[6] Q. Okay. What other projects do you [7] recall that you were---
[8] A. We had---
[9] Q. ---involved in during that---
[10] A. Yeah.
[11] Q. Let me finish my question.
[12] A. I'm sorry.
[13] Q. ---during that four-year period [14] from '81 to '85?
[15] A. We had a major contract from the [16] Occupational Safety and Health Administration. [17] They had -- before I went to work at Clement, [18] they had published something called the OSHA [19] carcinogen policy. And it was a notice and [20] they invited comments, and we reviewed the [21] comments to the notice, and helped draft a [22] final order for the OSHA carcinogen policy.
[23] Q. Okay.
[24] A. What other?
[25] Q. Anything else?

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[1] A. Yes. There were many more, but [2] what can I think of. We had another small [3] contract from OSHA to evaluate occupational [4] exposure to formaldehyde in the work place. [5] Had a contract from -- several [6] contracts from EPA sequentially to investigate [7] risk assessment methodology used for -- both [8] for prioritizing pollutant chemicals for [9] standard development, and for all actual [10] standard development itself. [11] I worked on private contracts in [12] that time.
[13] Q. Can you remember the names of any [14] of the companies that you worked with, [15] contracted for Clement's services?
[16] A. I remember one. We did a -- we [17] investigated the link between aspirin and [18] Reye's syndrome for the Aspirin Foundation, I [19] believe it was called. But a trade, you know, [20] organization. [21] Did some work for Tampax [22] Corporation on a strategy for establishing the [23] safety of their medical device products.
[24] Q. Is that in connection with the [25] toxic shock?

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[1] A. No. It was in connection, [2] basically, with the implementation of the

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1976 [3] medical device amendments, which would require [4] them to submit data to the Food and Drug [5] Administration to establish the safety of all [6] of their products. And we just outlined for [7] them the kind of testing they might have to do [8] and a proposal so they could go to FDA and say, [9] here's what we propose to do. What do you [10] think?
[11] Q. In your work with Clement, did you [12] have any contracts or did the company have any [13] contracts that you were aware of with any [14] herbicide manufacturers? Dow Chemical or [15] Diamond Shamrock?
[16] A. No. Certainly not. And we [17] probably -- particularly in those early years, [18] when we -- when we had the EPA contract from [19] Office Pesticides, we were legally prohibited [20] from any contractual engagement with any [21] pesticide manufacturing company. So I know we [22] didn't then. [23] We didn't have that contract after [24] about 1982 or '83. I vaguely recall we had a [25] contract with, I think, W.R. Grace; and they

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[1] won't have been a phenoxy herbicide [2] manufacturer. I think we did, in those later [3] years, have some; but nobody would be -- not a [4] Dow. Never a Dow. Never a Diamond Shamrock---
[5] Q. Chevron?
[6] A. ---while I was there. Now, I'm [7] going to stop. Did have a contract indirectly [8] with Dow. It was actually with something [9] called the III, the International Isocyanide [10] Institutes and the -- our contract or our [11] project officer was Larry Rampy, who was an [12] industrial hygienist at Dow Chemical Company. [13] And we reviewed the NTP, National Toxicology [14] Program bioassay of toluene diisocyanate for [15] them.
[16] MR. SCHULER: Did you get that, [17] toluene diisocyanate?
[18] THE WITNESS: Diisocyanate. You [19] can flag these and I'll spell them for you at [20] the break. But---
[21] MR. LUTZ: We haven't even started [22] yet.
[23] THE WITNESS: Yeah. Let's see. [24] Lost my train of thought. No other -- no work [25] for phenoxy herbicide manufacturers.

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[1] BY MR. SCHULER:
[2] Q. Let me just ask you a question with [3] regard to -- your contract or Clement's [4] contract was with III?
[5] A. Yes.
[6] Q. And your project manager was this [7] fellow from Dow---
[8] A. Right.
[9] Q. ---that you mentioned?
[10] A. Yes.
[11] Q. And the toluene diisocyanate was an [12] element of what type of product, if you know?
[13] A. It's a major building block for [14] manufacturing polyester resins.
[15] Q. Okay. All right.
[16] MR. WAGNER: I must say, that was [17] impressive that you were able to regurgitate [18] that.
[19] THE WITNESS: He stumbled a little.
[20] MR. SCHULER: My organic chemistry [21] background comes to the fore.
[22] Q. If you need to take a break on [23] occasion, we can---
[24] A. I'll let you know.
[25] Q. Just let me know.

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[1] A. Okay.
[2] Q. My last area of questioning, I was [3] trying to ask if you knew if Clement [4] Associates, Inc., had any contracts with any [5] herbicide manufacturers. I think you've [6] answered that. [7] Is there anything else that you can [8] recall that you wish to add to that answer?
[9] A. No.
[10] Q. And I think you basically gave me [11] the background of some of the other projects [12] that you remember during your time at Clement [13] Associates. Did most of the projects involve [14] review of literature, that type of thing and [15] analysis of scientific literature? I think [16] there was one or two that you mentioned that [17] you did some pro formas for the EPA and things [18] of this

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nature for clients to submit to the [19] EPA; correct?
[20] A. Yes. It was all literature and [21] writing and -- we did no laboratory work or had [22] no research facilities that would have allowed [23] original research.
[24] Q. Okay. You mentioned, I think, who [25] your initial boss was at Clement Associates.

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[1] Can you tell me, if there have been a series of [2] them, who the other people were that supervised [3] you?
[4] A. Oh, boy.
[5] Q. And if there's a whole bunch of [6] them, just give me the main people that you [7] worked with.
[8] A. Yeah. After Joe Rodricks left, it [9] would have been Dietrich, D-i-e-t-r-i-c-h. And [10] I can't remember his first name. That's kind [11] of embarrassing, I think, not to know your [12] boss' name. There were some odd things going [13] on organizationally at Clement at that time. [14] Gary Dietrich, that's his name. Gary Dietrich, [15] and I suppose that he was my direct supervisor [16] the remainder of the time I was there, although [17] we kept reorganizing and shifting titles. [18] One other name, who was probably -- [19] may have been my direct supervisor at one point [20] or another was Jay Turim, T-u-r-i-m.
[21] Q. Okay.
[22] A. That's basically covers it.
[23] Q. You mentioned that Clement [24] Associates was purchased by another company or [25] was absorbed into another company; is that

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[1] correct?
[2] A. That's correct.
[3] Q. What company was it absorbed into?
[4] A. It was purchased by a company [5] called ICF.
[6] Q. What does that stand for?
[7] A. I don't know. Before that -- we [8] was purchased in about 1983 by a strange [9] company. I don't know the name of it. And [10] then in about 1985, late 1985, Clement was [11] bought by ICF International, which still exists [12] and that's their parent company now. And it's [13] in Vienna, Virginia, and I don't know what ICF [14] stands for.
[15] Q. Vienna, Virginia, is the location [16] now of---
[17] A. Uh-huh.
[18] Q. ---where the old Clement would be?
[19] A. Yes. What's left of it. It's a [20] division of ICF.
[21] Q. Does that division still do the [22] government contract type of work?
[23] A. I don't think so. My recollection [24] is they do almost exclusively private work now.
[25] Q. All right. You left Clement

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[1] Associates; correct, in 1985?
[2] A. Well, I left them gradually.
[3] Q. Okay. Tell me about that.
[4] A. In 1983, I felt I was spending way [5] too much of my time doing administrative [6] functions and not nearly enough doing the [7] actual scientific work that I was qualified to [8] do. [9] And I approached the management of [10] Clement and said, I'd like to establish a new [11] relationship whereby I consult to your clients, [12] but on an hourly basis, and I'd like to [13] establish my own independent consulting [14] practice, not in competition with yours. And [15] they were very generous and very willing to do [16] that. [17] And that's the relationship that [18] existed from '83 to '85 when I was what was [19] referred to as a senior toxicology adviser at [20] Clement. In that period, about 80 percent of [21] my time, chargeable time was spent working on [22] Clement projects in Clement's offices; but I [23] did -- I was, in a sense, weaning myself away [24] from the company at that point.
[25] Q. Okay. So in 1983, you started this

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[1] COSAR, Inc.?
[2] A. Right.
[3] Q. And did primarily consultations [4] with Clement and then started to do some [5] outside consulting, as well; correct?

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[6] A. That's correct.
[7] Q. When did you begin medical/legal [8] consulting work, I'll call it, or working with [9] attorneys?
[10] A. I think we provided some -- we [11] provided litigation support while I was still [12] at Clement. And did some of that and then it's [13] been a part of my business ever since.
[14] MR. WAGNER: Before you move into [15] legal cases, could we take a quick break?
[16] MR. SCHULER: Sure.
[17] (A recess transpired.)
[18] BY MR. SCHULER:
[19] Q. Let's see. I think we were talking [20] about your employment with Clement and then [21] your beginning of COSAR, Incorporated, and your [22] medical/legal involvement or medical/legal [23] involvement -- your consulting with lawyers.
[24] A. Uh-huh.
[25] Q. When did you first get involved in

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[1] consulting in litigation type matters in terms [2] of chronologically? Can you tell us?
[3] A. Probably around 1983, sometime [4] right in the middle of my employment with [5] Clement Associates.
[6] Q. 1983?
[7] A. I'd guess that. Yes.
[8] Q. And can you recall the first [9] instance of your involvement? Was it a [10] herbicide case or was it some other matter?
[11] A. No, it wasn't herbicides. It was a [12] case involving DDT contamination in Alabama.
[13] Q. Do you have somewhere a list of [14] your case involvements, in cases where you've [15] testified, either deposition or trial?
[16] A. No.
[17] Q. I mean, it would save some time. [18] You know, if you've got the information [19] somewhere and have it, it'll save me some time [20] in questioning.
[21] A. I've got the information. And, in [22] fact, last night, I made a little handwritten [23] crib sheet to cover the last five years.
[24] Q. Okay.
[25] A. I brought that with me.

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[1] MR. WAGNER: I told him that you [2] were curious about that.
[3] MR. SCHULER: Yes, we like to know [4] those things.
[5] Q. Can I just take a look at that---
[6] A. Sure.
[7] Q. ---quickly and, again, it'll [8] probably save me some time if I can just glance [9] down here.
[10] A. I'll tell you, right off the bat, [11] almost none of them are phenoxy herbicide or [12] dioxin.
[13] Q. Okay. Well, that was probably [14] going to be my first question. Are any of [15] these cases phenoxy herbicide cases?
[16] A. I'm working on one other active [17] case.
[18] Q. Presently?
[19] A. Uh-huh.
[20] Q. Yes. You have to say?
[21] A. Yes.
[22] Q. Okay.
[23] A. Sorry.
[24] Q. And what case is that? What is it [25] about?

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[1] A. It's Pickering versus Dow. [2] Probably right up there at the top. I put them [3] in reverse order, I think, with the most [4] recent. It's Pickering versus Dow. The firm [5] is Hardin, Cook in Oakland, California. I [6] support the defense.
[7] Q. And is it a 2,4-D, a 2,4,5-T?
[8] A. It's a 2,4-D case.
[9] Q. Okay. And can you give me the bare [10] essentials of it? Was it somebody spraying it [11] occupationally? Worked in a factory?
[12] A. No. He worked in the Chevron in [13] Walnut Hills and got cancer and is claiming [14] it's from his occupational exposure.
[15] Q. What type of cancer? Do you [16] recall?
[17] A. I think it's also soft tissue [18] sarcoma, but. . .
[19] Q. Is this a recent case that was [20] filed within the last year or two?
[21] A. Yes. And it's not even as far [22] along as this one. I haven't been deposed.
[23] Q. And the Hardin, Cook Law Firm is [24] the defense firm representing

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Dow in that case?
[25] A. That's correct.

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[1] Q. Who represents the plaintiff?
[2] A. I don't know.
[3] Q. Gerson, Smoller, does that name [4] sound familiar to you?
[5] A. No. I really -- I don't even think [6] I've even seen it or heard it. We're very [7] preliminary into that.
[8] Q. All right. Let me take a look [9] here. Let me try and do another subset on a [10] question.
[11] A. Okay.
[12] Q. Maybe to eliminate, in the lingo [13] that you probably like to use. Do any of these [14] cases on this list that you gave me, which we [15] will mark as Plaintiff's 2, involve allegations [16] of cancer being caused by the substance [17] involved in the case?
[18] A. I'd need to look at the---
[19] Q. Sure.
[20] A. ---cases. This fourth case, John [21] Soublis, I am plaintiff's expert there. He has [22] skin cancer, which we believe to be related to [23] exposure to coal tar pitch volatiles.
[24] Q. Okay. Occupational exposure?
[25] A. Occupational exposure.

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[1] Q. All right. Where is that case [2] pending?
[3] A. In Atlanta, Georgia.
[4] Q. Is that where the firm is, Carr, [5] Tabb---
[6] A. Carr, Tabb & Pope is in Atlanta. [7] Yes.
[8] Q. All right. Any others involve [9] cancer?
[10] A. Boy, this is hard. I'm really [11] embarrassed, but these things tend to blend [12] together over time. Okay. There are two cases [13] here and I can't remember. [14] Coffee versus Tennessee Chemical, [15] where I was defense expert; and Blankenship [16] versus AMP. Both of these plaintiffs -- I was [17] plaintiff's expert here. Both of these [18] plaintiffs died. My recollection is it was [19] cancer; but for the life of me, as I sit here [20] today, I can't come up with the exact details [21] of either case.
[22] MR. SCHULER: Okay. All right. [23] Let me go ahead and mark this Plaintiff's 2 for [24] a moment here. [25] (PLF. EXH. 2, Handwritten List of

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[1] Cases, was marked for [2] identification.)
[3] BY MR. SCHULER:
[4] Q. We will get to this case, [5] eventually, I assure you.
[6] A. Yes. I've done this before.
[7] Q. Okay. Do you recall in the [8] Blankenship Case and the -- I think, you said [9] it was the Fort Drum Plaza Case?
[10] A. Yes. No. Coffee versus Tennessee [11] was the other.
[12] Q. Okay. Coffee and Blankenship?
[13] A. Yeah.
[14] Q. Do you recall what kinds of cancer [15] or what types of products were involved in [16] those cases?
[17] A. The chemicals involved in Coffee [18] versus Tennessee were -- it was a very [19] technical, legal case. He was claiming injury [20] from exposure to chromated copper arsenate wood [21] preservative. Tennessee Chemical manufactured [22] the copper component that was used by the [23] company he worked for in mixing up to make [24] chromated copper arsenate. [25] I had very limited testimony in

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[1] that case. That copper was not responsible [2] and, therefore, that specific defendant should [3] not be included in the case. So I really [4] didn't deal with copper cancer, except to say [5] that copper was not -- I don't remember what [6] kind of cancer he had.
[7] Q. All right. These cases that you've [8] listed on Plaintiff's 2 go back -- do these [9] cover all the cases where you've rendered some [10] type of testimony?
[11] A. Only back through '88.
[12] Q. '88?
[13] A. I stopped.
[14] Q. Okay.
[15] A. Backwards to the beginning of '88.
[16] Q. Okay. And so

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from '83, when your [17] first involvement, to '88, that five-year [18] period---
[19] A. There's probably another dozen or [20] so cases.
[21] Q. Okay. And would you have any of [22] those listed somewhere?
[23] A. Well, I can reconstruct -- all I [24] have is business records and files.
[25] Q. Okay. But you have the records

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[1] where you could reconstruct it?
[2] A. Yes, I could reconstruct it.
[3] Q. From '83 to '88, did you testify in [4] any cases that involved allegations of cancer [5] causation for particular chemicals?
[6] A. The best I can say is probably. I [7] can think of -- I can't think of any where I [8] testified or gave a deposition.
[9] Q. From '83 to '88?
[10] A. Yes.
[11] Q. So those would have all been review [12] of cases, but it never came to testimony?
[13] A. That's my recollection, without [14] looking at the records.
[15] Q. Were there any cases that you [16] recall that involved cancer allegations, of [17] cancer being caused by---
[18] A. No.
[19] Q. ---specific chemicals?
[20] A. I'm quite certain that there was no [21] cancer case where I was. . .
[22] Q. An expert?
[23] A. Yeah.
[24] Q. Okay.
[25] A. The majority of these cases are

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[1] really not personal injury cases in the classic [2] sense toxic tort, they're more, you know. . .
[3] Q. Pollution?
[4] A. Yeah. Pollution, nuisance, [5] property value, trespass kind of claims.
[6] Q. Okay. Other than the Pickering [7] Case and the Coffee Case and the Blankenship [8] Case, were there any other personal injury [9] cases in this group, in the list?
[10] A. Well, yes. This John Soublis that [11] I'm working on now.
[12] Q. Soublis?
[13] A. Yes. Brown versus Chlorox is a---
[14] Q. Let me stop you one second. The [15] Soublis Case involves what kind of injury?
[16] A. It's cancer, skin cancer.
[17] Q. That's a skin cancer case?
[18] A. With coal tar pitch volatiles.
[19] Q. All right.
[20] A. Ruffin versus Beazer is a personal [21] injury case. He's got chloracne, neurological [22] deficits, which I attribute to exposure to wood [23] preserving chemicals.
[24] Q. Okay. You're retained by [25] plaintiff's counsel in that case?

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[1] A. Yes.
[2] Q. Mr. McCracken?
[3] A. Yes.
[4] Q. And where's he out of?
[5] A. Augusta, Georgia.
[6] Q. Okay.
[7] A. Tucker versus Southern Wood [8] Piedmont is currently one of these property [9] cases, but I think will become a personal [10] injury case. And there it's neurologic damage, [11] dermatologic changes, and possibly a genetic [12] mutation involving, again, wood preserving [13] chemicals at Southern Wood Piedmont.
[14] Q. Okay.
[15] A. Brown versus Chlorox is a personal [16] injury case. I'm defense expert in that case [17] for Chlorox's local attorney. Brown claims [18] that she died of adult respiratory distress [19] syndrome. Her parents claim she died of adult [20] respiratory distress syndrome from -- Miller [21] versus---
[22] Q. Where is that case pending trial?
[23] A. That case would be in, I think, [24] Rock Hill, South Carolina, is where her [25] residence is. I don't know what court

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[1] jurisdiction that would be in.
[2] Q. Okay.
[3] A. My local counsel is here in [4] Columbia, Whaley, McCutchen.
[5] Q. All right.
[6] A. Miller versus Exide is a property [7] damage case involving lead pollution. I'm

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[8] plaintiff's expert there. [9] Anderson versus Muskegon County was [10] purely a nuisance kind of case. They didn't [11] even need a toxicologist, but I was plaintiff's [12] expert there. Telling them that sewage smelled [13] bad. [14] Lyons versus Beazer East, again, by [15] Beazer, you know it's wood preserving. These [16] two are related cases. They're primarily [17] nuisance, property damage, based on potential [18] adverse health effects including cancer from [19] wood preserving chemicals. [20] Bogart versus Sturgis Iron and [21] Steel, I was defense expert there. She claimed [22] multiple chemical sensitivity syndrome type [23] reaction to her exposure there. [24] Raven versus Greenville County is a [25] property damage case with a leaking landfill.

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[1] Farmer versus Weissman is a [2] silicone -- not silicone -- teflon. Here I was [3] defense expert. Teflon injection in the vocal [4] cord, medical malpractice type case.
[5] Q. You mean a solid teflon implant?
[6] A. No. It's called teflon paste.
[7] Q. Okay.
[8] A. Injected. Vanderlaan versus [9] Marathon is -- here I was plaintiff's expert. [10] Again, it's nuisance and property damage from [11] an oil refinery. [12] We talked about Coffee versus [13] Tennessee Chemical. That's the copper. [14] Gold Cup Springs never got very [15] far. That's a jet fuel oil spill in [16] Charleston, South Carolina. I was plaintiff's [17] expert in that one. [18] Blankenship versus AMP, we talked [19] about. That's a worker compensation case, and [20] he died. And boy, it just kills me. I can't [21] remember -- I suspect it was cancer, but the [22] chemicals were -- no. I know what it was. [23] That can't have been cancer. [24] It's coming back to me. I remember [25] now. He died of liver necrosis cirrhosis

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[1] fibrosis. Yeah. And it was a glycol ether and [2] a chlorinated hydrocarbon exposure. [3] Diehl versus ASARCO, I was defense [4] expert in that case. That's a property damage [5] case involving a lead smelter in Helena, [6] Montana. [7] Fort Drum Plaza was a -- oh, boy. [8] Now, I think about this one. I think Billy Joe [9] Moss died of cancer, leukemia, and it was [10] gasoline -- it was a gasoline spill at this---
[11] Q. Is that in Florida on the turnpike?
[12] A. Yeah. On the turnpike there. [13] That's one of the world's largest underground [14] gasoline spills, that service area on the [15] Florida turnpike. I was plaintiff's expert [16] there. [17] Laurinburg was an underground [18] gasoline -- leaking underground gasoline [19] storage tanks. That was a personal property [20] damage case. [21] Kelley versus Para-Chem Southern, [22] property damage case. I was plaintiff's [23] expert. That involved just property value from [24] pollution by a chemical plant adjacent to this [25] property.

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[1] Marshall versus Southern Wood [2] Piedmont is actually a precursor case of this [3] Tucker versus Southern Wood Piedmont, and this [4] went to a settlement for -- it was property [5] damage.
[6] Q. Where was that last case pending, [7] the Marshall Case?
[8] A. That's settled. This one is, [9] Tucker versus Southern Wood Piedmont is pending [10] in Augusta, Georgia.
[11] Q. All right. And these are, as far [12] as you know, a pretty exhaustive list of the [13] cases that you've been involved in?
[14] A. Since the beginning of 1988, yes.
[15] Q. All right. Other than this case, [16] the Moyer Case, and the Pickering Case, have [17] you ever done any work for Dow Chemical [18] Company?
[19] A. To my recollection, I've done no [20] other work for Dow Chemical Company, with the [21] qualification, Larry Rampy on that isocyanide [22] case was a Dow employee.

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[23] Q. Okay. The percentage of your time [24] over the last four years, roughly since 1988, [25] that's been involved in legal consulting is

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[1] what?
[2] A. About 10 percent.
[3] Q. Okay. And how can you break down [4] the other 90 percent?
[5] A. Well, for the last five years, [6] that's been about two-thirds private clients [7] and one-third government because, up until two [8] years ago, I had the VA contract which was [9] about -- on phenoxy herbicides, which was about [10] a third of my chargeable time each year on that [11] project. [12] Since that project's ended, I've [13] done in -- I've done -- so that's about the [14] last two years, I've done almost no government [15] work. Been almost exclusively private work the [16] last two years.
[17] Q. Okay. Is there one particular [18] client that's your main client or. . .
[19] A. Well, at the present time, as we [20] look at a snapshot today, I would say McGhan [21] Medical Corporation is about a third of my [22] chargeable time.
[23] Q. And how far back would that go [24] where McGhan was your---
[25] A. About two years.

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1] Q. And you became adjunct associate [2] professor at the University of South Carolina [3] in 1985?
[4] A. Correct.
[5] Q. And what was the background on [6] that? Why did you do that?
[7] A. My wife is an historian and has [8] always wanted to teach at the college level and [9] had looked for a teaching job for seven years [10] when we lived in the Washington metropolitan [11] area and was unable to find a permanent [12] position, although she had a one-year teaching [13] appointment every year for seven years at [14] different universities. [15] And so one of the reasons I started [16] to sever my ties with Clement was so that she [17] could look in a broader geographic sense for [18] the type of position she was looking for. So [19] in 1985, she got a job at the University of [20] South Carolina and, since they had an airport, [21] I came along and that's where we've been. [22] When I knew I was coming here, I [23] contacted the University, the Department of [24] Environmental Health Science; and they were [25] very gracious and said they would very much

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[1] like to have me affiliated with the [2] department. So it's worked out well, I hope, [3] for both of us since then.
[4] Q. Well, how much time do you spend in [5] your teaching responsibilities?
[6] A. I teach about ten lectures per [7] semester. So as a percentage of my time, it's [8] quite minimal. It's about 5 to 10 percent of [9] my time on teaching duties as a whole. I do a [10] little more than just come in and lecture. [11] In fact, the first five years we [12] were here, I maintained my office in the [13] department, on campus. So I do -- I don't [14] direct research, but students can come to me [15] for assistance and advice. I've served on [16] committees and, in general, participate.
[17] Q. In conjunction with your adjunct [18] associate professorship, do you teach regular [19] courses or just come in and do spot lectures?
[20] A. Well, I do both. I have been -- [21] the bulk of my lecturing is in one course that [22] I share with another faculty member. And, in [23] fact, one year, when we lost the faculty member [24] late in the year and couldn't replace her, I [25] had responsibility, in fact, for a course.

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[1] Hopefully, never again. But I do have one [2] course where the bulk of my lectures are given, [3] and then I give one or two a semester as a spot [4] lecturer in other courses.
[5] Q. What are the titles of some of the [6] courses that you've taught on a continuing

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[7] basis?
[8] A. Well, they're included on the very [9] last page of the CV that I've given you. And [10] the one that I teach in heavily is about [11] two-thirds of the way down, the 788, 789, [12] Concepts of Hazardous Materials Management I [13] and II, two semesters, basically, course. [14] That's the one where I do the bulk lecture.
[15] Q. Okay.
[16] A. And then I -- the first one on the [17] list, Concepts of Environmental Health [18] Sciences, is our introductory course for [19] first-year graduate students in the program, [20] and I usually lecture in there once a [21] semester. The others are come and go, now and [22] then.
[23] Q. Okay. So Applied Aquatic Sciences, [24] Risk Assessment and Interactions of [25] Environmental Toxicants are not on-going

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[1] courses that you give per se; correct?
[2] A. That's correct.
[3] Q. They're---
[4] A. Taught by other faculty members, [5] and I typically give a guest lecture, maybe not [6] even every year. We don't offer those courses [7] every year. They come when there's, you know, [8] sufficient registration to offer them.
[9] Q. Do you use a particular text in [10] your on-going courses?
[11] A. We are getting down to that, [12] finally. We never found one book that's [13] satisfactory for Concepts and Hazardous Waste [14] Management I and II. [15] We started out almost exclusively [16] with texts that we created by coping portions [17] out of other books. The copy center got a [18] little upset with us on that, and we now [19] purchase two different texts, one for each -- [20] have the students purchase a text for each [21] semester. I don't know what those are because [22] they're heavy toward the engineering and [23] regulatory aspects. [24] Everything I do for toxicology, I [25] hand out detailed class notes, plus I use a

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[1] book called RISK ASSESSMENT IN THE FEDERAL [2] GOVERNMENT. Yeah. RISK ASSESSMENT IN THE [3] FEDERAL GOVERNMENT and that's---
[4] Q. Who authored that book?
[5] A. Covello, C-o-v-e-l-l-o, and I think [6] he has a co-author; and it's published -- it's [7] unusual. It's printed by the federal [8] government, Government Printing Office; and [9] it's very inexpensive, but a very nice [10] resource.
[11] Q. All right. Any other texts that [12] you use or is that the only one?
[13] A. That's the only one.
[14] Q. All right. Other than your work [15] with McGhan and your legal consulting and your [16] teaching, that's -- actually the McGhan work [17] and the legal consulting and teaching combined [18] is about 50 percent of your time?
[19] A. Sounds like it.
[20] Q. And the other 50 percent is what?
[21] A. A variety of other clients. Many [22] of them kind of long-term things that go on. [23] For example, Chem Nuclear Systems, [24] Incorporated, operates a low level, radioactive [25] waste disposal facility down here in Barnwell,

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[1] South Carolina. [2] And in the years before they owned [3] that facility, some of the radioactive [4] materials that they put in the landfill down [5] there had chemical, liquid chemical [6] constituents; and some of those have escaped [7] the confines of the specific trenches in which [8] they were disposed of and have gotten into the [9] groundwater immediately underlying the site. [10] So they asked me to develop a [11] groundwater monitoring strategy for that site [12] and then they follow that strategy and I review [13] it, the results, and make recommendations [14] periodically for adjustments in the program and [15] so forth. [16] And, now, they have moved on. They [17] are developing sites in sev-

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eral other states, [18] and I'm developing and overseeing their [19] groundwater monitoring for non-radioactive [20] materials at those sites, also.
[21] Q. All right. And that takes up a [22] substantial portion of your time?
[23] A. No. That's the kind of thing that [24] takes, at most, one day a month, kind of thing; [25] but it's an on-going thing.

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[1] Q. Do you have a contract with these [2] folks?
[3] A. I suppose.
[4] Q. All right.
[5] A. I do. I'm being flip. I'm sorry. [6] I do have a contract with them, but it was [7] signed five years ago and it may or may not be [8] expired by now.
[9] Q. Okay.
[10] A. But I've never been a stickler [11] for -- I've never had a client -- well, I had [12] one client do me wrong once, but much of my [13] work is done on a handshake and word of mouth. [14] Right now, I'm very busy with a number of other [15] clients that manufacture medical devices. [16] I suppose, because of my [17] involvement in the silicone and mammary implant [18] issues, I had some visibility; and now [19] manufacturers of a variety of medical devices [20] are coming to me to help them develop a [21] strategy for testing the materials in their [22] devices, or the device as a whole, to meet the [23] requirements for the Food and Drug [24] Administration and to get approval for their [25] products to be marketed in the United States

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[1] and/or in the -- abroad.
[2] Q. Other than the silicone gel, [3] mammary breast implant devices, can you give me [4] some examples of other devices you're involved [5] with?
[6] A. Well, I've got to be very cautious [7] here because that's very much confidential [8] business information. But just in general [9] terms, I'm involved with denture materials, [10] with implantable devices for treating [11] arthritis, with external devices for use in the [12] therapy of cancer, and a couple of others I [13] just can't think of right now. But those, I [14] can't go into too much and it's not relevant.
[15] Q. I understand. Are those all [16] contracts with manufacturers?
[17] A. Yes.
[18] Q. All right. I asked you about your [19] testimony in legal proceedings. Have you ever [20] testified before governmental agencies? When I [21] say testified, I mean, given any type of -- [22] rendered any type of opinions or provided [23] information in an open type forum?
[24] A. I have presented to three [25] outside -- no. Four times, I've presented to

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[1] outside advisory boards or committees to the [2] Food and Drug Administration.
[3] Q. Four times?
[4] A. Yes.
[5] Q. And was that all in connection with [6] the silicone gel mammary implant?
[7] A. No, no.
[8] Q. Tell me what those were.
[9] A. Well, the first one was actually [10] while I was an employee of the Food and Drug [11] Administration, when I was branch chief in the [12] OTC drug division. [13] We initiated, from within FDA, an [14] initiative to reclassify paregoric from the [15] list of controlled substances. Basically, [16] reclassify it from being a drug for potential [17] abuse to one that was not, so that it could be [18] an ingredient in over-the-counter drug products [19] available without prescription. [20] And I presented that argument to [21] the advisory committee of the -- that would [22] have been -- oh, it's the National Institute -- [23] not National Institute of Drug Abuse, not NIDA, [24] but a sister agency. I can't think of what the [25] name of it is.

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[1] Q. You provided testimony on that [2] topic in any event?
[3] A. Yes.
[4] Q. About what year

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was that?
[5] A. Well, it was probably about 1980.
[6] Q. Okay. What are the other three [7] occasions, then, that you've testified?
[8] A. Then I testified -- the other three [9] were before device panels at the U. S. Food and [10] Drug Administration. Two were silicone mammary [11] implants.
[12] Q. Okay.
[13] A. In November of '90 and February [14] of -- sorry. November of '91 and February [15] of '92. And then I testified before a device [16] panel for that teflon paste, injectable teflon [17] paste for urinary incontinence indication and [18] that would have been either late 1990 or [19] early '91.
[20] Q. But those are panels set up by the [21] FDA to investigate these matters; correct?
[22] A. Yes.
[23] Q. And in your testimony on the [24] silicone gel or before the silicone gel special [25] panel, were you retained by McGhan or someone

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[1] else?
[2] A. By McGhan.
[3] Q. Were you testifying specifically as [4] a representative of McGhan during that panel?
[5] A. As a paid consultant to McGhan.
[6] Q. Okay.
[7] A. Yes. Not an employee or advocate [8] for McGhan.
[9] Q. Okay.
[10] A. Independent consultant, paid for by [11] them.
[12] Q. And do you have retained copies of [13] your testimony on the silicone gel matter?
[14] A. No, I do not. In that kind of [15] situation, I speak from notes; and there are [16] transcripts of both of those proceedings. I [17] don't have a copy.
[18] Q. That's really what I was asking, [19] whether you had a copy of the transcripts of [20] the proceedings?
[21] A. No, I do not.
[22] Q. Other than yourself, did anyone [23] else retained by McGhan testify, to your [24] knowledge, before the subcommittee?
[25] A. Oh, yes. In my mind, now, the two

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[1] hearings have kind of blended together. They [2] had their own employees presented to one or [3] both of those panels. Outside experts included [4] Gearheart Brand, several others. I can't [5] remember.
[6] Q. Okay. Have you ever had any -- I [7] know. I've kind of piecemealed this question, [8] but I want to make sure I've covered it. Have [9] you ever had any consulting arrangement with [10] any chemical, herbicide chemical manufacturer [11] or trade organization that deals with [12] agricultural chemicals?
[13] A. I think not. I'm pretty sure I [14] haven't.
[15] Q. Okay. How much do you charge for [16] your time in legal consulting type work?
[17] A. $125 an hour for preparation and [18] review of documents and so forth. And $150 an [19] hour for deposition time or time on the stand.
[20] Q. And can you give me an estimate, or [21] an exact number, perhaps, if you have it, of [22] how much time you have involved in this case up [23] to this date?
[24] A. I can only estimate that and it's [25] on the order -- before today, prior to 8

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[1] o'clock this morning -- probably 16 to 24 [2] hours.
[3] Q. Do you keep records of your time on [4] a computer?
[5] A. Yes. I don't do it in the [6] computer. I do it in my daily calendar.
[7] Q. Manually?
[8] A. Yes.
[9] Q. I asked you what percentage of [10] time. What percentage of your income is [11] represented by reviewing and testifying in [12] legal matters?
[13] A. Would be the same, 10 percent.
[14] Q. Okay.
[15] A. I don't charge higher rates.
[16] Q. Okay. Do you keep time sheets?
[17] A. Well, yes. I keep a time record in [18] my daily calender. I write -- at the end of [19] each day, I put down the hours I spent, [20] chargeable hours.
[21] Q. All right. Now,



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there was some [22] discussion off the record, I think, when I [23] first came in here this morning about the fact [24] that you have a somewhat sizeable library or, [25] at least, research resources that you keep. Is

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[1] that at home or in your office?
[2] A. That's in my office.
[3] Q. Can you just kind of describe for [4] me generally what you have and how it's [5] organized?
[6] A. Well, I have a copy of the [7] majority -- I hesitate to say exactly what [8] percentage, probably roughly 75 percent of all [9] the articles that are included in Volumes 3 [10] through 18, is it? 3 through 18 of the VA [11] review. [12] I probably have copies of [13] two-thirds to three-quarters of all the [14] articles in there, in file cabinets. Plus [15] another 4- or 500 articles that are either not [16] in that time frame or relate to dioxins and [17] furans, other than the ones that we were [18] concerned about for specifically the Vietnam [19] herbicides. And so those are all in a file [20] cabinet. [21] And then I have two bookshelves. I [22] probably have eight, ten, twelve book books, [23] monographs, I guess, on dioxin and Agent Orange [24] and things. I have, of course, a complete set [25] of the VA reports and synopses. I have

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[1] proceedings of all the International Dixon [2] Symposia that I attended, chemosphere volumes [3] covering those conferences, and some I didn't [4] go to. [5] Oh, and miscellaneous documents, [6] like the World Health associating criteria on [7] 2,4-D and dioxin and the EPA drinking water [8] criteria documents for dioxins and a number of [9] those kind of secondary references in this [10] area.
[11] Q. Okay. And you brought some [12] documents with you today?
[13] A. Yes, I did.
[14] Q. What documents did you bring with [15] you today?
[16] A. Basically, what I brought is [17] documents provided to me by Mr. Wagner relevant [18] to this case.
[19] Q. Before we get started on that, let [20] me just ask you a few preliminary questions [21] here. When were you first contacted about this [22] case?
[23] A. Forgot to look that up last night. [24] I think about last summer or last fall. It [25] would have been between July and November of

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[1] 1992, I think.
[2] Q. And who first contacted you?
[3] A. Well, Heidi Garwood, who's in the [4] office of Mr. Wagner.
[5] Q. And do you know how they got your [6] name?
[7] A. They got my name, I understand, [8] from Clement Associates. They had become aware [9] of the literature review and called Clement; [10] and Clement said, well, you need to talk to Dr. [11] Schulz because he was the key player there. [12] And that's how they got my name.
[13] Q. The literature search, [14] incidentally, that we've discussed at length at [15] the outset here. When I looked at that, and [16] maybe it's just a copy that I got, I didn't see [17] your name on it. Is there a reason for that?
[18] A. Well, that's something of the [19] nature of contract work to begin with. I'm [20] really not the author. Although, if you look [21] carefully, it's -- I don't know if it's in the [22] preface or the forward. I always get those two [23] mixed up. The responsible individuals are [24] identified. [25] You have one of the synopses. In

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[1] the synopses, I was not identified in that. [2] It's in the actual preface or forward of the [3] two volumes.
[4] Q. Well, let me show you this for [5] identification purposes. We can mark it, [6] and we don't have to attach it necessarily. Can [7] you take a look at that? Is that the most [8] recent synopsis of

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the dioxin articles that---
[9] A. Yes. If it's all here, that would [10] be it. Yes.
[11] Q. Can you just look at it to see [12] whether that's the complete synopsis, the best [13] you can tell? I probably don't have the---
[14] A. I think so. I think so.
[15] Q. All right. We'll mark it as [16] Plaintiff's 3. I'll just go ahead and put a 3 [17] on here. [18] This is the one that does not have [19] your name on it; correct?
[20] A. That's correct.
[21] Q. And I have a partial, I believe, [22] copy of what appears to be---
[23] A. That's the front page of one. [24] Yeah.
[25] Q. There's an introduction and then a

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[1] list of all the articles. This is, obviously, [2] far from complete.
[3] A. Yeah, it's part.
[4] Q. But take a look at this and tell me [5] which one of the aspects of the contract that's [6] a partial representative of.
[7] A. This would have been that critical [8] review portion.
[9] Q. Okay.
[10] A. One of the two volumes covering the [11] year -- the literature that was published in [12] 1990. And there's a cover page and a table of [13] contents and here's the forward and, right [14] there, it says, the project director for [15] Clements was me. The technical director and [16] principal author of the review was me.
[17] Q. Okay.
[18] A. And then there are other [19] contributors.
[20] Q. Project director, Wayne?
[21] A. Reichardt.
[22] Q. Reichardt?
[23] A. Uh-huh.
[24] Q. Was he your boss on that?
[25] A. In an administrative sense, yes.

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[1] Q. Okay.
[2] A. He had no oversight over the [3] technical completion. He just had to make sure [4] I didn't overrun my budget.
[5] Q. And then Sharon Segal and Sanjivani [6] Diwan, they were both employees?
[7] A. Of Clement. Yes.
[8] Q. Okay.
[9] A. And scientists and drafted specific [10] sections of the review.
[11] MR. SCHULER: All right. I guess [12] we'll mark that for discussion purposes as [13] Plaintiff's 4. [14] (PLF. EXH. 3, Fax Transmittal with [15] Synopsis of Scientific Literature [16] on Phenoxy Herbicides, was marked [17] for identification.) [18] (PLF. EXH. 4, Fax Transmittal with [19] Review of Literature on [20] Herbicides, was marked for [21] identification.)
[22] BY MR. SCHULER:
[23] Q. Are Plaintiff's 3 and Plaintiff's 4 [24] the most recent versions of what you did?
[25] A. They're the most recent versions of

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[1] what I did. That contract was re-awarded to [2] another vendor in -- whenever that would have [3] been. The year after that.
[4] Q. Okay. This purports to be a [5] summary of the literature from 1990.
[6] A. Uh-huh.
[7] Q. Was that the last year that you [8] were involved with it?
[9] A. That's correct.
[10] Q. And then do you know who has the [11] present contract?
[12] A. It's an outfit in Philadelphia, and [13] I can't remember their name.
[14] Q. All right. After you were [15] contacted about this case, what were you asked [16] to do initially?
[17] A. Well, in the initial contact, we [18] just discussed the very general aspects of the [19] case and what my experience was with phenoxy [20] herbicides and dioxins, and then I was sent a [21] number of these documents at that time to [22] review.
[23] MR. WAGNER: Before you go on with [24] this case, I need to take another break.
[25] MR. SCHULER: Sure.

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[1] MR. WAGNER: You might want to just [2] glance through those, give you a head start on [3] what's in there. [4] (A recess transpired.)

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[5] BY MR. SCHULER:
[6] Q. I think my last question to you, [7] Dr. Schulz, was what you were asked to do in [8] this case. And I think you told me that you [9] were asked to review this case and they were [10] going to send some documents to you with regard [11] to the allegations that Mr. Moyer's cancer was [12] caused by his exposure to the 2,4-D and silvex [13] that was involved in this matter; correct?
[14] A. Correct.
[15] Q. And were you asked to do anything [16] else?
[17] A. No.
[18] Q. What specifically were you supplied [19] with by the Defendants Dow and Occidental in [20] order to do your review? And you can take a [21] look at these documents here that I've gone [22] through. [23] Let's kind of put these documents [24] this way because these are the---
[25] A. Yeah, they're different.

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[1] Q. ---documents that you furnished, as [2] opposed to the ones that---
[3] A. That's correct.
[4] Q. ---were furnished you.
[5] A. That's correct. Initially, I was [6] furnished with the complaints and amended [7] complaints.
[8] Q. Why don't you just go through.
[9] A. Plaintiffs' Fifth Amended [10] Complaint, the proposed Sixth Amended [11] Complaint, Moyer's answers to the [12] interrogatories dated January 3rd, plaintiff's [13] answers to interrogatories dated January 5, [14] 1990, transcripts of Dr. Teitelbaum's [15] deposition, selected exhibits from Dr. [16] Teitelbaum's deposition. [17] Deposition summaries for Moyer, [18] Ellenbecker, Clapp, and one other, Sassick, [19] Nick Sassick, and. . .
[20] MR. WAGNER: Sudderam is in there.
[21] THE WITNESS: I think so and I just [22] don't find it initially. Oh, here it is. No. [23] I'm sorry. I thought I had a deposition [24] summary of Sudderam and it may be in there. I [25] just don't see it.

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[1] BY MR. SCHULER:
[2] Q. Maybe we can do it this way.
[3] A. That covers---
[4] Q. Let me go through that pile quickly [5] with you and I can kind of sort out---
[6] A. Okay.
[7] Q. ---just about everything. I think, [8] most of these things, I have already. [9] Is that part of it, too, there, [10] Allen?
[11] MR. WAGNER: Yes.
[12] BY MR. SCHULER:
[13] Q. I'll just stick this on here. You [14] received a copy of the Fifth Amended Complaint [15] which. . .
[16] A. It's under there.
[17] Q. A copy of the Sixth Amended [18] Complaint, Moyer's answers to expert [19] interrogatories dated January 3rd.
[20] A. And the 5th of January 1990.
[21] Q. Okay. I was going by the letter [22] here. Okay. Plaintiff's answers to [23] interrogatories dated January 5th. I guess [24] that's what that is. The expert [25] interrogatories may be here. Yes. Okay.

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[1] A transcript of Dr. Teitelbaum's [2] deposition with exhibits.
[3] A. These two are the actual [4] deposition.
[5] Q. Okay.
[6] A. And the exhibits are basically---
[7] Q. Part of this?
[8] A. Basically almost -- this is all [9] exhibits.
[10] Q. Medical toxicology.
[11] A. I think it goes all the way down to [12] the bottom of that.
[13] Q. Yes. Okay. This is it, too.
[14] A. Uh-huh.
[15] Q. Yes. Okay. And this was what you [16] were furnished with initially, along with this [17] cover letter of September 25, 1992?
[18] A. That's correct. And that about [19] sets the date. They probably sent me that [20] within a week or two of the initial contact.
[21] MR. SCHULER: Okay. I'll go ahead [22] and have the cover letter marked as a summary [23] of what we have. That will be Plaintiff's

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5, I [24] think. [25] (PLF. EXH. 5, Letter to Dr. Carl O.

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[1] Schulz from Heidi E. Garwood, [2] dated September 25, 1992, was [3] marked for identification.)
[4] THE WITNESS: I think those are [5] exhibits to Teitelbaum's.
[6] MR. WAGNER: Can I see the letter? [7] When you were going through -- I know we sent [8] him and here's the letter enclosing the public [9] record. The same thing that Dr. Smith got.
[10] MR. SCHULER: Yes.
[11] THE WITNESS: That's that.
[12] MR. WAGNER: Yes, but the summary [13] sheets aren't there.
[14] THE WITNESS: I think they're in [15] there somewhere.
[16] MR. WAGNER: They may be buried in [17] there. Okay. It's the same stuff that we sent [18] to Dr. Smith that was marked at his [19] deposition.
[20] MR. SCHULER: You mean Dr. Eaton?
[21] MR. WAGNER: And Dr. Eaton, as [22] well, yes.
[23] BY MR. SCHULER:
[24] Q. Okay. All right. And some of the [25] public records from Orange County. These are

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[1] the records that you were sent?
[2] A. Yes.
[3] Q. This goes with this?
[4] A. Yes.
[5] Q. Okay. Attach this.
[6] MR. WAGNER: As I say, I think [7] the -- there was a typewritten summary that I [8] don't see in there.
[9] THE WITNESS: I don't see it, but I [10] don't what you're talking about.
[11] MR. SCHULER: Okay. Let me go [12] ahead and have this marked as plaintiff's next [13] number. [14] (PLF. EXH. 6, Letter to Carl O. [15] Schulz from Heidi E. Garwood, [16] dated October 26, 1992, with [17] attachments, was marked for [18] identification.)
[19] BY MR. SCHULZ:
[20] Q. Okay. Were you furnished with [21] anything else by the defendants?
[22] A. Then at a later date, this is [23] described in the cover letter as -- no. I'm [24] sorry. This is Dr. Hardell's manuscripts, I [25] guess, that he supplied. And then I got, at a

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[1] later date, a transcript of his.
[2] Q. This is the transcript of Dr. [3] Hardell's deposition?
[4] A. Of his deposition, yes.
[5] MR. SCHULER: All right. Let me go [6] ahead and mark this as Plaintiff's 7. [7] (PLF. EXH. 7, Letter to Carl O. [8] Schulz from Alan F. Wagner, dated [9] November 19, 1992, with [10] attachments, was marked for [11] identification.)
[12] BY MR. SCHULER:
[13] Q. And what else were you furnished [14] with?
[15] A. This is Mr. Swanson's deposition.
[16] Q. That's the one that was taken [17] recently. All right. What else were you [18] furnished with?
[19] A. That's all.
[20] Q. Okay.
[21] A. I think. These are all mine. [22] Yeah.
[23] Q. There are some other documents that [24] you brought with you?
[25] A. Yes.

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[1] Q. And these are documents that you [2] furnished to the defendants?
[3] A. No.
[4] Q. Just notes?
[5] A. The first one, this clip is a [6] letter that I sent to Mr. Wagner with the [7] articles that I cited in there.
[8] Q. Okay.
[9] A. These others are just things I [10] brought today. I consider them publications [11] containing relevant information for this case.
[12] Q. Okay. The first letter and [13] articles that you mention is a letter of [14] October 22, 1992, from yourself to Mr. Wagner, [15] attaching some references and some articles [16] regarding exposure to TCDD?
[17] A. Correct.
[18] MR. SCHULER: Okay. Have this [19] marked as Plaintiff's 8. [20] (PLF. EXH. 8, Letter to Alan Wagner [21] from Carl O. Schulz, dated October [22] 22, 1992, with attachments, was [23] marked for identifi-

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cation.)
[24] BY MR. SCHULER:
[25] Q. And then what is this next packet

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[1] here?
[2] A. That is a series of journal [3] articles describing studies of epidemiologic [4] studies of cancer related to dioxin exposure.
[5] MR. SCHULER: Okay. I think we'll [6] mark this Plaintiff's 9. [7] (PLF. EXH. 9, Series of Journal [8] Articles on Cancer Epidemiology, [9] was marked for identification.)
[10] BY MR. SCHULER:
[11] Q. What's this next group?
[12] A. This is a series of three articles [13] from the published literature describing [14] studies of exposure assessment to phenoxy [15] herbicides and dioxin.
[16] MR. SCHULER: Mark this as [17] Plaintiff's 10. [18] (PLF. EXH. 10, Three Articles on [19] Exposure Assessment to Phenoxy [20] Herbicides and Dioxin, were marked [21] for identification.)
[22] BY MR. SCHULER:
[23] Q. And then this last packet with the [24] rubber band around it?
[25] A. These are a series of documents

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[1] that are relevant to tissue levels of dioxins [2] and furans in the general public and in [3] occupationally exposed populations.
[4] MR. SCHULER: Okay. Let's mark [5] this as Plaintiff's 11. [6] (PLF. EXH. 11, Series of Documents, [7] were marked for identification.)
[8] BY MR. SCHULER:
[9] Q. All right. Have you reviewed [10] anything else or looked at any other [11] documentation with regard to this case that's [12] helped you in the formulation of your opinions?
[13] A. Well, my opinions are based on ten [14] years or more of experience and review of all [15] the scientific literature available on it. But [16] other than that and these documents and so [17] forth, no, I have not.
[18] Q. Okay. You're testifying as a [19] toxicologist in this case; correct?
[20] A. That's correct.
[21] Q. And you're not a medical doctor, [22] obviously?
[23] A. That's correct.
[24] Q. You have neither examined nor [25] treated cancer patients or patients that have

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[1] been exposed to phenoxy herbicides; correct?
[2] A. That's correct.
[3] Q. And if I understand, when you talk [4] about your experience, your experience is based [5] on your review of the literature in this field, [6] as opposed to generating any independent [7] literature on your own or research on your own; [8] correct?
[9] A. Correct.
[10] Q. All right. Have you formulated, [11] then, some opinions that you can state for me [12] generally with regard to this case and then [13] we'll get to the specifics of it?
[14] A. Yes, I have.
[15] Q. And what are those opinions?
[16] A. Opinion is that, to a reasonable [17] degree of scientific certainty, Mr. Moyer's [18] cancer was not caused by an exposure that he [19] experienced while employed for Orange County in [20] the summers of -- in the years 1976, 1977.
[21] Q. Okay. And factually -- and I know [22] these are broad questions, but we'll get to the [23] specifics. Factually, generally, what do you [24] base that opinion on?
[25] A. I base that opinion on the fact

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[1] that there's no credible evidence that he was [2] exposed to any meaningful quantity of a [3] chemical or agent hypothesized or known to [4] cause human cancer, including soft tissue [5] sarcoma.
[6] Q. Okay. Let me explore that with you [7] for a few minutes here.
[8] A. Okay.
[9] Q. When I hear words like not exposed [10] to any meaningful quantity, that seems to be [11] somewhat of a broader or vague term. Let me [12] start with this question. Do you believe that [13] TCDD is a human carcinogen?
[14] A. Yes, I do.

[15] Q. And so, at some level of exposure, [16] you believe that that can cause cancer?
[17] A. Yes, I do.
[18] Q. Is your opinion here today, that [19] Mr. Moyer was not exposed to a sufficient [20] amount of TCDD in his time with Orange County, [21] to enable you to say, within a reasonable [22] degree of scientific certainty, that that [23] exposure causes cancer?
[24] A. That's correct.
[25] Q. Okay. And so are you telling me

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[1] that the exposure that Mr. Moyer had at Orange [2] County, you have deduced from the facts of this [3] case, did not rise to that level that would [4] permit you to say that that caused his soft [5] tissue sarcoma?
[6] A. That's correct.
[7] Q. So if I understand you correctly, [8] again, to paraphrase, your saying it's not [9] probable that Mr. Moyer's exposure at Orange [I0] County caused his cancer, but it might be a [11] possibility?
[12] A. It's not likely. Right.
[13] Q. Okay. But it's a possibility?
[14] A. Extremely remote.
[15] Q. Okay. But a possibility [16] nevertheless?
[17] MR. WAGNER: Object to form. Asked [18] and answered. Vague.
[19] BY MR. SCHULER:
[20] Q. Correct?
[21] A. I answered. Not likely.
[22] Q. As far as TCDD being a human [23] carcinogen is concerned, would you agree that [24] the scientific literature supports the fact [25] that TCDD is a human carcinogen?

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[1] A. Yes, I would.
[2] Q. When we say a human carcinogen, we [3] are referring to a substance that causes cancer [4] in human beings; correct? I mean, it's the [5] obvious, but I need to ask that.
[6] A. Yes, that's correct.
[7] Q. Okay. Do you believe that TCDD is [8] associated with the cause of certain types of [9] cancer?
[10] A. Not -- well, I don't -- I think [11] I -- well, I do not think that TCDD is the [12] classic site specific carcinogen in that it [13] causes only one kind of cancer and no other [14] kind. I think it causes a broad variety of [15] cancers.
[16] Q. And would soft tissue sarcoma be [17] among those?
[18] A. There are studies that suggest that [19] there's an elevated incidence of soft tissue [20] sarcoma among manufacturing workers heavily [21] exposed to dioxin. I hesitate to -- I don't [22] feel that there's very solid evidence that [23] dioxin causes soft tissue sarcoma. [24] It's a very poorly defined category [25] of cancers. It's not -- soft tissue sarcoma is

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[1] not a type of cancer in the since that lung [2] cancer is a type of cancer or leukemia is a [3] type of cancer.
[4] Q. What's different about soft tissue [5] sarcoma?
[6] A. Soft tissue sarcoma are types of [7] cancers of different cell types that arise or [8] occur in all different tissues and organs of [9] the body. The only unifying theme of the [10] category is that they arise in the so-called [11] soft tissues. [12] But they essentially have been [13] lumped together because each and every [14] individual type is generally rare and a very of [15] them is even thought to be understood and so [16] they're just put in this kind of catch-all [17] category for the purpose of classification, if [18] you will.
[19] Q. The commonality is that they arise [20] from the mesenchymal type tissue; correct?
[21] A. That's correct.
[22] Q. And the same tissues gives rise to [23] the lymphomas; correct?
[24] A. Yes, there are -- yes.
[25] Q. Okay. Now, with regard to Mr.

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[1] Moyer's specific case -- well, let me strike [2] that. [3] Do you believe that silvex is a [4] human carcinogen?
[5] A. No, I do not.
[6] Q. Would you agree that silvex [7] contains

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TCDD?
[8] A. Silvex, which we have to talk about [9] in the past tense, doesn't exist any more, [10] probably was contaminated with TCDD in---
[11] Q. I'm sorry. I didn't mean to cut [12] you off. Is that---
[13] A. In the past. Yes.
[14] Q. I understand that it's no longer [15] available or hasn't been available, I guess, [16] since, what, '79 or '80?
[17] A. About then. I can't specifically [18] say when.
[19] Q. And silvex was first manufactured [20] when, 1953, approximately?
[21] A. I don't know.
[22] Q. 2,4,5-T is that the same as silvex?
[23] A. No.
[24] Q. Okay. What's the difference?
[25] A. 2,4,5-T is

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[1] 2,4,5-trichlorophenoxyacetic acid and various [2] esters thereof. Silvex is [3] 2,4,5-trichlorophenoxy propionic acid and [4] various esters thereof. So they are [5] structurally related first cousins, perhaps, [6] but they're different compounds.
[7] Q. Structurally similar, but not [8] identical?
[9] A. Correct.
[10] Q. And the applications are [11] essentially the same, are they not? Or were [12] when they were being used?
[13] MR. WAGNER: Object to the form.
[14] THE WITNESS: That's beyond my area [15] of expertise.
[16] BY MR. SCHULER:
[17] Q. Does 2,4,5-T or did 2,4,5-T contain [18] TCDD?
[19] A. Historically, yes, it was probably [20] contaminated.
[21] Q. Other than TCDD, historically, have [22] other contaminants been found in either silvex [23] or 2,4,5-T?
[24] MR. WAGNER: Object to form.
[25] THE WITNESS: I need you to repeat

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[1] the question.
[2] BY MR. SCHULER:
[3] Q. I'll repeat it.
[4] A. Okay.
[5] Q. I'll repeat it. I said, other than [6] TCDD, have other contaminants been found in [7] either silvex or 2,4,5-T?
[8] MR. WAGNER: Same objection.
[9] THE WITNESS: I think so.
[10] BY MR. SCHULER:
[11] Q. Okay. Are you familiar with what [12] other contaminants have been found in those [13] commercial grade products over the years?
[14] A. I think small quantities of other [15] chlorinated dioxins and furans have been [16] identified in 2,4,5-T. I'm not familiar with [17] what's been found in silvex.
[18] Q. Do you know whether any of the [19] other contaminants that have been found in [20] 2,4,5-T are carcinogenic, or do you have an [21] opinion as far as that's concerned?
[22] A. Well, other---
[23] Q. When I say carcinogenic, by the [24] way, I'm always referring to in humans unless [25] we talk about something else.

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[1] A. Okay. In my opinion, other [2] chlorinated dibenzo-p-dioxins and dibenzo [3] furans, in which the lateral ring positions are [4] occupied by -- the four lateral ring positions [5] are occupied by chlorine atoms, contribute to [6] the carcinogenic activity. So that includes a [7] category of tens of individual compounds. Not [8] all of which were likely to be present in [9] 2,4,5-T, but I'm not prepared to testify [10] exactly which one were and weren't present.
[11] Q. You say that these are present in [12] 2,4,5-T, but you don't have an opinion as to [13] silvex?
[14] A. I have not seen any information on [15] contaminant levels. I've not seen factual [16] information. I have an opinion that the [17] contamination pattern of silvex, historically, [18] was probably similar to that of 2,4,5-T.
[19] Q. All right. Have you, from your [20] review of the literature, noted that [21] heptacholorodibenzo dioxin is a contaminant of [22] either silvex or 2,4,5-T?


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[23] A. I don't know.
[24] Q. What about hexacholorodibenzo [25] dioxin?

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[1] A. I don't know specifically.
[2] Q. What about octachlorodibenzo [3] dioxin?
[4] A. I think that's very unlikely, but I [5] don't -- I say, I did not -- I'm not prepared [6] to testify on which specific ones were there [7] and were not.
[8] Q. Okay.
[9] A. Other than TCDD, 2,3,7,8.
[10] Q. Would that answer be the same if I [11] asked you about furans?
[12] A. Yes.
[13] Q. And would it be the same if I asked [14] you about xanthones?
[15] A. Yes.
[16] Q. Do you have an opinion as to [17] whether any of the furans may be carcinogenic?
[18] A. I'd hoped my earlier answer covered [19] that, but the same rule applies for furans as [20] dioxins. That those that are occupied by [21] chlorine in the four lateral positions have the [22] potential to cause a carcinogenic response, [23] yes.
[24] Q. What about the xanthones?
[25] A. I have no opinion on the xanthones.

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[1] Q. Other than TCDD, would Mr. Moyer [2] have had any exposure to any carcinogenic [3] material, from your review of this case, in any [4] of the other chemicals he used? And I, also, [5] for the purpose of this question, want to [6] exclude our discussion of furans and xanthones [7] and the other dioxins.
[8] A. Uh-huh.
[9] Q. What I'm getting at, to make the [10] question clearer, is were there any other [11] chemicals or any other contaminants of any [12] other chemicals that you're aware of that he [13] used that, in your opinion, were potentially [14] carcinogenic?
[15] MR. WAGNER: You mean while [16] spraying in Orange County?
[17] MR. SCHULER: Right.
[18] THE WITNESS: Right. My review of [19] the list of those chemicals indicate -- [20] products and chemicals indicates none that I am [21] aware of that have been shown to be [22] carcinogenic in animals or humans.
[23] BY MR. SCHULER:
[24] Q. Okay. Do you have an opinion as to [25] what the exposure level would have to be, for

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[1] example, to something like TCDD in order to [2] make you suspect or opine that that would be a [3] cause of human cancer in an individual?
[4] A. No.
[5] Q. So there's no minimum safe level of [6] exposure to TCDD; is that correct?
[7] MR. WAGNER: Object to form.
[8] THE WITNESS: I said -- no. I [9] didn't say that. I said, I had no opinion on [10] what a safe level would be.
[11] BY MR. SCHULER:
[12] Q. Okay. As far as Mr. Moyer's [13] exposure was concerned -- I'm using that term [14] generically, exposure to. And, again, I'm [15] focusing, right now, just completely on his [16] time spraying chemicals for Orange County. [17] Did you do any calculations with [18] regard to what you thought his exposure was to [19] either any chemical or any contaminant of any [20] chemical?
[21] A. I have not made a quantitative [22] estimate of the amount of any herbicide or [23] contaminant therein that he might have been [24] exposed to.
[25] Q. Okay. How did you determine that

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[1] his exposure then was not meaningful?
[2] A. Well, it's based on an overview of [3] all the evidence and a number of [4] considerations; but, essentially, he handled [5] silvex very rarely, at widely separated time [6] points, perhaps, if at all. I think there's [7] some question whether he ever handled silvex; [8] but, even if he did, he handled it rarely. [9] Widely separated intervals with [10] very little total use. When he was handling [11] it, exposure in any way in which he could have [12] experienced systemic absorption was minimal



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[13] because he wore protective clothing, full [14] protective clothing. [15] When he sprayed it, the spray was [16] not in a form that would have caused a [17] respirable mist or spray that he could have [18] inhaled and or ingested to any great degree. [19] And his -- any conceivable exposure to silvex [20] or contaminating impurities was so small, [21] compared to his background exposure, as to be [22] negligible. [23] And the evidence, the factual [24] evidence indicates that he did not experience [25] any exposure because he has no body burden

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[1] of -- he had no body burden of the common [2] contaminating impurity when it was checked.
[3] Q. Okay. So you didn't make any [4] calculations per se, but based on those [5] observations, from the information that you [6] were provided, that's essentially what you're [7] basing your opinion on?
[8] A. Correct.
[9] Q. You don't dispute the fact, by the [10] way, that Bob Moyer had soft tissue sarcoma; [11] correct?
[12] MR. WAGNER: Object to form and no [13] predicate. As you said, he's not a medical [14] doctor. I don't know that if he could diagnose [15] it or is qualified to.
[16] THE WITNESS: Yeah. I'm not a [17] pathologist. I can't review the diagnosis. [18] Although there is some question in my mind, as [19] a biologist, with training in nisthology, I [20] cannot understand this terminology, epithelioid [21] sarcoma. It's like saying having a headache of [22] the toe.
[23] BY MR. SCHULER:
[24] Q. Okay. Did you see anything, other [25] than the fact that it was called epithelioid

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[1] sarcoma, which would give you any reason to [2] doubt that he had soft tissue sarcoma?
[3] A. No.
[4] Q. Was there any significance to you, [5] in arriving at your opinion, regarding the fact [6] that Bob Moyer's cancer was diagnosed in 1985 [7] and his first exposure would have been in 1976?
[8] A. Yes.
[9] Q. In other words---
[10] MR. WAGNER: Object to form. Wait [11] a minute. Let me get an objection. No [12] predicate with respect to the exposure or to [13] what you're referring.
[14] BY MR. SCHULER:
[15] Q. In other words, was there anything [16] about the latency period, from first exposure [17] to diagnosis, that was signature to you?
[18] MR. WAGNER: Same objection.
[19] MR. LUTZ: I'd join in the [20] objection.
[21] THE WITNESS: Yes. I thought the [22] latency was very short, too short to link his [23] cancer to the exposure.
[24] BY MR. SCHULER:
[25] Q. What latency period do you believe

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[1] is sufficient or would be a typical latency [2] period, assuming a cause and effect [3] relationship?
[4] A. Yes. I think that latency like [5] incidence is a function of the intensity and [6] duration of the exposure for a type cancer in [7] general that is caused by a chemical or [8] physical agent. And so, therefore, the vast [9] majority of cancer latencies range from 10 to [10] 30 years following initial exposure. And the [11] peak of these are 15 to 25. Some types of [12] tumors have even longer peak latencies. [13] But, you know, if there's a short [14] latency tumor that is quite clearly related to [15] a given cause, the literature suggests that the [16] exposure, the initial exposure was very [17] intense.
[18] Q. Well, again, assuming a cause and [19] effect relationship here for the purpose of the [20] hypothetical question and Bob Moyer's latency [21] period would have been approximately nine [22] years; correct, from initial exposure?
[23] A. No. Seven years.
[24] MR. WAGNER: Let me object to the [25] form of the question.

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[1] MR. LUTZ: I join.
[2] MR. WAGNER: Maybe we can clear it [3] up. You're asking him to a

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sume exposure to [4] TCDD in 1976?
[5] MR. SCHULER: Correct.
[6] MR. WAGNER: Okay. That's my -- no [7] predicate objection.
[8] MR. LUTZ: I join.
[9] MR. WAGNER: And that that exposure [10] caused his cancer?
[11] MR. SCHULER: That's correct.
[12] THE WITNESS: It's hypothetical.
[13] MR. LUTZ: I join.
[14] THE WITNESS: Nine years, yes. '76 [15] to '85 is nine years. Yes.
[16] BY MR. SCHULER:
[17] Q. And if he was exposed in 1977, it [18] would have been eight years; right?
[19] A. Correct. Seven and a half.
[20] Q. Okay. I mean, that's not that far [21] out of the spectrum, is it, the 10 to 30 years [22] that you just gave me?
[23] MR. WAGNER: Object to form.
[24] MR. LUTZ: Object to form.
[25] THE WITNESS: It's very short.

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[1] BY MR. SCHULER:
[2] Q. But within the reasonable area of [3] argument; correct?
[4] MR. WAGNER: Object to form. [5] Argumentative. And it doesn't have the [6] predicate that he provided as to latency being [7] a function of duration and intensity.
[8] MR. LUTZ: Join.
[9] THE WITNESS: I just don't -- you [10] know, I feel that that, the short latency in [11] this case is a strong piece of evidence in my [12] argument that it is not a cause and effect [13] relationship.
[14] BY MR. SCHULER:
[15] Q. Okay. And the short latency is [16] short by about a year or two years?
[17] MR. WAGNER: Object to form.
[18] MR. LUTZ: Join.
[19] THE WITNESS: No. You know, I said [20] in the range, 10 to 30 years, with the peak [21] latency occurring at 15 to 25. It's [22] exceptionally rare to see. There are, I think, [23] some latencies under 10 years reported in the [24] literature; but extremely rare incidences. [25] I don't consider, for example, any

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[1] epidemiology study that doesn't have a [2] significant percentage of members of the cohort [3] or cases far in excess of 10. I would say a [4] minimum of 15 years of potential latency before [5] the study can be considered to be a valid [6] epidemiologic study.
[7] BY MR. SCHULER:
[8] Q. So you disregard studies as not [9] valid that have latency periods shorter than 15 [10] years?
[11] MR. WAGNER: Object to form.
[12] MR. LUTZ: Join.
[13] THE WITNESS: And to answer the [14] question, if a study is negative and the [15] latency is less than 15 years, then I don't [16] consider it to be a true negative finding.
[17] BY MR. SCHULER:
[18] Q. Let's talk about the issue of [19] protective clothing for a minute.
[20] A. Uh-huh.
[21] Q. That has to do with Bob Moyer's [22] rate of absorption of the chemical; correct, [23] potentially?
[24] MR. WAGNER: Objection.
[25] THE WITNESS: No. It has to do

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[1] with the amount that actually -- that he was [2] actually exposed to getting and then, as a [3] derivative of that, the amount that was [4] absorbed. Yeah.
[5] BY MR. SCHULER:
[6] Q. Well, let's assume for the moment [7] hypothetically that, in Bob Moyer's time at [8] Orange County, he never wore any protective [9] clothing. In fact, let's assume that he never [10] wore any clothing at all.
[11] A. Uh-huh.
[12] Q. Would he have been -- if he was out [13] there spraying without any clothing on, from [14] the air boat, would he have been exposed to [15] sufficient carcinogenic agents in the 2,4,5-T [16] silvex or 2,4-D to have been able to cause his [17] cancer?
[18] MR. WAGNER: Object to form. [19] Missing predicates and missing factual [20] information from which he could give an answer [21] that was meaningful.
[22] MR. LUTZ: Join.
[23] BY MR. SCHULER:
[24] Q. The answer is



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no?
[25] A. No.

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[1] Q. So then protective clothing really
[2] is not an issue?
[3] A. Just gives me an extra degree of
[4] confidence in my opinion.
[5] Q. And so the same might be said about
[6] the issue of the spray not being, for example, [7] a mist as opposed to a steam; correct?
[8] MR. WAGNER: Object to form. Loads.
[9] MR. LUTZ: Join.
[10] THE WITNESS: Correct.
[11] BY MR. SCHULER:
[12] Q. Irrespective of whether it was a
[13] mist or a stream, he wasn't exposed to enough
[14] carcinogenic agents at Orange County to cause
[15] his cancer; correct?
[16] A. That's correct.
[17] Q. I'm having trouble reading my own
[18] writing here.
[19] MR. WAGNER: You're as bad as I am [20] about that. I've noticed that.
[21] BY MR. SCHULER:
[22] Q. Okay. I think the third point that
[23] you made was that the exposure that he received [24] at Orange County was small compared to [25] background exposure. That's a very general

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[1] statement, but would that be accurate for a
[2] general proposition?
[3] A. That's correct.
[4] Q. And are you speaking specifically
[5] with regard to TCDD, or are you speaking with
[6] regard to any carcinogenic agents which may
[7] have been present in these chemicals?
[8] A. I'm talking specifically about
[9] polychlorinated dibenzo dioxins and dibenzo [10] furans, with heavy emphasis on 2,3,7,8
[11] tetrachlorodibenzo dioxin.
[12] Q. Okay. By the way, in formulating
[13] your opinion, are you assuming total absence of [14] TCDD in the 2,4-D that he sprayed?
[15] A. Yes, I am.
[16] Q. And so, is it fair to say then,
[17] that you don't believe that there was any TCDD [18] in the 2,4-D back in '76 and '77?
[19] A. That's correct.
[20] Q. And what do you base that on?
[21] A. I base that on my own review of the
[22] literature and the conclusion reached by the
[23] EPA independently in 1988 in their drinking
[24] water criteria document that TCDD has not been [25] detected in 2,4-D by modern, valid chemical

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[1] analyses.
[2] Q. Do you have a copy of that EPA
[3] document?
[4] A. Yes, I do. At my office.
[5] Q. That's in your library?
[6] A. Yes.
[7] Q. Have you seen any documentation [8] from either Dow Chemical Company or any other
[9] defendant in this case that indicated that the [10] TCDD contaminant was found in 2,4-D?
[11] A. No, I haven't seen any.
[12] Q. Have you seen any scientific
[13] articles that found TCDD in 2,4-D?
[14] A. No, I haven't.
[15] Q. All right. As far as 2,4-D is
[16] concerned, are there any other carcinogenic
[17] contaminants that you're aware of in 2,4-D?
[18] A. No.
[19] Q. Do you consider 2,4-D itself to be
[20] carcinogenic?
[21] A. No, I do not.
[22] Q. And when I say carcinogenic, now,
[23] I'm speaking of carcinogenesis in general, as [24] opposed to---
[25] A. Okay.

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[1] Q. ---a specific type of cancer.
[2] A. Still stand by my answer.
[3] Q. Okay. You're aware of the various
[4] studies that have apparently seen a
[5] relationship between 2,4-D and other types of
[6] cancer, such as non-Hodgkin's lymphoma;
[7] correct?
[8] A. Yes, I'm familiar with those.
[9] Q. And the Sheila Hoarizom and Company
[10] article dealing with that?
[11] A. Yes.
[12] Q. And I think there are some others,
[13] as well; correct?
[14] A. Yeah, I suppose. Some people say [15] some other studies suggest that.
[16] Q. So you're not suggesting here that

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[8] instance, between cigarette smoke and cancer [9] and other health effects. [10] You can do a state-of-the-art [11] epidemiologic study and perhaps miss a true [12] causal association. So there are inherent [13] limitations in the methodology of the science, [14] but there are also -- it depends on the nature [15] of the effect and so forth, too.
[16] MR. WAGNER: Before you ask your [17] next question, I've been saying object to the [18] form, frankly, to avoid long speaking [19] objections. I assume that's okay with you?
[20] MR. SCHULER: Sure. That's a rule [21] of civil procedure. All objections are [22] reserved except as to those as to form. That's [23] fine. I understand.
[24] MR. LUTZ: You agree that all I [25] need to do is say, join, and I'm okay, too? Or

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[1] do you want me to---
[2] MR. SCHULER: That's fine.
[3] MR. LUTZ: Okay.
[4] MR. SCHULER: That's fine. In [5] fact, you can say amen, if you want to.
[6] MR. LUTZ: Join. How about if I [7] say nothing?
[8] MR. SCHULER: Y'all want to take a [9] break for lunch or how do you want to work [10] this?
[11] MR. WAGNER: Whatever your pleasure [12] is.
[13] THE WITNESS: Yeah, I think a [14] break.
[15] MR. SCHULER: We've been going for [16] probably two and three-quarter hours. [17] (A luncheon recess transpired.)
[18] BY MR. SCHULER:
[19] Q. The summary of articles that you [20] did, Dr. Schulz, for the Veteran's [21] Administration, included, did it not, articles [22] that demonstrated or concluded that there was a [23] relationship between 2,4-D and cancer?
[24] A. I don't believe so.
[25] Q. Okay. Was Sheila Hoarizom's

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[1] research included in your group?
[2] A. I'm pretty sure, yes. I think the [3] timing is such that we must have included it in [4] the years I was involved.
[5] Q. Okay. And in her conclusions, as [6] we discussed earlier -- I don't want to beat a [7] dead horse here -- were that there was a [8] relationship between 2,4-D and cancer; correct?
[9] MR. WAGNER: Object to the form.
[10] THE WITNESS: Yes.
[11] BY MR. SCHULER:
[12] Q. Were there any other articles that [13] you included in your summary of the literature [14] for the years that we discussed earlier that [15] concluded that there was a relationship between [16] 2,4-D and cancer? And this is not a memory [17] test. If you need to look at this or. . .
[18] A. Well, that's a related study, [19] basically, by the same group in Eastern [20] Nebraska, I believe. The first author of that [21] was Weisberger or Weisenberger or something [22] like that. And I'm talking, I think, now from [23] faulty memory. They also found an increased [24] rate of non-Hodgkin's lymphoma with farming, [25] but I'm not sure they were able to establish

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[1] that it was related to 2,4-D use. [2] Of course, there is a large number [3] of epidemiologic studies of potential [4] association of cancer of various forms and [5] exposure to herbicides. The only other study I [6] know where the exposure was essentially 2,4-D, [7] not confounded by other phenoxy herbicides and [8] stuff, was the occupational study done by, I [9] believe, Greg Bond at Dow, who -- they looked [10] at their 2,4-D production workers and found no [11] excess risks of any form of cancer in that [12] cohort.
[13] Q. Was that study published?
[14] A. Yes.
[15] Q. Is that part of your summary?
[16] A. It'd be in the review.
[17] Q. Okay.
[18] A. Those are the only ones where we're [19] talking -- in my recollection, where we're [20] talking about 2,4-D specifically. It's [21] essentially impossi-

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[17] there is a total lack of scientific evidence [18] linking 2,4-D with cancer; correct?
[19] MR. WAGNER: Object to form. No [20] predicate.
[21] THE WITNESS: Yes, I am.
[22] BY MR. SCHULER:
[23] Q. You don't believe Sheila Hoarizom's [24] results, then?
[25] A. That's correct. Well, I don't.

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[1] Now, that's -- let me qualify that. I believe [2] her results, what she observed. She's a good, [3] competent researcher, the people in her group. [4] I don't agree with the conclusion that she and [5] most of the other people have reached, that her [6] work shows -- is evidence of causal [7] relationship between exposure to 2,4-D and any [8] form of cancer.
[9] Q. Okay. Let's go back to my initial [10] question and make sure we're on the same page [11] here. There is not a total lack of scientific [12] support for a cause and effect relationship [13] between 2,4-D and carcinogenesis; correct?
[14] MR. WAGNER: Object to form.
[15] BY MR. SCHULER:
[16] Q. I mean, her article exists; right?
[17] MR. WAGNER: Object to form.
[18] THE WITNESS: Her article exists, [19] yes.
[20] BY MR. SCHULER:
[21] Q. So I mean, there is evidence out [22] there, at least in some observer's view, who [23] have done actual epidemiological studies that [24] there is a relationship between 2,4-D and [25] cancer; correct?

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[1] MR. WAGNER: Object to the form.
[2] MR. LUTZ: Object to the form.
[3] THE WITNESS: I really don't think [4] there's any evidence for an association. I [5] think you can -- it all crumbles away, and that [6] a good scientific reviewer would not come to a [7] conclusion that there's any evidence.
[8] BY MR. SCHULER:
[9] Q. Okay. Maybe we're mincing words [10] here.
[11] A. Yes.
[12] Q. When I say that there is no [13] evidence and -- when I say that, I'm referring [14] to the fact that there are articles out there, [15] by qualified scientists, well qualified [16] scientists that link 2,4-D with cancer; [17] correct?
[18] MR. WAGNER: Object to form.
[19] THE WITNESS: Where the authors [20] concluded that there that was a link. Yes.
[21] BY MR. SCHULER:
[22] Q. You just don't agree with the [23] conclusions of those articles?
[24] A. That's correct.
[25] Q. And you don't agree with the

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[1] conclusions of those articles because you [2] believe that certain assumptions made within [3] the studies are probably not accurate; correct?
[4] MR. WAGNER: Object to form.
[5] MR. LUTZ: Join.
[6] THE WITNESS: Correct.
[7] BY MR. SCHULER:
[8] Q. And you would agree with me that [9] you can basically take nearly any [10] epidemiological study and dissect its [11] assumptions and dispute its conclusions, could [12] you not?
[13] MR. WAGNER: Object to form.
[14] MR. LUTZ: Object to form.
[15] THE WITNESS: I wouldn't make a [16] sweeping generalization to that effect, no.
[17] BY MR. SCHULER:
[18] Q. Okay.
[19] A. There's a complete continuum of [20] quality to epidemiologic studies, as there is [21] to any other form of studies. I think [22] epidemiology is an imperfect tool, limited in [23] what you can do with it. And, in general, I [24] think any epidemiology study is probably [25] subject to some criticism; but whether or not

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[1] the conclusions of that study supports, are [2] valid or not, is not a function only of the [3] quality of the study, but is a function of the [4] nature of the results as well. So you can do a [5] pretty -- just as an example, I think you can [6] do a pretty sloppy methodological epidemiology [7] study and still find an association, for

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ble to find cohorts or cases [22] where people were exposed to just one phenoxy [23] herbicide or where they have any recollection [24] that's of any accuracy.
[25] Q. Well, that brings up another point

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[1] that you raised. I mean, these chemicals, the [2] phenoxy herbicides are generally used in [3] combination, either with one another or with [4] other chemicals, are they not?
[5] MR. WAGNER: Object to form.
[6] MR. LUTZ: Join.
[7] THE WITNESS: They're often used in [8] combination, yes.
[9] BY MR. SCHULER:
[10] Q. I mean, I know you're not a farmer, [11] but you've reviewed the literature and it's [12] pretty easy to see that -- I mean, that's been [13] the history of the use of these chemicals over [14] the last 30 or 40 years; correct?
[15] MR. WAGNER: Object to form.
[16] MR. LUTZ: Join.
[17] THE WITNESS: Yes.
[18] BY MR. SCHULER:
[19] Q. And that would be something that [20] anyone that has even a passing familiarity with [21] agriculture or the use of herbicides in [22] agriculture, and certainly a manufacturer of [23] these chemicals, should be familiar with; [24] correct?
[25] MR. WAGNER: Object to form.

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[1] MR. LUTZ: Object to the form.
[2] THE WITNESS: Probably, yes.
[3] BY MR. SCHULER:
[4] Q. Are there any studies that you're [5] aware of that discuss the issue of whether the [6] use of these chemicals -- and when I say these, [7] I'm referring specifically to 2,4-D silvex or [8] 2,4,5-T in combination -- potentiates the [9] effect of the carcinogenic elements that may be [10] in, for example, 2,4,5-T.
[11] MR. WAGNER: When you say---
[12] THE WITNESS: Can you restate the [13] question?
[14] MR. LUTZ: I'll object to the form.
[15] BY MR. SCHULER:
[16] Q. Are there any studies that you're [17] aware of that discuss the issue of whether the [18] use of these chemicals in combination, meaning [19] 2,4-D, 2,4,5-T or silvex, enhances the [20] carcinogenic impact of those elements that may [21] be in 2,4,5-T or silvex that are carcinogenic?
[22] A. I'm not aware of any.
[23] Q. Do you have any opinions about [24] that, one way or the other?
[25] A. I don't think that 2,4-D, 2,4,5-T

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[1] or anything else is in -- moderates or modifies [2] the carcinogenic activity of the dioxins and [3] furans.
[4] Q. Is 2,4-D being studied right now by [5] the Environmental Protection Agency?
[6] A. Not that I'm aware of.
[7] Q. Are you aware of any agency of the [8] government or any private institution, for that [9] matter, that is -- other than what a [10] manufacturer might be doing for its own uses -- [11] that is conducting any intensive research with [12] 2,4-D with regard to its potential [13] carcinogenesis?
[14] A. I'm not aware of any on-going [15] studies, but I don't -- haven't made an effort [16] recently to check that. When I stopped doing [17] the review two years ago, nobody that I know [18] nor my common sources were doing any specific [19] toxicological investigation of 2,4-D.
[20] Q. Have you reviewed, at one time or [21] another, any of the testimony before the EPA or [22] the Department of Agriculture, for that matter, [23] or any of its subcommittees with regard to the [24] potential removal of 2,4,5-T or silvex from the [25] market in the 1970s?

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[1] A. I've seen very, very little of [2] that. I, of course, worked with two people who [3] played a key role in that hearing in '78, '79, [4] Ian Nisbet and Mary Paxton; and they -- I read [5] the document that they put together. I think [6] they published that actually. It was [7] specifically related

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to dioxins and 2,4,5-T [8] specifically.
[9] Q. Who is Ian Nisbet?
[10] A. Ian Nisbet is a risk assessor, who [11] is now an independent consultant, was, at that [12] time, employed by Clement Associates.
[13] Q. What about Mary Paxton?
[14] A. She's a toxicologist with the [15] American Petroleum Institute, who was at [16] Clement Associates at that time.
[17] Q. And this document prepared by [18] Nisbet and Paxton, was that done by Clement [19] Associates when they were there or not?
[20] A. Well, they were -- yeah. They were [21] at Clements. It was probably part of a [22] contract thing. It was before I went to work [23] there. They were still working there when I [24] came, and I knew them then and I read this [25] document at some point.

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[1] Q. That was prepared specifically for [2] the hearings in '78, '79?
[3] A. Yes, it was.
[4] Q. And was it prepared for a [5] particular client?
[6] A. Well, I expect that the review was [7] probably requested by EPA.
[8] Q. You have a copy of the document, I [9] assume?
[10] A. I don't know.
[11] Q. You may or may not?
[12] A. I may or may not.
[13] Q. And where could a copy of that [14] document be obtained, if you don't have one?
[15] A. I believe it was published, and I [16] don't have a reference to it. It would [17] certainly be in the docket of those hearings at [18] EPA.
[19] Q. All right. We've been discussing [20] kind of studies in general here, the [21] epidemiological studies.
[22] A. Uh-huh.
[23] Q. Are there certain epidemiological [24] studies with regard, for example, to TCDD that [25] you consider more reliable than others?

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[1] A. I always take a weight of the [2] evidence approach, which involves a review of [3] all the studies; and as I think I alluded to [4] earlier, there's very much a continuum of [5] quality in these studies. And no study is [6] totally worthless and no study is excellent. [7] And I suppose I could go through an [8] exercise of ranking the quality to some degree; [9] but, basically, I just feel quite strongly that [10] the evidence is that the only possible [11] association shown by all of these epidemiology [12] studies is that there may be an increased risk [13] of cancer of all sites associated with very [14] intense, long-term exposure to the chlorinated [15] dioxin and furans.
[16] Q. Okay. I guess my question, though, [17] was and maybe you don't have an answer for [18] this. My question is, are there one or two or [19] three studies that come to mind as being the [20] best ones in your opinion, that you would rely [21] upon for that type of opinion?
[22] A. No. I would hesitate to single out [23] any specific studies as being totally the [24] reliable ones, to the exclusion of the others. [25] I think they're all---

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[1] Q. I didn't say to the exclusion of [2] the others. I'm just talking about -- I mean, [3] if you don't---
[4] A. And, again, it depends on what [5] the -- you know, there are different end points [6] we're looking at here. Different exposure [7] populations and all that. There's a certain [8] degree of comparing apples and oranges, so we [9] have studies that are -- we have case control [10] studies. We have cohort studies. [11] We have people who are exposed [12] primarily through application in agricultural [13] use. We have people who are exposed in [14] Vietnam. We have people who are exposed [15] through the manufacture and production. [16] So it depends on which one of those [17] areas. I think that I'm very much impressed by [18] the methodology and the care with which the [19] studies were

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done in New Zealand by Allen Smith [20] and Neal Pierce and that group on sprayers. I [21] consider those studies to be very definitive, [22] upstanding. [23] The manufacturing studies, I think [24] that the Fingerhut study is very good. IOSH [25] study, whatever you want to call it. It's the

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[1] same. Although I have problems with it. The [2] IARC, I-A-R-C, study is good only in the size [3] of the study. It's got some very significant [4] flaws. Again, these are manufacturing exposed [5] populations. [6] I think in some ways the NCI study, [7] Sheila Hoarizom studies and aspects of those [8] studies are very good. I just think they [9] really dropped the ball on the whole exposure [10] issue. Made a terrible leap of faith there [11] that isn't justified.

[12] Q. Now, we've been talking in terms of [13] studies and the epidemiological studies, and I [14] understand that you are not an epidemiologist; [15] correct?

[16] A. Well, that's correct. Yes.

[17] Q. And I guess what I'm trying to get [18] at, I mean, I understand that, apparently in [19] this area of science, there's a certain overlap [20] between toxicology and epidemiology. Would [21] that be a fair statement?

[22] A. I think that's quite fair to say.

[23] Q. And from the standpoint that a [24] toxicologist, at least to some extent -- and [25] correct me if I'm wrong -- rely on

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[1] epidemiological studies as far as their [2] opinions are concerned, to some degree; [3] correct?

[4] A. They should depend very heavily on [5] them, yes.

[6] Q. And that's why I asked the question [7] about whether you considered some studies more [8] reliable than others.

[9] A. Correct.

[10] Q. And I think you've answered that. [11] Now, you mentioned that you believe that the [12] exposure that Mr. Moyer had, in terms of his [13] spraying chemicals for Orange County and in [14] terms of his exposure to TCDD, was small [15] compared to general background exposure to [16] TCDD; correct?

[17] A. Correct.

[18] Q. And what do you base that on?

[19] A. Well, I base that on the very [20] limited use that he possibly or allegedly made [21] of any herbicide that might have been [22] contaminated with 2,3,7,8-TCDD. [23] And then, as I said earlier, from [24] that -- in addition, the fact that he wore [25] protective clothing, the methods that they used

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[1] to apply the herbicides and so forth. So his [2] exposure was small and, if there was [3] contamination, the contamination level was [4] quite low. [5] And then, of course, the other half [6] of that conclusion is the fact that we're all [7] exposed to dioxins, including 2,3,7,8-TCDD as [8] part of our daily, day-to-day existence.

[9] Q. What was the contamination level of [10] the silvex and 2,4,5-T and---

[11] A. I don't know.

[12] Q. Well, let me finish my question. [13] Otherwise, it wouldn't make any sense. Back in [14] 1976 or '77 with the materials that Mr. Moyer [15] was spraying?

[16] A. I'm not qualified to totally [17] address that issue. I'm very confident it was [18] less than 1 part per million, and I'm quite [19] confident that it was significantly less than 1 [20] part per million. I have now rushed to answer [21] your question. This is silvex.

[22] Q. Right.

[23] A. Yes. Silvex.

[24] Q. Would you have the same opinion for [25] 2,4,5-T, 1 part per million or less?

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[1] A. If there were 2,4,5-T involved, [2] it'd be a similar level.

[3] Q. And what about 2,4-D?

[4] A. No.

[5] Q. You don't believe there was any [6] TCDD in that?

[7] A. Well, I would

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say, unlikely to have [8] been more than a part per billion because [9] that's all that has been able to be reliably [10] measured. I don't think there'd be any, from a [11] chemical point of view. The only way it could [12] get in there is from cross-contamination or [13] something. But chemically, it just doesn't [14] form in the manufacture of 2,4-D or its [15] precursors.
[16] Q. So because it doesn't form in the [17] process of manufacturing 2,4-D, it would have [18] to be a cross-contamination type of situation?
[19] A. If there were any. And, yes.
[20] Q. Cross-contamination being using the [21] same shipping vessels to ship the 2,4-D as were [22] used for 2,4,5-T?
[23] A. Anything. Anything.
[24] Q. Okay. Do you know or do you have [25] any information with regard to the type of



[1] testing that was done by manufacturers in 1976 [2] or 1977 to determine what levels, if any, TCDD [3] were in silvex, 2,4,5-T or 2,4-D?
[4] A. There's very little information in [5] publicly available literature about such [6] testing and whether it was done and how often [7] and what methods were used. So, no, I don't [8] really have much first-hand information.
[9] Q. Do you have any information with [10] regard to any testing that was done by [11] manufacturers on their commercial grade product [12] 2,4-D or 2,4,5-T in terms of health effects, [13] either on animals or man?
[14] A. What formulations are we talking [15] about now?
[16] Q. Commercial grade 2,4-D or 2,4,5-T [17] or silvex.
[18] A. Gee, my recollection is imperfect. [19] I believe there are studies in the published [20] literature in the '70s, '60s, perhaps, by Dow [21] people on the health effects of 2,4-D or [22] 2,4,5-T; but I really -- without going back and [23] looking through my bibliographies, I can't say [24] that for sure.
[25] Q. Let me be clear that I'm being



[1] specific because I don't want to mislead you by [2] my question.
[3] A. Yeah.
[4] Q. There have been or at least there's [5] some indication that we've found in the Dow [6] Company records that there was some testing [7] with regard to trichlorophenol and then, [8] ultimately, TCDD and, initially, some of these [9] tests were done on rabbit ears.
[10] A. Uh-huh.
[11] Q. And at some point in the 1960s, [12] there was some testing on some prisoners at the [13] Harrisburg Prison with, I believe, TCDD. It [14] may have been trichlorophenol. I can't recall [15] at this point in time. [16] My question is specifically with [17] regard to testing of the commercial grade [18] product 2,4-D, silvex---
[19] A. That's how I understood it. I'm [20] familiar with the dioxins studies, both [21] published and unpublished.
[22] Q. Okay.
[23] A. I'm not -- at this point, can't [24] drag up out of my memory specifically [25] commercial formulations, which is, you know,



[1] how I interpreted your question to be. I can't [2] remember whether I saw some of those. Whether [3] they published any of that, I don't know.
[4] Q. Okay. We took this side road. [5] Let's get back to main branch here of my [6] initial question that is that your opinion that [7] the exposure to Moyer was small in '76 and '77 [8] compared to the general background exposure to [9] TCDD? [10] You were, in that opinion, [11] specifically focusing on TCDD; correct?
[12] A. Well, no. All of the chlorinated [13] dioxins and furans. But if silvex is [14] contaminated with dioxins, it's almost [15] exclusively 2,3,7,8-TCDD.
[16] Q. All right. And how do you make [17] that judgment? I mean, you've

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told us that you [18] haven't calculated any numbers; but how do you [19] make the general judgment? What is your [20] knowledge, for example, of background exposure [21] to TCDD that would permit you to render that [22] opinion?
[23] A. Well, I prepared that report for [24] Mr. Wagner. In the references, I cited several [25] authors who have compiled whatever able data

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[1] they can find. [2] You can actually estimate daily [3] intakes in two ways. You can put together a [4] list of all the ways we might be exposed and [5] anything you can find on the concentration of [6] those things in what we're exposed to and [7] calculate from how much food we eat, for [8] instance, how much dioxin we'll ingest every [9] day. [10] You can work back the other way [11] now. If you know what kind of levels, [12] concentrations of TCDD we carry around in our [13] body, then you back calculate to how much we [14] have to ingest every day to achieve that kind [15] of level in our tissues. [16] And so doing it both ways, you come [17] out with pretty similar estimates from a [18] biological sense. A thousand-fold difference [19] is not unusual.
[20] Q. I think you've completely befuddled [21] me here.
[22] A. Okay.
[23] Q. But let me approach it this way.
[24] MR. WAGNER: Good job.
[25] BY MR. SCHULER:

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[1] Q. That's your job; right? Got to [2] have some humor about this.
[3] A. Just so you're befuddled and the [4] jury isn't.
[5] Q. If I'm befuddled, I guarantee you [6] the jury is. Believe me. Okay. [7] I'm looking at your report here [8] that we've marked as Plaintiff's Number 8, and [9] you talk about or mention in this report five [10] articles that document daily exposure of the [11] general population to TCDD from environmental [12] sources, and it's primarily the diet.
[13] A. Uh-huh.
[14] Q. That's based on others' work. But [15] from your review of others' work, you believe [16] that that's the primary source of daily [17] exposure to TCDD, through the diet?
[18] A. Correct.
[19] Q. And why is that?
[20] A. Well, because diet -- because TCDD [21] and related dioxins and furans tend to [22] accumulate in the food cycle. They [23] bioaccumulate and bioconcentrate.
[24] Q. Is that from herbicide use on the [25] plants, the vegetables and things?

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[1] A. We don't have a good understanding [2] of all the source of dioxin into the [3] environment. In a talk given about - well, [4] it's been about three years ago now, by Curt [5] Travis, who went through all the identified [6] sources of TCDD and related dioxins and furans [7] in the environment, he came to the conclusion [8] that if we -- all the known sources only [9] accounted for about 5 to 15 percent of our [10] daily known intake. [11] So it suggests to me that there's [12] still important sources of these compounds in [13] the environment that we haven't identified [14] yet. And, basically, when you go to the [15] International Dioxin Conference -- I like to [16] kid about the source of the year. Every year [17] you go, they're discussing some new source of [18] dioxins and furans in the environment as being [19] the most important one. And it is for a year [20] or so, and then we move on to something else. [21] So I don't think -- I think [22] agricultural use of pesticides is a very minor, [23] minor source of dioxins in the environment. [24] Essentially, any time you have chlorine, [25] hydrocarbons and heat, in almost any

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[1] combination, the potential exists to form [2] dioxins and furans and that's where they get [3] into the environment. But anyway. [4] So ther once they're in the [5] environment, they move up the food chain.

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If [6] they're in vegetable matter, cows graze on them [7] and so forth. If they're in plankton and [8] algae, the fish and aquatic organisms eat them [9] and so forth. [10] So that the highest levels in the [11] environment tend to concentrate in animal fat, [12] which we eat a lot of. So that part of our [13] diet, meat, dairy products. Meat, especially [14] fish, for reasons that aren't totally clear to [15] me, dioxins and furans concentrate in fish [16] about three times the level they do in [17] terrestrial animal tissues. [18] So if somebody has a diet that's [19] high in fish, they tend to get even a higher [20] daily dose of dioxins and furans.
[21] Q. It's probably from all those paper [22] mills; right?
[23] A. A lot of it's paper mills. That's [24] a major source.
[25] Q. The---

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[1] A. Was. Was a major source.
[2] Q. Okay. The diet then, what you're [3] describing, you just gave me an example of how [4] TCDD can get in certain types of---
[5] A. Uh-huh.
[6] Q. ---animal life that we eat; [7] correct?
[8] A. Right.
[9] Q. Okay. The non-occupational [10] exposures you mention in Paragraph 2 of your [11] letter, you say range from 40 to 240, I just [12] want to make sure I understand this, pg per [13] day. What is that?
[14] A. Picograms per day.
[15] Q. What is a picogram?
[16] A. Picogram is -- well, it's 10 to the [17] minus 12th grams.
[18] Q. Okay.
[19] A. It's one trillionth of a gram.
[20] Q. Okay. In any event, the diet [21] source that you're referring to -- well, let me [22] strike that. [23] In Paragraph 2 here, these 40 to [24] 240 picograms per day, you're referring only to [25] diet or is that from all sources?

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[1] A. That's all sources.
[2] Q. Okay. And of that all source [3] exposure, you're saying diet may be, what, 5 to [4] 15 percent? Is that what you're saying?
[5] A. No. More like 75 to 80 percent.
[6] Q. So diet is 75 to 80 percent of the [7] total intake in general---
[8] A. Yes.
[9] Q. ---of TCDD? And the diet, [10] obviously, if you're exposed to TCDD through [11] diet, you're being exposed after the [12] consumption of the food that's going through [13] your digestive tract; correct? I mean, it gets [14] into your system, I would assume, through the [15] digestive tract in some form; correct?
[16] A. Yes.
[17] Q. Okay. And those are estimates that [18] you're making; correct? You mention here from [19] background concentrations; right?
[20] A. These are not estimates I'm [21] making.
[22] Q. Someone else is making?
[23] A. Yes.
[24] Q. And you're reciting here; right?
[25] A. Yes.

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[1] Q. Okay. And the 40 to 240 picograms [2] per day, you state from your review of the [3] literature, represent the amount of the [4] compound that is actually absorbed, as opposed [5] to what's taken in?
[6] A. Correct.
[7] Q. All right. There's great [8] variability in that, isn't there? I mean, the [9] amount that's absorbed through diet, for [10] example, from individual to individual?
[11] A. I don't believe a great [12] variability. Every biological process has a [13] lot of variability; but I don't think there are [14] distinct classes of people, some who absorb and [15] some don't, in this case. No. I'd say it's [16] relatively not variable, based on from [17] individual to individual.
[18] Q. The reason, I was looking at your [19] summary here and I'll show this to you. In the [20] section on dioxins in tissues, I think this is [21] in the -- right before the con-

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clusion section. [22] It states, there is clearly a great deal of [23] variability among individuals in how much [24] dioxin they tend to absorb and how quickly it [25] is eliminated from the body.

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[1] Would you agree with that [2] statement?
[3] A. Yes, if---
[4] Q. I'm reading from Plaintiff's 3.
[5] A. Yes. In context, I agree. I don't [6] feel that's inconsistent with what I just said.
[7] Q. Okay. Some people who are [8] unquestionably heavily exposed to dioxins in [9] the past have blood concentrations in the [10] normal range, whereas other individuals with [11] little or no known exposure have elevated [12] concentrations. [13] Do you agree with that statement?
[14] A. That's correct.
[15] Q. And so my question is, it's [16] difficult to make a statement as to what a [17] particular individual will retain or absorb [18] from a given exposure. Is that what you're [19] saying?
[20] A. Yes. I've used the term absorb in [21] two different things there. In the latter, I [22] am describing specifically absorption from the [23] stomach, for example, the GI tract; whereas, in [24] there, I'm talking in broader terms about the [25] relationship between environmental

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[1] concentration and the amount that gets into the [2] actual system, the body.
[3] Q. So are you saying it's easier to [4] predict what's absorbed from---
[5] A. The stomach.
[6] Q. ---consumption of the stomach?
[7] A. Food. Yes.
[8] Q. ---than it is from environmental [9] exposure?
[10] A. Yes.
[11] Q. And what are the factors that you [12] need to look at to determine absorption from an [13] environmental source?
[14] A. Okay.
[15] Q. And we've probably mentioned some [16] of those already, but. . .
[17] A. Well, first, of course, the [18] chemical and physical form of the dioxin or [19] furan in the environmental media and even, for [20] example, in the soil. Mike Gallo and his group [21] up at Rutgers did some really interesting [22] studies, where different soil types, when [23] ingested by rats, you'd absorb more or less [24] percentage-wise of the dioxin. [25] I think the same happens. Dioxin

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[1] that's inhaled, if it's absorbed on particulate [2] matter in the air, which is the most common [3] source, would be less likely to be absorbed [4] into the body than if it's free, volatile [5] dioxin in the air. So the form that it's in [6] before i goes into body is important. [7] And then in my conclusion over [8] there, that involved not just absorption, but [9] also elimination. And I do think that there's [10] quite a bit of inter-individual variability in [11] the rate at which dioxins and furans are [12] eliminated through the body, where they're [13] stored.
[14] A fat person, like me, is going to [15] be able to pick it up a little better than a [16] skinny guy because we have more place to put [17] it.
[18] MR. WAGNER: Skinny guy, like none [19] of us here.
[20] BY MR. SCHULER:
[21] Q. Okay. What other factors involve [22] or affect absorption, if any others?
[23] A. Those are the important ones.
[24] Q. And now getting back to Bob Moyer's [25] situation and the spraying of these chemicals.

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[1] A. Uh-huh.
[2] Q. Would it affect absorption if he [3] wasn't wearing protective clothing?
[4] A. Oh, yes, of course.
[5] Q. Okay.
[6] A. Well, again, we're misusing the [7] word absorption here. Would that affect, say, [8] internal dose, is the word I think we want to [9] use, the term we want to use. And, clearly,

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[10] the internal dose would be higher if he wasn't [11] wearing protective clothing, than it would be [12] if he was wearing protective clothing. Yes.
[13] Q. Maybe we can look at it this way. [14] There's the exposure initially; correct, to a [15] particular chemical?
[16] A. Yes.
[17] Q. And that, in order to be converted [18] to what the internal dose is, one of the [19] factors is the rate of absorption, is it not?
[20] A. Yes.
[21] Q. Okay. And that rate of absorption [22] can be affected by the barrier, for example, [23] whether there's clothing there or not?
[24] A. Well, okay. To me, the clothing is [25] affecting the exposure.

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[1] Q. Okay.
[2] A. The absorption is only the rate at [3] which it goes through the skin or through the [4] stomach lining or through the lung.
[5] Q. All right. I understand you. So [6] the absorption is affected, the way you're [7] interpreting absorption, is the rate at which [8] it goes through the skin, the medium that it's [9] in, as you've described, the chemical form that [10] it's in; correct?
[11] A. Correct.
[12] Q. The condition of the skin would [13] also affect that, too, would it not?
[14] A. Yes, it would.
[15] Q. I mean, if there was an open wound, [16] for example, that the chemical was exposed to, [17] as opposed to a clean skin and healthy [18] condition, that would affect absorption and, [19] subsequently, dose?
[20] A. Correct.
[21] Q. Do you know whether Bob Moyer, in [22] the course of his spraying either 2,4,5-T, [23] silvex or 2,4-D, had any open wounds or sores?
[24] A. I don't know whether he did or not.
[25] Q. Would that make any difference to

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[1] you in your opinion?
[2] A. Not really.
[3] Q. Why not?
[4] A. Because, as I said earlier, whether [5] or not he wore protective clothing is not [6] important. This exposure was so short term and [7] so small a quantity that, you know, we're [8] quibbling over nets in this little exercise. I [9] feel relatively confident that if he was bare [10] naked and had sores all over him and dunked his [11] hand down in the tank each day he used it and [12] all, he still -- his exposure for the few days [13] that he used it over a widely scattered point, [14] would have been extremely minimal.
[15] Q. Okay. I just need to understand.
[16] A. Yeah.
[17] Q. Some of my questions may seem [18] basic.
[19] A. Yeah.
[20] Q. So now we can not only do away with [21] the clothing, but even if we do away with part [22] of the skin, it still wouldn't affect your [23] opinion because the overall amount---
[24] A. Amount. Yeah.
[25] Q. ---of the TCDD was too small, in

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[1] your opinion, to rise to the level of a [2] probable carcinogen in his case?
[3] A. Correct.
[4] Q. Okay. While we're at it, I want to [5] finish this topic. Are there any other factors [6] that you didn't mention that may affect the [7] rate of absorption and, ultimately, the dose [8] for an individual?
[9] A. Well, as soon as I say no, I'll [10] probably think of one; but I don't think there [11] are any others that are important.
[12] Q. I know we went through this [13] initially, as far as the gear that Bob Moyer [14] had; but did you make any other assumptions? [15] And in talking about it, you also talked about [16] the spray, the form of the spray. Did you make [17] any other assumptions with regard to conditions [18] under which Bob Moyer applied either silvex, [19] 2,4,5-T or 2,4-D?
[20] A. Well, I assumed that Mr. Swanson's, [21] Mr. Sassick's recall was pretty accurate. That [22] the records the county kept of what was sprayed [23] when and

what quantities were used, I assumed [24] they were pretty accurate. [25] So I relied, I think, on the

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[1] testimony of a lot of people, including Mr. [2] Moyer himself, which he, you know, admitted [3] that he wore protective clothing. He seemed to [4] have pretty faulty recall about what he sprayed [5] when, but that's not unusual. I think, at this [6] point, 15-year recall would be -- I would find [7] pretty unreliable for anybody; but the records, [8] I assumed, were pretty accurate.

[9] Q. Any other assumptions or does that [10] pretty much cover it?

[11] A. That pretty much covers it.

[12] Q. Did you have occasion to read, [13] other than -- and, incidentally, did you [14] actually read Bob Moyer's depositions?

[15] A. No. A summary of it. I'm sorry.

[16] Q. And did you read the summaries of [17] all of the depositions or---

[18] A. At one point or other, I think I [19] covered it all. Ellenburger's and the other [20] ones. I didn't in preparation for today. I [21] haven't looked at any of those probably since I [22] first received them.

[23] Q. The depositions of Dr. [24] Ellenbecker---

[25] A. Ellenbecker.

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[1] Q. ---Dr. Clapp, I mean, you read [2] summaries of those or not?

[3] A. I can't remember whether -- I think [4] they're summaries, yes.

[5] Q. Did you read the depositions of any [6] other people that we haven't discussed? For [7] example, the deposition of any of the [8] defendants' experts that have been taken to [9] date? I think it's Dr. Smith.

[10] A. No.

[11] Q. And Dr. Eaton?

[12] A. No.

[13] Q. And Mr. Nigg?

[14] A. No.

[15] Q. Have you discussed this case with [16] any of those people, any of the other experts?

[17] A. No. No. I have sent -- I have [18] sent some papers to Kenny Crump's office.

[19] Q. What papers are you referring to?

[20] A. I think I sent him a copy of this.

[21] Q. Referring to Plaintiff's 8, the---

[22] A. Yes.

[23] Q. ---letter of October 22, 1992---

[24] A. Yes. And the papers.

[25] Q. Hold on a second. We can't talk at

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[1] the same time.

[2] A. Yes.

[3] Q. The letter of October 22, 1992?

[4] A. Yes. And the references cited [5] therein. I---

[6] Q. The -- I'm sorry.

[7] A. I also sent Kenny copies of the two [8] most recent epidemiology studies done by Argall [9] and Eriksson I think Eriksson is the first [10] author on those, but I don't remember how it [11] works.

[12] Q. Anything else?

[13] A. That's all.

[14] Q. To get back to the background [15] exposure to TCDD, what is the background, [16] quote/unquote, normal background TCDD [17] absorption, I guess, or retention in the [18] average individual?

[19] A. I'd have to look at that. Well, [20] like I say here, the range reported is [21] from .04 -- well, I've only figured it for an [22] 80 kilogram adult, which was Moyer's size at [23] that time. 40 to 240 picograms per day.

[24] Q. Okay. Is that intake or what?

[25] A. No. That's the amount that

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[1] actually gets into the body.

[2] Q. Into the body?

[3] A. Yeah.

[4] Q. Is that retained in the body or is [5] it ultimately eliminated?

[6] A. Well, it's eliminated; but so [7] slowly as to be -- I mean, that's the daily [8] intake; and the amount that goes out is a [9] function of how much is already in the body. [10] But, generally, we -- even from environmental [11] sources, we tend to intake a little more than [12] we excrete on a daily basis. So that the [13] general population's concentrations increase [14] with age. [15] Now,

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we seem to be reversing that [16] in the last five or ten years, but that's---
[17] Q. Since silvex was taken off the [18] market? I'm just kidding.
[19] A. Gosh.
[20] MR. WAGNER: Got to watch him.
[21] BY MR. SCHULER:
[22] Q. Go ahead.
[23] A. In a more -- yeah. It's a fairly [24] complex relationship between what comes in and [25] what goes out. But, again, the key important

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[1] thing here is that it's very well retained and [2] that the half life for elimination is on the [3] order of seven years or more to clear, what, [4] half of what is in us, if we had no more [5] exposure.
[6] Q. Okay. Let me see if I can get it [7] maybe into its simplest form without confusing [8] the issue here myself. [9] If you take an individual of a [10] given age and a given weight and assuming that [11] they live a normal, American life style, [12] without any undue vices and they don't work in [13] a---
[14] MR. WAGNER: That's not a normal [15] American life. You've screwed up the question.
[16] BY MR. SCHULER:
[17] Q. That's right. They don't work in [18] Dow Chemical Plant or spraying this stuff in [19] one form of another. Is there a number that [20] you say that an individual can be expected to [21] test positive to if you're looking for retained [22] dioxin?
[23] A. Well, I do have a lot of data on [24] what levels are in people in the normal [25] population. And people do tend to carry a --

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[1] even people with no known extraordinary [2] exposure do have measurable body burdens of all [3] the dioxins and furans including 2,3,7,8-TCDD. [4] Yes.
[5] Q. Well, I guess what I'm looking for [6] is, is there a number, a range of a number?
[7] A. Well, the number, it's really [8] difficult; but I believe that NHATS, 1982, [9] concluded, I think---
[10] Q. That N-H-A-T-S?
[11] A. N-H-A-T-S, all capitals, National [12] Human Adipose Tissue Survey, 1982. I think [13] their geometric mean TCDD concentration was 7 [14] parts per trillion in body fat. And I'm doing [15] this from strict memory. It's setting in your [16] pile of documents there somewhere.
[17] Q. And that's without regard to age [18] or. . .
[19] A. As I said, the relationship with [20] age is changing. Those were all adult or -- I [21] don't know if they broke -- I'm sorry. I don't [22] know if they broke those down by age. Those [23] samples were more likely heavily skewed toward [24] the adult population because they're taken [25] randomly when people have surgery. And I would

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[1] say a lot more adults are undergoing surgery [2] than children.
[3] Q. There were studies done of certain [4] populations, some Vietnam veterans that [5] supposedly had been exposed to Agent Orange [6] with regard to the TCDD and their body fat; [7] correct?
[8] A. Correct.
[9] Q. And the results of those were that [10] the TCDD was not found to be elevated beyond [11] the normal background in that group as well; [12] correct?
[13] A. That's correct.
[14] Q. You think that was an accurate [15] assessment from your review of that [16] information?
[17] A. Yes. Because I feel that the vast [18] majority of Vietnam veterans were not heavily [19] exposed to phenoxy herbicides or their dioxin [20] contaminants. So if you take one guy, three [21] guys, six guys, who were heavily, very heavily [22] exposed, put them in a group of people of [23] hundreds or thousands of people who weren't [24] exposed at all, the average is going to not [25] look different than the total population.

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[1] Q. Wasn't there, though, a study done [2] specifically on those involved in Operation [3] Ranch Hand that supposedly were involved in


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the [4] distribution of Agent Orange and still a normal [5] result?
[6] A. No. It's not normal. There are [7] ranch handers that do have very elevated levels [8] of dioxin and -- but, again---
[9] Q. I don't mean to interrupt, but I'm [10] not talking about a couple. I'm talking about [11] the overall study.
[12] A. The overall study, I think if you [13] compare all ranch handers with the comparison [14] group, the mean levels are not statistically [15] significantly different, although the ranch [16] handers do have higher body burdens because of [17] these few guys that are in the -- do have the [18] high levels. And they're just a smaller case [19] of Vietnam veterans in general. [20] The population of that Ranch Hand [21] Study includes, you know, the pilots and [22] co-pilots that came out of their cushy officers [23] quarters when the plane was all loaded up, [24] climbed up into cockpit and flew, and all the [25] herbicide was behind them. You know, came



[1] back, parked the plane, walked back in. [2] You know, it includes a fair number [3] of administrative personnel. It includes [4] people who were assigned to Ranch Hand for two [5] years and people who were assigned for three [6] months. So you have the same kind of [7] distribution of exposure in Ranch Hand cohort [8] as you've got -- but, in general, they had [9] higher exposure. But I emphasis, again, that a [10] few of them did have high levels -- do have, do [11] have high levels of dioxin.
[12] Q. In this case, do you know what the [13] measurement was for Bob Moyer's body fat for [14] retained TCDD?
[15] A. Yeah. It was less than 5 parts per [16] trillion.
[17] Q. Of what significance is that to [18] you, if any?
[19] A. That means that he's very normal, [20] perhaps below average.
[21] Q. And where did you get that [22] information from?
[23] A. From the attachment, an exhibit [24] with Dr. Teitelbaum's deposition.
[25] Q. The Triangle Lab---



[1] A. Research or Triangle Labs. Yes.
[2] Q. And do you have that with you here [3] today?
[4] A. Yes, I do.
[5] Q. Why don't you pull that out of [6] there for a second?
[7] A. You've messed up my wonderful [8] order. There we go.
[9] Q. Do you have it there in front of [10] you?
[11] A. Yes, I do.
[12] Q. Okay. Before I get into that with [13] you, I just want to know that you have that [14] there. And I also see that Krumel report [15] there.
[16] A. Yeah.
[17] Q. I'm going to ask you to keep that, [18] because I'm going to ask you some questions [19] about that, too. I think you told us about the [20] measurements -- I'm trying to relate your [21] measurements of 40 to 240 picograms per day to [22] what -- well, I'm talking about apples and [23] oranges here.
[24] A. Yeah, you are.
[25] Q. Let me, before we get into that



[1] analysis and the Research Triangle Lab, ask [2] you, do you know or have an estimate for what [3] amount of TCDD that Bob Moyer was exposed to [4] when he was spraying chemicals for Orange [5] County?
[6] A. I have not made that calculation. [7] I'll leave that to Dr. Nick and Dr. Crum.
[8] Q. Okay. All right. That's fair [9] enough. Have you seen any calculations that [10] they have done?
[11] A. No.
[12] Q. All right. Let's go to that [13] study. Where did you see the measurement, I [14] think, of less than, you said, five parts per [15] trillion?
[16] A. Okay. It's on this page here.
[17] Q. Do you have a page number there?
[18] A. Page 1 of 2.
[19] Q. Okay. Let me just-- why don't you [20] take a---
[21] A. Got a yellow sticky?

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[22] Q. Yes. Here.
[23] MR. WAGNER: It's Exhibit 10 to
[24] Teitelbaum's Deposition.
[25] BY MR. SCHULER:

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[1] Q. Why don't you just tag it?
[2] A. And it says here, 2,3,7,8-TCDD not
[3] detected. Detection 5.1.
[4] Q. Okay. Is it unusual not to detect
[5] TCDD in an individual of that age?
[6] A. Not unusual.
[7] Q. Okay.
[8] A. I'm a little surprised at that
[9] detection limit in this day and age. This is
[10] 1990. It's routine to have detection limits of [11] 1 part per trillion or less. And I'm not
[12] enough of analytical chemist to understand what [13] the problem with Moyer's sample was, but five [14] is a fairly high detection limit to see on [15] these kinds of studies now. [16] But all you can say is that it's [17] possible he had a level of five, you know. [18] Although, typically, that might show up as what [19] they call a trace or a que.
[20] Q. The exposure of an individual to
[21] TCDD would result -- I mean, if an individual
[22] had -- let me strike that. [23] What would you call a relatively
[24] intense exposure?
[25] MR. WAGNER: Object to form.

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[1] MR. LUTZ: Join.
[2] BY MR. SCHULER:
[3] Q. Is it possible for you to say?
[4] A. What?
[5] Q. Is it possible for you to say?
[6] A. Well, I'm not sure. The relatively
[7] intense exposures are those experienced by the
[8] people who worked in the manufacture and
[9] production of trichlorophenol, phenoxy
[10] herbicides and related compounds in the '50s [11] and '60s. That's my definition of intense [12] exposure. I can't put a number on that.
[13] Q. Okay.
[14] A. Nobody measured those levels then.
[15] Q. You can't give me any numbers on
[16] that, so I'll just move along. What about the [17] retained TCDD in the body fat of something, [18] let's say, higher than 5 percent per trillion. [19] Say 5.5. What would that signify to you?
[20] A. That's still within the range of
[21] normal.
[22] Q. What is the range of normal?
[23] A. I don't really have a good opinion
[24] on that. Certainly up to 10 and maybe roughly [25] as high as 15 parts per trillion would not be

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[1] terribly surprising in an individual with no
[2] known occupational or accidental exposure.
[3] Q. All right. You also note on that
[4] laboratory result the fact that there were
[5] other dioxins found; correct?
[6] A. That's correct.
[7] Q. Or at least measures taken of other
[8] dioxins?
[9] A. Correct.
[10] Q. One was the heptacholorodibenzo
[11] dioxin; correct?
[12] A. Correct.
[13] Q. And 41.7 was the number on that?
[14] A. Correct.
[15] Q. That have any significance to you?
[16] A. Not at all. Just, again, a very
[17] normal guy.
[18] Q. Hexacholorodibenzo dioxin, 20.9, I [19] believe?
[20] A. Well, 20.9 for 1,2,3,6,7,8 isomer,
[21] but total hexa was 20.4, other ball park.
[22] Q. Okay. Any significance to that?
[23] A. No. Very normal.
[24] Q. The octachlorodibenzo dioxin, 233?
[25] A. Yeah. That's an estimated

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[1] concentration. Actually, it's a little bit
[2] low.
[3] Q. Any significance to that?
[4] A. No. We all have -- again, a very,
[5] American profile.
[6] Q. So those are not uncommon [7] measurements in your view?
[8] A. Not at all. If anything, he's [9] below average in total.
[10] Q. And there's no significance to
[11] those measurements as far as you are concerned, [12] other than the fact that they're normal?
[13] A. Yeah, they're

significant -- yeah, [14] that's all. He's just -- they don't reflect [15] any unusual exposure.
[16] Q. Okay. None of those are a marker [17] of any particular exposure?
[18] MR. WAGNER: None of these levels?
[19] MR. SCHULER: Right.
[20] THE WITNESS: No. Other than [21] normal background exposure.
[22] BY MR. SCHULER:
[23] Q. Do you have an opinion as to the [24] probable source of any of those dioxins?
[25] A. Well, I've already addressed

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[1] sources. Many different sources, ultimate [2] sources. His direct exposure and yours and [3] mine is mostly in the diet. How it gets into [4] the food chain to begin with, we don't fully [5] understand.
[6] Q. Do you have any opinions with [7] regard to the relative health effects of any of [8] those dioxins in Mr. Moyer?
[9] A. I don't think that these -- I think [10] that these levels do not reflect any levels [11] that suggest concern for any particular health [12] effect.
[13] Q. Other than your opinion that the [14] chemicals Mr. Moyer used at Orange County did [15] not cause his cancer, do you have any opinion [16] as to what did cause his cancer?
[17] A. No. We don't know the ideology of [18] most human cancer and this odd class of [19] cancers, referred to as soft tissue sarcomas, [20] are probably more poorly understood than any -- [21] than other groups of cancer. [22] Within this group, Kaposi sarcoma [23] is a soft tissue sarcoma and we know it's [24] associated with AIDS; but it's not only caused [25] by AIDS because it's been around. Dr. Kaposi

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[1] discovered it long before we knew about AIDS. [2] Mesothelioma is another soft tissue sarcoma. [3] That's caused by asbestos. [4] But by and large, the rest of the [5] soft tissue sarcomas, we have not identified [6] specific causes for. Which is true of most [7] cancers. I mean, if we understood what caused [8] them and understood how they happened, the [9] mechanism, then we'd probably be able to cure [10] them.
[11] Q. Well, in terms of causes of cancer, [12] I mean, you don't have to understand absolutely [13] the mechanism in order to determine that [14] something causes cancer, do you?
[15] MR. WAGNER: Object to form.
[16] MR. LUTZ: Join.
[17] THE WITNESS: Well, I'm going to [18] get up on my soapbox here a little bit. I [19] think there's too much speculation about the [20] mechanism of cancer induction, with too little [21] scientific, factual basis for it. [22] In answer to your question, [23] directly, no, you don't have to understand the [24] mechanism to know whether something causes [25] cancer or not.

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[1] BY MR. SCHULER:
[2] Q. I mean, I understand -- to talk [3] about a different issue. I mean, the tobacco [4] companies still deny that their product causes [5] lung cancer.
[6] A. Uh-huh.
[7] Q. But you wouldn't agree with that, [8] would you?
[9] A. I would not agree with that.
[10] Q. Okay.
[11] A. I would agree with the statement [12] that tobacco smoke doesn't cause all lung [13] cancer and that there is lung cancer out there [14] of unknown ideology. And even something that [15] we know so well as that, there are cases of [16] lung cancer. [17] I had a very good friend die [18] recently of lung cancer. She never smoked, [19] wasn't the type that could smoke. Never lived [20] with anybody that could smoke, that would [21] smoke. It's a complete mystery.
[22] Q. Just lived next to a Dow Chemical [23] Plant.
[24] MR. WAGNER: Now, now. Don't get [25] tired. Keep your guard up.

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[1] THE WITNESS: That's right.
[2] BY MR. SCHULER:

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[3] Q. You mentioned mesothelioma on [4] another issue. Have you ever testified in any [5] asbestos cases?
[6] A. No. But I've written the book on [7] it.
[8] Q. Okay. What is the name of that [9] book?
[10] A. It's SILICONE AND SILICATES, [11] INCLUDING ASBESTOS; and it's in the [12] not-yet-published fourth edition of Patties' [13] Industrial Hygiene and Toxicology.
[14] Q. And when is that going to be [15] published?
[16] A. Probably later this year. I've [17] just received the galley proofs this week.
[18] Q. Is that another area where you have [19] expertise, the asbestos area, in terms of its [20] relationship to causing mesothelioma?
[21] A. Yes. I'd say the area of fiber [22] toxicology, of which asbestos is a subcategory.
[23] Q. But you haven't testified---
[24] A. No.
[25] Q. ---before any committees or

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[1] anything of that nature---
[2] A. There is no science in that.
[3] Q. No science in testifying or no [4] science in---
[5] A. Well, that too; but there's. . .
[6] Q. Does TCDD have an effect on the [7] immune system, in your view?
[8] A. In experimental animals, TCDD has [9] quite potent effect on the immune system, yes.
[10] Q. What about in humans?
[11] A. There is no evidence, no credible [12] evidence that I've seen that TCDD exposure [13] alters immune function or status in humans.
[14] Q. Can you extrapolate the animal [15] studies to humans in this instance?
[16] A. Well, I think you can. I mean, I'm [17] basically an animal toxicologist, and I have a [18] certain degree of faith in the predictability [19] of data we get in certain animal studies. And [20] I believe that 2,3,7,8-TCDD and related dioxins [21] and furans probably can somehow affect the [22] immune system in humans, but I've seen no [23] verifying evidence of that in studies of [24] humans.
[25] Q. I'm sorry. I didn't hear the last

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[1] part of your answer.
[2] A. I've seen no verifying evidence of [3] that in studies of exposed humans.
[4] Q. Let me ask you to refer to that [5] Krumel, Krommel, I'm not sure how it's [6] pronounced at this point, memo.
[7] A. I don't either.
[8] Q. Okay.
[9] A. I've got it here.
[10] Q. Okay. We've marked that an exhibit [11] to other depositions. I don't think there's [12] any tag on that one, but I don't think there's [13] any need to mark it.
[14] Have you reviewed the memorandum?
[15] A. I've gone through it superficially, [16] yes.
[17] Q. Does that memorandum indicate that [18] with respect to 2,4-D that there were any [19] chloracnegenic elements discovered in 2,4-D in [20] your opinion?
[21] A. In my opinion, there's a reference [22] to the fact that there are chloracnegenic [23] materials in process materials, and I think [24] that's waste, of the 2,4-D manufacture [25] process. There's nothing in here that directly

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[1] tells me there are chloracnegens in the 2,4-D [2] produced by this process.
[3] Q. What chloracnegens are referred to [4] in that memorandum that you considered?
[5] A. Well, he doesn't -- he identifies [6] two component -- or they identify two [7] components of the mix, which I think they [8] attribute chloracnegenic potential to; and I [9] don't agree with that.
[10] Q. What are the elements?
[11] A. They are 1,3,6,8-tetrachloro [12] xanthone and 1, 1 prime, 3, 3 prime, 6, 6 [13] prime, 8, 8 prime, octachloro, 9, 9 prime, [14] spirobixanthene.
[15] Q. Okay. You don't agree with his [16] assessment that


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those by-products are [17] chloracnegenic?
[18] A. That's correct.
[19] Q. Why not?
[20] A. Well, they're not of the structural [21] type, the geometric shape to be in the group of [22] compounds that we know from structure activity [23] relationships cause chloracne.
[24] Q. Are there any other by-products [25] identified in that report as chloracnegenic?

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[1] A. I don't think so. I found this [2] report extremely difficult to understand.
[3] Q. The two by-products that you [4] mentioned just now, do you believe those [5] by-products are immunotoxic?
[6] A. I have no basis to say yes or no. [7] I believe they're not, again, based on [8] structure activity principles.
[9] Q. Do you believe that by-products are [10] carcinogenic?
[11] A. I have no factual basis, other [12] than, again, from structure activity [13] relationship considerations. I think not.
[14] Q. May I see that memorandum just for [15] one second?
[16] A. Uh-huh.
[17] Q. Is chloracne, in your opinion, a [18] marker of relatively intense exposure to TCDD?
[19] MR. WAGNER: Object to form. Marker [20] is unclear and relatively intense is unclear.
[21] MR. LUTZ: Join.
[22] THE WITNESS: Chloracne is a marker [23] of heavy dioxin exposure, but's it not entirely [24] reliable.
[25] BY MR. SCHULER:

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[1] Q. Is there any significance to you, [2] from your review of the literature -- well, let [3] me strike that. [4] Is there any pattern that you've [5] noticed, in your review of the literature, with [6] regard to cancer causation as to whether it's [7] related to evidence of chloracne? [8] Let me just can the whole [9] question. Let me ask it this way. [10] Is chloracne a marker, a potential [11] marker of an exposure sufficient enough to [12] cause cancer?
[13] MR. WAGNER: Object to form.
[14] THE WITNESS: I have to give [15] probably a pretty long-winded answer to that. [16] Chloracne is a pretty good indicator that a [17] person is at an increased risk of cancer. The [18] absence of chloracne provides no assurance that [19] the person won't get cancer. Is that clear?
[20] BY MR. SCHULER:
[21] Q. I understand.
[22] A. That helps you.
[23] Q. Any answer you have to think about [24] doesn't help me. Okay.
[25] THE COURT REPORTER: Is this a good

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[1] place for a break?
[2] MR. SCHULER: Yes. We've been [3] going for about an hour and a half.
[4] (A recess transpired.)
[5] BY MR. SCHULER:
[6] Q. Was there anything in the medical [7] history of Bob Moyer that you saw that was [8] significant to you from exposure point of view?
[9] A. No. Well, in medical history, [10] there was one thing that raised questions and [11] that was the fact that he worked with the [12] cutting oil at the aircraft factory. I think [13] that was subsequent to -- I can't remember. [14] Whenever he worked there.
[15] Q. Do you know what kind of cutting [16] oil he worked with?
[17] A. No.
[18] Q. It would make a difference, [19] wouldn't it?
[20] A. To some degree. Although, I [21] disagree with Teitelbaum that it's only certain [22] kinds. Almost all cutting oils are [23] carcinogenic in experimental animals, except [24] the newer ones that have been specifically [25] designed to make them not.

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[1] Q. And so the only significance would [2] be, potentially, he was working with a [3] substance that could be carcinogenic in humans, [4] in your view?
[5] A. Yes. But I don't -- I think that [6] probability is low, also. Certainly the type [7] of cancer he had would probably not be [8] associated with that exposure either.

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[9] Q. That was going to be my next [10] question. Has cutting oil been linked to a [11] soft tissue sarcoma?
[12] A. Not to my knowledge, no.
[13] Q. Anything else in his medical [14] history that was significant from an exposure [15] standpoint, in your view?
[16] A. No. He generally seemed to be a [17] healthy, moderately clean living individual.
[18] Q. Did you have an opportunity to see [19] any of the videotape deposition that was taken [20] of Mr. Moyer?
[21] A. No, I did not.
[22] Q. Anything else about his medical [23] history that was significant to you in any way?
[24] A. No.
[25] Q. What about his living history?

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[1] Anything in his living history that was [2] significant to you, other than the fact that he [3] sprayed the chemicals for Orange County? When [4] I say living history, I'm talking about [5] locations, where he was born and raised, that [6] type of thing.
[7] A. No, no. I don't think anything [8] there was particularly noteworthy. He smoked, [9] but I think briefly.
[10] Q. Well, I was going to get to that [11] under personal hygiene.
[12] A. Okay.
[13] Q. I'm just now talking about---
[14] A. No. His living history, his [15] parents, there was familia cancer; but it was [16] not -- that's not the kind that would [17] genetically predispose him to cancer.
[18] Q. Okay. Other than the cutting oil [19] that you mentioned, anything else about his [20] employment history that would be significant to [21] you?
[22] A. Not that I saw.
[23] Q. Anything about his personal habits, [24] hygiene history, I call it, that was [25] significant to you?

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[1] A. Well, he smoked; but I think [2] briefly and at a fairly low level. And, again, [3] I don't think soft tissue sarcoma is one of the [4] smoking cancers. Again, it's hard to say since [5] soft tissue sarcoma is a poorly defined [6] category.
[7] Q. You mentioned, just a moment ago, [8] that you had disagreed with Dr. Teitelbaum and [9] one of the statements he made, I guess, about [10] the cutting oil.
[11] A. Uh-huh.
[12] Q. One of the areas that I have been [13] told that you are going to testify about is [14] potential rebuttal testimony to Dr. [15] Teitelbaum. Based on your review of his [16] deposition or -- well, I guess you had the full [17] deposition for him. [18] Based on your review of his [19] deposition, what comments or criticisms do you [20] intend to offer in this case with regard to his [21] testimony?
[22] MR. WAGNER: And I told you, it's [23] purely preliminary at this point since we [24] haven't finished Dr. Teitelbaum.
[25] MR. SCHULER: I understand.

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[1] THE WITNESS: That's a pretty broad [2] question.
[3] BY MR. SCHULER:
[4] Q. I understand. But I mean, I'm [5] trying to -- you know, I mean, there's 300 and [6] some odd pages of testimony. And the [7] alternative is to go through it line by line. [8] I thought we might focus---
[9] A. All right. Well, my overall [10] impression is that---
[11] MR. WAGNER: Before you start [12] that. Frankly, I told him -- and I don't mind [13] him answering. He can take care of himself. [14] But I told him to focus on his other areas in [15] preparing for this deposition, as opposed to [16] doing a line-by-line analysis that I do [17] contemplate at some future point, once it's [18] finished. [19] But with that in mind, go ahead [20] and -- he has reviewed Teitelbaum, and he has [21] told me, at least, what his general criticisms [22] are. And feel free to respond to the question.
[23] THE WITNESS: My overall impression [24] was that Dr.

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Teitelbaum did not have a good [25] grasp of the entire body of the available

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[1] information. He used information available to [2] him very selectively to pull documents and even [3] statements in documents out of context that [4] supported his performed opinion.
[5] BY MR. SCHULER:
[6] Q. And what, specifically, are you [7] referring to there?
[8] A. Well, I'm referring to his heavy [9] reliance, for example, on the studies of [10] Hardell and Eriksson, to the exclusion of [11] others. And his -- oh, I can't even come up [12] with specific examples, but -- well, I'm having [13] trouble recalling specific examples. [14] Again, I'm talking about general [15] impressions; and I'll be prepared at some later [16] date to address specific issues. [17] So then he -- I felt he was [18] careless in referring to evidence relevant only [19] to non-Hodgkin's lymphoma, as relevant to a [20] possible causal association between compounds [21] and soft tissue sarcoma. [22] I thought he was careless about [23] differentiating between phenoxy herbicides [24] likely to be contaminated with tetrachlorinated [25] and higher dioxins from those that were

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[1] unlikely to be. And just in balance, not a [2] very credible or expert witness.
[3] Q. Okay. I mean, I understand that [4] you're probably not fully prepared on this; but [5] the credibility and the grasp and so forth are [6] opinions. What I'm looking for is specifics [7] and you gave me the issue of relying on the [8] Hardell studies. I assume, from your statement [9] there, that you don't think the Hardell studies [10] are very credible either?
[11] A. I just think that they have some [12] severe limitations, that are potential [13] explanation for why these few studies appear to [14] be inconsistent. And I emphasis the word [15] appear. Appear to be inconsistent with the [16] overall body of evidence.
[17] Q. Are you familiar with the -- and I [18] brought a copy with me here today, and I [19] discussed this with Dr. Smith in his [20] deposition. Are you familiar with this EPA -- [21] and I have September of 1992. I don't even [22] know whether it's been revised since then or [23] not, but this preliminary review draft of [24] epidemiology in human data on dioxin?
[25] A. No, I haven't gotten a copy of that

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[1] yet. I know the process is going on.
[2] Q. Did you have any input into this [3] process?
[4] A. Extremely little. We talked about [5] it at the dioxin conference a year and a half [6] ago in Raleigh, but I had no formal involvement [7] whatsoever.
[8] Q. Do you know Charles Pool or David [9] Balitz of Stephen Baird, who they cite here as [10] people that put this together?
[11] A. Yes.
[12] Q. And what is your knowledge of them, [13] as far as---
[14] A. Well, they're all risk assessors [15] that have worked in the Office of Health [16] Effects at EPA for a number of years. They, in [17] this particular exercise, are primarily [18] reporters or compilers of data. The key [19] decisions on what's going on, they're being [20] made by people on the committee.
[21] Q. Well, let me ask you about the [22] process then. And if you don't know, tell me.
[23] A. Uh-huh.
[24] Q. I don't want you to speculate. I [25] mean, are these people that put together this

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[1] report reporting to a committee who is going to [2] make the final adoption or take the final [3] stance with regard to dioxin? Is that the [4] function of this report?
[5] A. Yes. And that is a draft. The [6] history of the situation is that the pulp and [7] paper industry in the United States has taken

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[8] every possible avenue or recourse possible to [9] attempt to get a stamp of authoritative [10] approval on their position that dioxin isn't as [11] bad for you as everybody says it is. [12] And their lobbying paid off with [13] the EPA about four years ago, three years ago, [14] when EPA said, we will re-review the risk [15] assessment and evidence for dioxin in humans. [16] And this is an interim product of that process.
[17] Q. So the pulp and paper makers, is [18] that what you're saying, initiated a process [19] to---
[20] A. Get EPA to reconsider their risk [21] assessment for dioxin. And so this whole [22] process is taking place very much in a [23] fishbowl.
[24] Q. You haven't seen this report yet?
[25] A. No, I haven't.

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[1] Q. So it wouldn't do me any good to [2] ask you if you agree or disagree with the [3] conclusions; is that correct?
[4] A. That's correct.
[5] Q. And if this report also placed [6] reliance on Dr. Hardell's studies, would you [7] feel that these people were also careless in [8] their analysis?
[9] A. I didn't say you can't rely on Dr. [10] Hardell's data. I say you can't take them [11] exclusively and, in the whole weight of [12] evidence, they just don't carry much weight.
[13] Q. Are you familiar with the study by [14] Ling in Denmark?
[15] A. Yes, I am.
[16] Q. And do you consider that to be a [17] credible study?
[18] A. Not very. It's what's called a [19] record linkage study, which is one of the [20] weakest types of epidemiologic studies you can [21] do.
[22] Q. Are you familiar with the study by [23] Manz, M-a-n-z, from Germany?
[24] A. Yes. That's in my pile.
[25] Q. Okay. Do you think that's a

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[1] credible study?
[2] A. Yes. Fairly. I mean, again, these [3] are all degrees. It has flaws. It's a pretty [4] good study.
[5] Q. And I think you mentioned before [6] the Fingerhut, IOSH as it's called, study; [7] correct?
[8] A. Yes.
[9] Q. And you do you consider that to be [10] credible, also?
[11] MR. WAGNER: Object to form.
[12] THE WITNESS: I consider it to be a [13] pretty good study. I have some problems with [14] it. They cut the cohort in size after the [15] study was underway. That's never been [16] satisfactorily explained.
[17] BY MR. SCHULER:
[18] Q. One of conclusions that they make [19] in this study is that of all the cancers [20] examined in both case control and follow-up [21] studies, soft tissue sarcoma provides the [22] strongest evidence of an association with [23] TCDD. [24] Do you disagree with that?
[25] MR. WAGNER: Object to form.

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[1] MR. LUTZ: Object to the form.
[2] THE WITNESS: I don't fully [3] subscribe to that statement. As I said [4] earlier, I think that TCDD -- the evidence is [5] that TCDD causes cancer at many different [6] sites. And to say that the evidence is [7] stronger for one or another is playing a little [8] fast and loose with the data. But I've never [9] said, today, that I don't think that TCDD [10] doesn't cause or isn't associated with soft [11] tissue sarcoma. That's a given.
[12] BY MR. SCHULER:
[13] Q. They state, in their conclusions in [14] this report, that the original report by [15] Hardell and colleagues of an association [16] between soft tissue sarcoma and exposures [17] involving TCDD contaminated phenoxy herbicides [18] have stood up to extensive criticism and a [19] great deal of subsequent research. [20] Do you agree with that or disagree [21] with that?
[22] MR. WAGNER: Object to form. Would [23] you identify the page, so we can -- you're [24] reading a sentence

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out of a lengthy text. And [25] since he's never seen the text, it's difficult

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[1] for him to even say whether it's in context or [2] out of context. That's the basis of my [3] objection.
[4] MR. LUTZ: I join.
[5] BY MR. SCHULER:
[6] Q. This is page 7-39 of the report of [7] September 10, 1992, review draft, United States [8] Environmental Protection Agency, Chapter 7, [9] epidemiology/human data. And I'm reading from [10] that page virtually the entire first paragraph [11] of the conclusion section. [12] Want me to read back that sentence [13] that I---
[14] A. Yes, please.
[15] Q. Okay. What I read from here, [16] referred to here is that the conclusion of the [17] folks that put this draft together were that [18] the original report by Hardell and colleagues [19] of an association between STS and exposures [20] involving TCDD contaminated phenoxy herbicides [21] have stood up to extensive criticism and a [22] great deal of subsequent research. [23] And my question was, would you [24] agree with that conclusion?
[25] MR. WAGNER: Object to form. Same

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[1] problem.
[2] MR. LUTZ: Same objection.
[3] THE WITNESS: I can't agree to that [4] in toto. I would not word it that way.
[5] BY MR. SCHULER:
[6] Q. Would you think that conclusion [7] would be careless or not very credible?
[8] MR. WAGNER: Object to the form. [9] Compound and vague.
[10] MR. LUTZ: I object to the form; [11] but, also, no predicate.
[12] THE WITNESS: As worded, I don't [13] think that conclusion is supported by the [14] evidence.
[15] BY MR. SCHULER:
[16] Q. And they go on to say, in the next [17] sentence in the same first paragraph on the [18] same page, the degree of increased risk, as [19] estimated in later studies by Hardell's [20] research group and several others, does not [21] appear to be as great as originally indicated, [22] but the association with TCDD exposure appears [23] more certain. [24] Would you agree with that [25] conclusion?

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[1] MR. WAGNER: Object to the form. [2] And, also, that seems to be directly contrary [3] to the sentence you read two seconds ago that [4] says that their work had withstood scrutiny. [5] But my same problem, reading from this review [6] draft, not even final, and a document that he [7] hasn't reviewed.
[8] MR. LUTZ: Join.
[9] THE WITNESS: That particular [10] sentence doesn't make any sense.
[11] BY MR. SCHULER:
[12] Q. Finally, they say that moreover no [13] persuasive case has been made that the entirety [14] of the association in these studies, referring [15] to the Hardell studies, is due to selection [16] bias, differential exposure, misclassification, [17] confounding, or change. [18] Would you agree with that [19] conclusion?
[20] MR. WAGNER: Same objection. Also, [21] that is a conclusion that is vague and [22] ambiguous as to its meaning.
[23] MR. LUTZ: Join.
[24] THE WITNESS: That's really a [25] funnily worked statement. They're essentially

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[1] admitting the recall bias, which is one of the [2] serious flaws of the Hardell studies is -- [3] they're saying, it's there, it's just not bad [4] enough to account for. Which is the weakest [5] defense of the Hardell study I've heard.
[6] BY MR. SCHULER:
[7] Q. So you don't agree with that [8] statement, I take it?
[9] A. Well, actually---
[10] MR. WAGNER: Same objection.
[11] THE WITNESS: ---I agree with [12] elements of it, but I wouldn't -- it's really [13] twisted logic.
[14] BY MR. SCHULER:
[15] Q. Not careless or very credible?
[16] MR. WAGNER: Object to the form.

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[17] THE WITNESS: I'll reserve. Won't [18] use those words.
[19] BY MR. SCHULER:
[20] Q. The other studies that were cited [21] in this report I mentioned. We have discussed [22] the Fingerhut study.
[23] A. Uh-huh.
[24] Q. And they mention the Sevaso study, [25] and we discussed -- which I don't think we

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[1] discussed here today. The IARC Registry cohort [2] study and the New Zealand sarcoma study.
[3] A. Uh-huh.
[4] Q. Those are all studies that you're [5] familiar with; correct?
[6] A. Yes.
[7] Q. Were any outside consultants [8] involved in the preparation of this, if you [9] know?
[10] A. I don't know about outside [11] consultants.
[12] MR. WAGNER: You mean, non-EPA [13] employed people? From outside?
[14] MR. SCHULER: Yes.
[15] THE WITNESS: I think -- it's a [16] committee headed by Linda Burnbaum, and I think [17] the members are from -- they're all from [18] government agencies. Although, whether they're [19] all just from EPA or not, I can't recall. [20] Isn't there, up at the front -- of [21] course, that's a volume of other volumes. [22] Isn't there a list of the committee members in [23] the first few pages?
[24] BY MR. SCHULER:
[25] Q. Not that I see. But the three

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[1] people that are listed are the ones---
[2] A. It's because that's Chapter 7. I'm [3] sure that if there's a Chapter 1, it'll be in [4] there. My recollection is that it's people [5] from several different offices of EPA and, [6] possibly, people from NIEHS, the National [7] Institutes of Environmental Health Sciences are [8] involved in that overall.
[9] MR. WAGNER: Since we've read from [10] that so much and referred to it, let's -- you [11] can keep your hard copy, but I'd like a copy [12] sooner or later.
[13] MR. SCHULER: Sure.
[14] MR. WAGNER: And let's make it a [15] part of this. I just note, specifically on the [16] front, it says: Do not quote or something. [17] What does it say?
[18] MR. SCHULER: Do not cite or quote.
[19] MR. WAGNER: Do not cite or quote. [20] Since we're citing and quoting that, let's get [21] a copy of it for the record.
[22] MR. LUTZ: Join. That may be a [23] felony or something.
[24] MR. SCHULER: Probably wouldn't be [25] the first one I've committed. We'll go ahead

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[1] and mark it as the next exhibit. Go ahead and [2] put a sticker on it. I'll furnish everybody a [3] copy of it.
[4] (DFT. EXH. 12, EPA Draft Document, [5] Chapter 7, September 1992, was [6] marked for identification.)
[7] BY MR. SCHULER:
[8] Q. Have you heard of the Syracuse [9] Research Corporation because they're listed in [10] here?
[11] A. Yes, I have.
[12] Q. What do you know about the Syracuse [13] Research Corporation?
[14] A. They're a consulting firm.
[15] Q. Similar to the one that you were a [16] member of?
[17] A. Yes.
[18] Q. Do you know any particular [19] individuals at that firm?
[20] A. I doubt if I know anybody who's [21] there now. I can't even remember who I used to [22] know there. I'm not even going to say his name [23] because I don't know how to spell, but I used [24] to know some people there. I don't know if [25] they still work there. I've not done any work

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[1] with them ever.
[2] Q. Are they in Washington or are they [3] in Syracuse, New York?
[4] A. Well, they have offices in both [5] places. Their headquarters is Syracuse, New [6] York.
[7] Q. Are they associated with the [8] university there? Do you know?
[9] A. I supposed that in their original [10] history, like Stan-

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ford Research Institute, they [11] were probably founded by university faculty; [12] but to the best of my knowledge, they're not [13] now affiliated.
[14] Q. Do you know---
[15] A. It's a private company.
[16] Q. Do you know Carol Haynes, [17] environmental criteria and assessment officer, [18] apparently?
[19] A. No.
[20] Q. Who worked on this as project [21] officer?
[22] A. No.
[23] Q. And it's an accurate statement that [24] you have never read or seen this report before?
[25] A. I've never seen that.

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[1] Q. Have you seen any other sections of [2] the dioxin report that -- it's about eight or [3] nine volumes, I think with that?
[4] A. No, I haven't seen any of them that [5] have been -- the whole process has been [6] somewhat contained because of the political [7] sensitivity.
[8] Q. Do you know how long these volumes [9] have been available? I assume they've been [10] available since September of '92.
[11] A. That's not a good assumption. The [12] date on there doesn't typically reflect -- [13] there's typically about a three to six month [14] lag. So it's probably been available since the [15] end of last year, three months ago or four [16] months ago.
[17] Q. I assume you're going to get it and [18] review it?
[19] A. Going to try.
[20] Q. It is in your area of expertise?
[21] A. Right.
[22] Q. One of your areas of expertise; [23] right?
[24] A. Right.
[25] MR. WAGNER: I'm going to hold you

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[1] to that admission.
[2] BY MR. SCHULER:
[3] Q. I'm looking now at your synopsis [4] that we've marked as Plaintiff's 3.
[5] A. Uh-huh.
[6] Q. And I want to ask you some [7] questions about some specific statements in [8] there.
[9] A. Okay.
[10] Q. It's your understanding that [11] 2,4,5-T has not been used in the United States [12] since 1979 or '80; correct?
[13] A. Correct.
[14] Q. And in terms of the dioxin [15] compounds, there's a statement, and I'm [16] referring to page 1 now of Plaintiff's 3---
[17] A. Uh-huh.
[18] Q. ---third paragraph. The dioxin [19] compounds, it says here, and the amounts of [20] them that were present in phenoxy herbicide [21] preparations varied from preparation to [22] preparation and perhaps even from batch to [23] batch. [24] Do you agree with that statement?
[25] A. In the Vietnam era, yes.

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[1] Q. What about in the 1970s?
[2] A. No.
[3] Q. Okay. What is your understanding [4] when the change took place?
[5] A. It wasn't overnight and that's [6] important to remember. I think the first real [7] sensitivity to a need to reduce the amount of [8] dioxin occurred around 1968, '67, '68; and was [9] probably -- everybody was probably on board by [10] about 1970.
[11] Q. So after 1970, there was no more [12] variability in the amount of dioxin compounds?
[13] A. Well, there was variability, but [14] not in the sense that I was talking about [15] there, and very little variability because [16] there was much more control on the raw material [17] manufacture.
[18] Q. And what information do you point [19] to to support that conclusion?
[20] A. Well, it's mostly second-hand [21] information included in books. Oh, Warren [22] Krumet writing in the history of this issue [23] for -- he was a former employee of Dow [24] Chemical, and I think Al Young has written some [25] information about this, though, I can't

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[1] remember.
[2] Q. Krumet is

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K-r-u-m-e-t or how do you spell it?
A. I think that's correct.
Q. And do you remember the particular article or book?
A. It would probably be a chapter, and I don't remember what book it would be in.
Q. Is TCDD a potent carcinogen in your opinion?
MR. WAGNER: Object to form.
THE WITNESS: Well, I have a little trouble with the term potent; but to try and help you and to answer it, the amounts required to cause cancer in experimental animals are extremely low. And by that definition, it is a potent carcinogen.
BY MR. SCHULER:
Q. Of all the dioxins is it the strongest carcinogen that you're aware of?
A. Well, it is a -- of all the carcinogens, is it?
Q. I said, of all the dioxins.
A. 2,3,7,8 is the strongest, yes.
Q. In terms of carcinogenic

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capability?
A. Correct. Although, possibly very closely followed by 1,2,3,7,8-pentachlorofuran, dibenzofuran.
Q. That's in pentachloro phenol? Is that contained in pentachloro phenol?
A. Ah---
Q. Well, let me. The furan that you just referred to---
A. There would be very little of it in pentachloro phenol.
Q. Is that contained in any of the phenoxy herbicides?
A. If at all, at extremely low levels.
Q. Would 2,4-D in 1976 and 1977 contain small quantities of dioxins?
A. Not tetra and higher.
Q. Which ones would it contain in your opinion?
A. Di and trichlorodibenzo dioxin.
Q. Are these carcinogens in your opinion?
A. No.
Q. When you say that TCDD is a carcinogen, and you do discuss this in your

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synopsis here, you talk about it as a promoter; correct?
A. Well, I don't know if I used that term. That is a term that comes up in the discussion. I don't consider it to be purely a promoter.
Q. You also consider it to be an initiator, as well?
A. Well, I'll need to talk about that a little bit. I believe promoter is an operational term, rather than a precise, mechanistic term because I don't understand the mechanism by which dioxin causes cancer. I think if we did, again, we'd cure cancer. But anyway, promoter is simply a definition of how it behaves in a certain assay that's designed to identify or separate this one form of cancer induction from another. And in those types of assays, TCDD very clearly operates as a promoter. Interestingly, it isn't very effective as an initiator in those assays; but it does cause cancer by itself in experimental animals, so there will be some initiating aspect to its activity. But it is not what we

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call a genotoxic carcinogen. It doesn't initiate the carcinogenic process by causing a gene mutation or chromosomal damage. It has this effect, this carcinogenic effect through its interaction with the AH receptor. But what happens from that step on, to the development of a tumor, I don't think is known. And anybody who thinks they know what happens is presumptuous and a little foolish.
Q. Well, do you have your own theory as to what happens?
MR. WAGNER: Object to form.
BY MR. SCHULER:
Q. I know you're not a medical doctor, but---
A. Well, you don't need to be a medical doctor. That's not an aspect of a medical doctor's understanding or

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training. [20] But I have my current theory, which changes at [21] every month or each paper I read or so forth, [22] but I think that its carcinogenic effect is the [23] result of the way it regulates or deregulates [24] the gene in the genetic material of the cell. [25] And that it is simply altering the way the cell

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[1] responds to endogenous growth factors, which [2] essentially the cell loses its ability to [3] control growth and becomes a cancer cell.
[4] Q. That's what your present opinion [5] is?
[6] A. Yeah. That's this week's theory.
[7] Q. This week's theory?
[8] A. Yes.
[9] Q. Okay. I touched on this at a very [10] early stage in your deposition, but do you feel [11] that even one molecule of TCDD could initiate [12] this type of reaction?
[13] A. That's not -- I think that that's [14] extremely unlikely in that the one hit model, [15] which that is a verbal expression of, is [16] probably not the most appropriate model; but it [17] can't be ruled out by -- on the basis of the [18] evidence that we have now. So I guess a very [19] honest and easy answer is I can't reject that [20] hypothesis.
[21] Q. Do you feel that TCDD or material [22] such as silvex or 2,4,5-T that might contain [23] TCDD -- and I want to be careful the way I [24] choose my words here because I know that [25] there's some terms of art that you use. Let me

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[1] start over again. [2] Do you feel that the chemical [3] exposure and ultimate cancer in those that have [4] had sufficient exposure to TCDD through the [5] medium of these phenoxy herbicides can be site [6] specific? And what I mean by that is, if an [7] individual -- I think there's some mention in [8] one of the studies about some sprayers that [9] carried backpacks that leaked and there's some [10] comment about tumors occurring or the disease [11] occurring in proximity to where the leakage [12] was. [13] And Moyer's testimony in this [14] case---
[15] A. On his right arm.
[16] Q. ---about the---
[17] A. ---with the gun and all that.
[18] Q. I think it was the left arm.
[19] A. Oh.
[20] Q. But discussed the issue of the [21] leaking of the gun onto the arm area. What's [22] your opinion as to whether or not this can [23] be -- there's a relationship between the [24] exposure site for example on a human's body and [25] the cancer?

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[1] MR. WAGNER: Object to form. And no [2] predicate.
[3] MR. LUTZ: Join.
[4] THE WITNESS: My opinion is that, [5] if it were, in fact, a skin cancer, that might [6] be a little more credible. I do believe that, [7] to some extent, dioxin 2,3,7,8-TCDD is a point [8] of contact carcinogen. That explains why the [9] animals in -- and I may reverse the studies -- [10] but the animals in the NTP study got nasal [11] cancers, whereas the animals in Cosiba study [12] did not. In Cosiba, they were intubated. [13] In the NTP study, they ate it in [14] the diet, so the dust got into their nasal [15] passages and so forth. And since there has [16] been an association of dioxin with stomach [17] cancer in some cases, lung cancer in other [18] cases, I feel that there is some evidence that [19] 2,3,7,8 may be a point of contact carcinogen, [20] as well as a systemic one. [21] But I don't believe that's relevant [22] to Moyer's case because that soft tissue is [23] underneath and inside and it's not an area [24] where the dioxin would go. If the dioxin got [25] into the skin, it would stay in the skin or be

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[1] taken by the vasculature, which overlies the [2] soft tissue, to the systemic circulation. So [3] it's not a credible hypothesis to me.
[4] BY MR. SCHULER:
[5] Q. And that hypothesis that you've [6] just

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enunciated would not change, even assuming [7] that there was some type of breakage in the [8] skin area where Moyer was exposed?
[9] A. No. It would have to be, you know, [10] a deep puncture wound going into the soft [11] tissue, which is -- and, again -- well, that's [12] it.
[13] Q. Okay. I didn't mean to cut you off [14] earlier, unless you were finished at this point [15] with your criticisms of Dr. Teitelbaum. We got [16] kind of side tracked.
[17] A. I'd rather not -- I did not make [18] marks in his transcript. I haven't read it all [19] in the last 24 hours. I just went back last [20] night and re-reviewed it. I was only prepared [21] today to give general impressions. If I could [22] take some time and go through it and find [23] specific examples of what I'm talking about, [24] but I'd prefer to save that for a later date, [25] when I have all his material before me.

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[1] Q. Let me ask you the same question [2] then with respect to Dr. Hardell's deposition, [3] since you also had that---
[4] A. Uh-huh.
[5] Q. ---and you've been offered as a [6] critiquer, if you will, of his testimony as [7] well.
[8] A. Uh-huh.
[9] Q. What about his testimony do you [10] wish to criticize at this point?
[11] A. Well, maybe I should be careful [12] since he's careful to always say he's not a [13] toxicologist. But, generally, I had very [14] little problem with his deposition. I thought [15] he was open and honest and careful. I can't [16] think of a single specific statement of his [17] that I would say is absolutely wrong. Again, I [18] think he carries a bias. It's understandable. [19] We're all biased.
[20] Q. All right. Let me ask you about [21] effects on the immune system, which I touched [22] on before.
[23] A. Uh-huh.
[24] Q. Do you feel that TCDD is [25] immunotoxic?

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[1] A. In experimental animals, it's [2] clearly immunotoxic. Yes.
[3] Q. And can that be extrapolated to [4] man?
[5] A. Well, to some degree and -- but the [6] few studies that have been done to look for it [7] in humans, have failed to confirm a real [8] effect.
[9] Q. So your opinion is that it can or [10] you're uncertain at this time or it can't?
[11] A. I would say that we ought to [12] regulate it or treat it as if it can cause [13] immune effects in humans. One of the [14] interesting things that's not clear to me is [15] whether those effect might be immunosuppressive [16] or immunostimulatory. [17] If it's immunostimulatory, it [18] might, in fact, be anti-carcinogenic in that [19] sense. Some of the animal evidence indicates [20] that that is the nature of the immuno effect. [21] But, in general, in experimental animals, it's [22] immunosuppressive.
[23] Q. Or it could be both, couldn't it?
[24] A. It could be both at different doses [25] and that's a very important and potential

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[1] issue.
[2] Q. Have you spoken with anyone at Dow [3] Chemical Company regarding this case, any [4] aspect of it?
[5] A. No.
[6] Q. Are you familiar with anyone at Dow [7] Chemical Company, other than, I think we've [8] mentioned a few names on and off here, that was [9] actively involved in the research regarding [10] 2,4-D and 2,4,5-T as far as toxicity is [11] concerned?
[12] MR. WAGNER: When you say familiar, [13] do you mean does he know them personally?
[14] MR. SCHULER: Does he know them [15] personally. Yes.
[16] THE WITNESS: Sure.
[17] BY MR. SCHULER:
[18] Q. Who are you familiar with?
[19] A. Well, Dick Cosiba, Bernie Schwetz.
[20] Q. How do you spell that last name?
[21] A. Schwetz, S-c-h-w-e-t-z.


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[22] Q. Are they both toxicologists?
[23] A. Yes. Bernie is no longer with [24] Dow. He's now, I believe, at CIIT, which is [25] the Chemical Industry Institute of Toxicology.

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[1] Oh, gee. I know others. I've known other [2] people at Dow. Whether they participated in [3] the dioxin studies, I can't remember for sure. [4] Perry Gehring and Phil Watanabe, [5] W-a-t-a-n-a-b-e. Gehring is G-e-h-r-i-n-g. [6] Q. Have you discussed, at one time or [7] another, any of the issues with them that we're [8] involved with in this case?
[9] A. No, no. I don't talk to any of [10] those guys very frequently or particularly [11] recently, except Dick Cosiba, who goes to all [12] the international dioxin meetings. But we just [13] talk in general terms.
[14] Q. Are you familiar with the process [15] that a company like Dow Chemical goes through [16] in order to comply with registration [17] requirements for these chemicals?
[18] MR. WAGNER: Object to form. Time [19] period.
[20] THE WITNESS: I have assisted [21] pesticide manufacturers in assembling the [22] information for a registration petition to EPA, [23] if that's what you're seeking, yes.
[24] BY MR. SCHULER:
[25] Q. That's what I'm seeking.

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[1] A. Yes.
[2] Q. And since you've participated in [3] the registration process, then I assume you are [4] familiar with the types of information that [5] needs to be supplied to the EPA in order to get [6] a pesticide registered; correct?
[7] A. Yes, I am.
[8] MR. WAGNER: Same objection.
[9] BY MR. SCHULER:
[10] Q. And can you tell me what types of [11] information are required to be provided?
[12] MR. WAGNER: Same objection.
[13] THE WITNESS: Oh, boy. [14] Manufacturing information, toxicity information [15] to the target species and to non-target [16] species. Non-target species include humans, [17] terrestrial organisms and aquatic organisms. [18] All of these depending on the intended use of [19] the product. So if the intended use would not [20] result in any exposure of humans or terrestrial [21] organisms, whatever, you don't have to do that [22] kind of data.
[23] BY MR. SCHULER:
[24] Q. Let me stop you for one second [25] before you go on.

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[1] A. Okay.
[2] Q. Because I want to make one point [3] clear. The type of information that you're [4] talking about the manufacturer needs to supply, [5] is this pursuant to rules and regulations under [6] the FEFRA or FIFRA Act?
[7] A. FIFRA. Right. Yes.
[8] Q. And have essentially the same [9] requirements been in effect since the [10] early '70s?
[11] MR. WAGNER: Object to form. No [12] predicate.
[13] THE WITNESS: Yeah, I'd say the [14] general requirements. Well, let's see. [15] Early '70s. The general broad areas that I'm [16] talking about, yes. The guidelines for what [17] studies to do when and that kind of thing have [18] evolved quite a bit since the early '70s. [19] I'm trying to think when sub-part [20] G. The tox guidelines, I think, were published [21] in about 1978 or -- oh, even later than that. [22] When I was -- well, maybe not. '78 to '82, [23] somewhere in there. And that represented, you [24] know, quite a bit of change in how much safety [25] data and so forth was needed.

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[1] BY MR. SCHULER:
[2] Q. Prior to that publication of [3] sub-part G, those are the toxicology [4] guidelines?
[5] A. Uh-huh.
[6] Q. Yes?
[7] A. Yes.
[8] Q. Were there still requirements for [9] toxicological data to be supplied, it's just [10] that they were less stringent? Is that what

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[11] you're saying?
[12] MR. WAGNER: Object to form.
[13] THE WITNESS: There were -- yeah, [14] less stringent is a possible word. Less [15] formalized more than anything else. There was [16] more give and take. [17] In the old days, the manufacturer [18] used to come into EPA and sit down with the [19] guys and say, if we do this study and that and [20] this, will that be okay? And they'd say yes or [21] no. Then they'd go back. And you look at some [22] of those old registration packages, and there's [23] a tremendous difference in the amount of data. [24] So the promulgation of standards or [25] guidelines like those in sub-part G was an

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[1] attempt to get a handle on this so that [2] everybody was playing on a level playing field, [3] is the expression they use. [4] It was a very informal process in [5] the early days when -- even when I was at Food [6] and Administration. There was very little in [7] the way of written guidance to a sponsor [8] wanting to submit something for approval.
[9] BY MR. SCHULER:
[10] Q. Was there any type, to your [11] knowledge, and I understand you're a [12] toxicologist and haven't been involved in the [13] process, is there any type of continuing [14] obligation to provide information if a [15] manufacturer comes across some information in [16] the course of manufacturing a particular [17] chemical that might be relevant to its [18] toxicological properties?
[19] MR. WAGNER: Object to form. Over [20] broad as to time. Also, no predicate and it [21] suggests itself to ask for a legal opinion.
[22] THE WITNESS: Yeah. I'm not [23] qualified to talk about the regulatory [24] requirements for -- across the broad for a [25] manufacturer of agricultural chemical. I'm not

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[1] familiar with all parts of the FIFRA regs.
[2] BY MR. SCHULER:
[3] Q. That's fair enough. I'm just [4] asking within your expertise, having [5] participated in the process.
[6] A. I think there now is---
[7] MR. WAGNER: Same objection.
[8] THE WITNESS: I think now that [9] there are requirements to submit and it may [10] even be under TSCA, rather than under FIFRA; [11] but I don't know what the requirements were in [12] the '70s.
[13] BY MR. SCHULER:
[14] Q. Do you know Larry Silverstein at [15] Dow Chemical Company?
[16] A. No.
[17] Q. V. K. Row?
[18] A. Well, I know of V. K. He's the [19] grandfather of the whole group.
[20] Q. Have you ever been to Midland, [21] Michigan, and---
[22] A. Yes, I have.
[23] Q. ---and seen the Dow Plant?
[24] A. Yes.
[25] Q. When did you go there?

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[1] A. In 19 -- well, probably a year [2] after, two years after I went to work for FDA. [3] I inspected it as part of the bioresearch [4] monitoring project. I sent a week there with [5] an FDA inspector, and we inspected their old [6] toxicology laboratory.
[7] Q. And that was in connection with [8] your FDA employment?
[9] A. Yes.
[10] Q. Were there drugs being made or [11] something that you were interested in looking [12] at at the laboratory?
[13] A. Data that Dow submitted to the Food [14] and Drug Administration. Yes, they had FDA [15] regulated products that were tested there.
[16] Q. Any other time that you've been to [17] Midland, Michigan, to Dow?
[18] A. No.
[19] (Off-the-record conference.)
[20] BY MR. SCHULER:
[21] Q. Do you know how long, from your [22] review of the literature, Dow was aware that [23] certain of the chlorinated organic compounds it [24] manufactured could cause chloracne?

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[25] MR. WAGNER: Object to form.

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[1] MR. LUTZ: Join.
[2] MR. WAGNER: No predicate.
[3] THE WITNESS: And I---
[4] MR. WAGNER: Asking knowledge of [5] another person.
[6] THE WITNESS: I'm not aware, no.
[7] BY MR. SCHULER:
[8] Q. Well, I'm asking -- I mean, all [9] your knowledge is from other people because [10] you're quoting---
[11] A. Right. I just---
[12] Q. My question was carefully worded, [13] from your review of the literature. Your [14] answer would be the same?
[15] A. I don't know.
[16] Q. Okay.
[17] A. They had an accident there and the [18] workers got chloracne, and I can't remember [19] what year that was; but they must have made a [20] connection then, if not later.
[21] Q. Do you remember what decade the [22] accident---
[23] A. '60s, I think.
[24] Q. Do you know when Dow Chemical first [25] may have started testing compounds to determine

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[1] what the source of the chloracne was in its [2] manufacturing process?
[3] MR. WAGNER: Same objection.
[4] THE WITNESS: No, I don't.
[5] BY MR. SCHULER:
[6] Q. Have you seen any internal Dow [7] documentation with regard to any testing that [8] was done on TCDD within the company prior to [9] 1977?
[10] A. No.
[11] Q. Are you familiar with the German [12] company, Boehringer?
[13] A. There are several German companies [14] that have Boehringer in their name.
[15] Q. Okay. I'm referring specifically [16] to the chemical manufacturing company.
[17] A. Well, I think what you're looking [18] for is Boehringer-Ingelheim. There's [19] Boehringer-Mannheim, also.
[20] Q. Okay.
[21] A. And they're both chemical [22] manufacturers.
[23] Q. Have you seen any research that [24] Boehringer-Ingelheim has done with respect to [25] TCDD?

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[1] A. Yeah. It's one of those papers in [2] the cancer epidemiology. It's called the [3] Hamberg study. Let me. That's the Manz [4] study. This is Boehringer-Ingelheim.
[5] Q. That's the study that we discussed [6] earlier---
[7] A. Yes.
[8] Q. ---that you felt was a credible [9] study with regard to cancer mortality?
[10] A. Yes.
[11] Q. Okay. To get back to the specifics [12] of this case for a moment. I've asked you, and [13] I think you've gone through most of the bases [14] of your opinion here, at least the ones that [15] I've written down. [16] Are there any other bases for your [17] opinion that we haven't discussed here today?
[18] A. Not that I know of. I think I laid [19] them out carefully.
[20] MR. SCHULER: This might be a good [21] place to stop. Let me just check my notes for [22] a few minutes.
[23] (A recess transpired.)
[24] BY MR. SCHULER:
[25] Q. Let me just ask you a couple of

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[1] questions to clear up a couple of things, at [2] least in my mind, about your opinion. You make [3] the statement in Plaintiff's 8, your letter of [4] October 22, 1992, that the estimated daily [5] intake of TCDD from non-occupational exposures [6] ranges from 40 to 240 picograms per day for a [7] 176 pound man; correct?
[8] A. Yes.
[9] Q. And that's an average that you get [10] from your review of the literature? Is that [11] what you're saying?
[12] A. Correct.
[13] Q. Okay.
[14] A. It's a range I get from my review [15] of the literature.
[16] Q. That's not done from independent [17] research and it's not---
[18] A. No.
[19] Q. ---something that you arrived at [20] independent of what

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someone else has put [21] together; correct?
[22] A. Right.
[23] Q. All right. And you state that this [24] measurement is obtained from background [25] concentrations of this compound in the blood

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[1] and adipose tissues and, therefore, represent [2] the amount of this compound that is actually [3] absorbed each day.
[4] A. Uh-huh.
[5] Q. Correct?
[6] A. Correct.
[7] Q. So that you're saying, because I [8] want to be clear I understand it, that 40 to [9] 240 picograms on the average, per day, are [10] absorbed in a 176 pound man?
[11] A. Correct.
[12] Q. And we discussed, I think, earlier, [13] the sources of that and I won't get into that. [14] Then you go on to say, it's my opinion that if [15] Mr. Moyer were exposed to TCDD as a result of [16] application of herbicides during his employment [17] by Orange County in 1976 and 1977, the minute [18] amount of that compound that he would have [19] absorbed and retained would be negligible [20] compared to the total amount that he absorbed [21] from the general environmental sources in the [22] same two year period. [23] And my question is, how do you make [24] the comparison? I mean, you made some general [25] statements before about that he used the

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[1] chemical sporadically, and used very small [2] amounts of it over the time that he was with [3] Orange County. [4] What I'm getting at is what [5] specifically -- what type of comparison are you [6] making here? I mean, are you just making a [7] general statement based upon the general [8] statements in the depositions or do you have [9] some type of number or measurement that you can [10] point us to? [11] And I understand you didn't [12] calculate numbers for this and that's---
[13] A. Yeah.
[14] Q. ---probably going to be somebody [15] else doing that.
[16] MR. WAGNER: Object to form.
[17] MR. LUTZ: Join.
[18] THE WITNESS: What it's based on is [19] that if -- the documents show that if Mr. Moyer [20] used a dioxin contaminated preparation at all, [21] it would have been silvex on anywhere from one [22] to three days, very small amounts. The [23] contamination of that silvex, because it was in [24] the late '70s, would have been well, well, well [25] under one part per million dioxin.

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[1] BY MR. SCHULER:
[2] Q. Let me just stop you for a second, [3] then we'll piece this together. When you say [4] small amounts, what are you referring -- what's [5] your understanding of the evidence in the case [6] with regard to that?
[7] A. My understanding of the evidence in [8] the case is that probably the maximum amount of [9] silvex preparation used of the concentrate was [10] zero to ten gallons.
[11] Q. Okay.
[12] A. And if Moyer was exposed to that, [13] his exposure could have been none or three or [14] six or nine, basically in that range. And that [15] it was contaminated with 2,3,7,8 dioxin or its [16] equivalence at a level of probably a tenth of a [17] part per million or less. And that's just -- [18] then it wouldn't get onto his skin. What [19] little bit did get onto his skin, there's not [20] 100 percent absorbed, not even 50 percent [21] absorbed through the intact skin. So---
[22] Q. You're assuming the skin was [23] intact?
[24] A. I don't even think I have to do the [25] calculation, you know.

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[1] Q. All right.
[2] A. It's one cigarette compared to a [3] two-a-day smoker, you know.
[4] Q. Okay.
[5] A. It's that kind of comparison in my [6] mind.
[7] Q. All right. I understand what [8] you're saying. So without doing the [9] calculation,

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you're just saying that -- making [10] the assumption that his skin was intact, making [11] the assumption that he used zero to ten galls [12] of the concentrated form, using the assumption [13] that there was .1 part per million or less in [14] the concentrate---
[15] A. Uh-huh.
[16] Q. ---and the other things that you've [17] discussed already with me earlier in the [18] deposition, you just don't think that his [19] exposure to TCDD at Orange County would have [20] materially elevated or materially been greater [21] than the background exposure?
[22] A. That's right.
[23] MR. LUTZ: I object to the form of [24] the question.
[25] BY MR. SCHULER:

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[1] Q. To TCDD; correct?
[2] MR. WAGNER: So do I.
[3] THE WITNESS: Correct.
[4] MR. SCHULER: Okay. That's all the [5] questions I have today. [6] (The deposition was adjourned at
[7] 3:53 PM.) [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]

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[1] SIGNATURE OF DEPONENT [2] [3] I, the undersigned, Carl O. Schulz, [4] do hereby certify that I have read the [5] foregoing deposition and find it to be a true [6] and accurate transcription of my testimony, [7] with the following corrections, if any: [8] [9] PAGE LINE CHANGE REASON [10] [11] [12] [13] [14] [15] [16] [17] [18] [19]

[20] CARL O. SCHULZ
Date [21] [22] [23] [24] [25]

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[1] CERTIFICATE OF REPORTER [2] [3] I, Wanda K. Cecil, Court Reporter and [4] Notary Public for the State of South Carolina
[5] at Large, do hereby certify: [6] That the foregoing deposition was taken [7] before me on the date and at the time and [8] location stated on page 1 of this transcript; [9] that the witness was duly sworn to testify to [10] the truth, the whole truth, and nothing but the [11] truth; that the testimony of the witness and [12] all objections made at the time of the [13] examination were recorded stenographically by [14] me and were thereafter transcribed by [15] computer-aided transcription; that the [16] foregoing deposition as typed is a true, [17] accurate, and complete record of the testimony [18] of the witness and of all objections made at [19] the time of the examination. [20] I further certify that I am neither [21] related to nor counsel for any party to the [22] cause pending or interested in the events [23] thereof. [24] [25]

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[1] Witness my hand, I have hereunto affixed [2] my official seal this 25th day of March, 1993, [3] at Columbia, Lexington County, South Carolina. [4] [5] [6] [7]
Wanda K. Cecil
[8] Notary Public My Commission expires [9] March 27, 1997 [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]

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Department of Veterans Affairs

# Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins No. 9–(Volumes XIX and XX)

Veterans Health Administration

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# SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS NO. 9 – (Volumes XIX and XX)

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## PREFACE

This synopsis is the ninth in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. Synopsis No. 1 of Volumes I–IV was published in July 1985. Subsequent synopses were published as follows:

October 1985 (Synopsis No. 2 – Volumes V and VI)

October 1986 (Synopsis No. 3 – Volumes VII and VIII)

July 1987 (Synopsis No. 4 – Volumes IX and X)

September 1988 (Synopsis No. 5 – Volumes XI and XII)

October 1989 (Synopsis No. 6 – Volumes XIII and XIV)

May 1990 (Synopsis No. 7 – Volumes XV and XVI)

August 1991 (Synopsis No. 8 – Volumes XVII and XVIII)

This current synopsis, a review of Volumes XIX and XX, continues the effort of the Department of Veterans Affairs (VA) to provide for the general public a summary in laymen's terms, of the scientific literature published during 1991 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

Environmental Agents Service

Department of Veterans Affairs

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## 1. Introduction

In May 1992, Information Venture, Inc., a scientific information company in Philadelphia, Pennsylvania, completed a review of the literature published during 1991 on the health effects of Agent Orange and related compounds. A critical review and an annotated bibliography of this literature have been published as Volumes XIX and XX of the ongoing *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. This synopsis summarizes the important new information that became available during 1991.

Phenoxy herbicides are a group of structurally–related chemicals that have been used in agriculture and forestry to kill weeds in cultivated crops and unwanted tree species in coniferous forests, and to clear vegetation from road beds and fence lines. The phenoxy herbicides that have been most frequently used in the United States are 2,4–D and 2,4,5–T. The latter has not been used in the United States for a number of years, and its use has been banned in most countries around the world. Another phenoxy herbicide, MCPA, has been used extensively in Scandinavian countries. Several herbicides were used by the U.S. Air Force in Vietnam from 1963 to 1971 in Operation Ranch Hand to remove leaves from trees in heavily forested areas so as to be able to see enemy troop movements and supply operations. Agent Orange, a mixture of 2,4–D and 2,4,5–T was, by far, the herbicide used most frequently.

Commercial phenoxy herbicide preparations manufactured from the 1940s until the early 1970s contained small quantities of chlorinated dibenzo–p–dioxins as contaminating impurities. The terms "dioxins" or "dioxin" have frequently been used as shorthand for this family of chemical compounds. The exact dioxin compounds and the amounts of them that were present in phenoxy herbicide preparations varied from preparation to preparation and perhaps even from batch to batch. Commercial preparations of 2,4,5–T contained small amounts of one particular dioxin, 2,3,7,8 –tetrachlorodibenzo–p–dioxin, which is frequently abbreviated as 2,3,7,8–TCDD or just TCDD. TCDD was present in the Agent Orange that was used in Vietnam. The effects of TCDD on experimental animals have been extensively studied since it is believed to be the most toxic member of the dioxin family of compounds. While 2,4–D contained small quantities of dioxins, TCDD was not one of them. When it was recognized that phenoxy herbicides were contaminated with dioxins, manufacturing processes were changed so as to reduce or eliminate them. Some other herbicidal preparations that were used in Vietnam contained cacodylic acid and/or picloram. These herbicides were used in much smaller quantities than Agent Orange, however, and they were not contaminated with dioxins.

## 2. Description of the literature published in 1991

There were 350 papers published during 1991 about the health effects of phenoxy herbicides and other herbicides used in Vietnam. This is a slightly larger number than the year before and above the average of the last five years. It indicates that there continues to be a high level of scientific interest in this area of investigation. Public controversy surrounding the dioxins has if anything increased over the past year. Consistent with previous years, much of the literature described studies of the effects of dioxins and related compounds in animals and various experimental systems because scientists are very interested in learning how this family of compounds causes the wide variety of toxic effects that it does. At the same time, the results of a number of studies of possible health effects in humans who may have been exposed to phenoxy herbicides and/or dioxins were published in 1991. Furthermore, many papers reported on studies in which



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the concentration of dioxins in human blood, body fat, and breast milk were measured, and attempts were made to relate these concentrations to past exposure to phenoxy herbicides or dioxins and to any adverse health effects that were experienced.

### 3. Studies of Vietnam veterans

The past 10–15 years has seen much research devoted to the issue of whether the health of Vietnam veterans has been adversely affected by their service in Vietnam, in general, and by exposure to phenoxy herbicides, in particular. The question of lasting effects of Vietnam service in general is easier to address than that of the effects of herbicide exposure, because it is much easier to determine whether a veteran served in Vietnam, and to locate detailed service records, than to determine whether he or she was exposed to herbicides while there.

It is difficult, if not impossible, to answer the question of whether there is an association between exposure to herbicides in Vietnam and adverse health effects, especially cancer. One reason for this is the difficulty of accurately determining any given individual's exposure to herbicides, and to phenoxy herbicides in particular, so many years after the war. Another reason is that exposure to herbicides is just one aspect of military service in Vietnam that might have had a long lasting impact on health, and it is not possible to separate all the factors. For example, careful study of the available information on herbicide application missions in Vietnam, indicates that the ground troops that were most likely to have been exposed to herbicides during, or just after, their application were the same troops that were most likely to have been involved in combat. The stress of constant exposure to combat situations is known to have adverse consequences for physical health.

How can exposure to phenoxy herbicides be assessed among Vietnam veterans? Three basic approaches have been attempted. The first is to ask veterans whether they were sprayed with herbicides. This method is inaccurate for several reasons. First, other chemicals such as insecticides, were sprayed in Vietnam, and ground troops had no way of knowing what was being sprayed. Second, a number of independent studies have shown that a veteran's recall of herbicide exposure is influenced by his or her belief regarding lasting health effects of that exposure, i.e., veterans who do not believe that they are in poor health as a result of herbicide exposure are less likely to remember being exposed, even if objective evidence indicates that they were. Finally, troops could have entered an area that had been sprayed only several hours or a day or two earlier, in which case they would not have realized that they were exposed.

A second approach to assessing herbicide exposure is to combine records of herbicide application missions with individual service records in order to determine if an individual was in a specific area at the same time that a herbicide application mission took place. This method also is not completely reliable. Service records identify only the military units to which individuals were posted and may not reflect such details as temporary assignments. Second, unit records are unlikely to identify the areas in which patrols and small units might have operated, and the individuals who participated in these actions. Finally, even the accuracy of data on herbicide spray missions may be questionable, since for example, aircraft often jettisoned the herbicide when they came under enemy fire.

The development of sensitive and specific methods for the analysis of TCDD and other dioxins in biological specimens such as blood and body fat, has provided the opportunity for a third approach to

assessing herbicide exposure in Vietnam, since many of the phenoxy herbicides used in Vietnam were contaminated with TCDD. While it might seem unlikely that there would be enough of this substance still remaining in the body to measure after so many years, in fact the body content only drops by half in about 6 to 10 years. As a result, individuals who were heavily exposed in Vietnam still might have elevated levels of this compound in their blood.

Over the past six years a number of studies have been conducted in which blood samples from Vietnam veterans, from workers who were exposed to dioxins in chemical manufacturing plants, from civilian populations exposed to dioxins as a result of accidental environmental pollution, and from members of the general population, have been analyzed to determine their TCDD content. These studies have shown that: a significant portion of the general population of industrialized countries has measurable concentrations of TCDD in their blood, without evidence of unusual exposure; a number of individuals who did experience relatively heavy exposures to phenoxy herbicides or dioxins and related compounds in the past currently have concentrations of TCDD in their blood that are clearly higher than those found in the general population; and, many individuals who were unquestionably exposed to these substances in the past have levels of TCDD in their blood that are no higher than those found in people with no known unusual exposure.

Because of these findings, measurements of the concentration of TCDD in the blood of Vietnam veterans cannot be used as the sole basis for estimating their exposure to herbicides. Elevated levels of TCDD in the blood do occur in Vietnam veterans who experienced exposure to phenoxy herbicides, but the vast majority have blood TCDD concentrations that are no different from those found in the general population, even in some cases where other evidence indicates that they indeed suffered such exposure. A good example of this is provided by the results of the analysis of blood samples taken from 888 Air Force veterans who participated in the herbicide application program (Operation Ranch Hand) in Vietnam. The concentrations of TCDD in the blood of these veterans were compared to those in blood samples from 856 Air Force veterans who did not participate in Operation Ranch Hand. While the average concentration of TCDD in the blood of Ranch Hand personnel was higher than in the blood of comparison subjects, even within this group which was responsible for spraying herbicide there was considerable variation. Officers, who on the whole did not actually handle the material, had average blood TCDD levels that were only slightly above those of personnel unassociated with the operation, as would be expected. The highest levels were found in the enlisted groundcrew, followed by enlisted flyers, but even among these two unquestionably exposed groups, there was a 25–fold variation between individual blood levels.

Studies of mortality and health status among Vietnam veterans have fairly consistently indicated that there are differences between these individuals and military veterans of the same era who did not serve in Vietnam, as well as between Vietnam veterans and the general population of the United States. In earlier surveys, Vietnam veterans believed that they had more health problems than do other veterans and the general population. There has been a marked decline in the expression of such feelings. Other objective findings have for the most part not indicated any major health problems associated with service in Vietnam, and exposure to phenoxy herbicides in particular, but some changes have been recorded. The general health study of U.S. Air Force personnel involved in the Ranch Hand operation, for example, has not shown major problems among this group which was clearly associated with herbicide exposure. It has revealed, however, a correlation between a higher percentage of body fat and elevated levels of TCDD in the blood, suggesting that the dioxin may be affecting fat metabolism. Another finding has been that higher blood



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TCDD levels are associated with changes in properties of components of the blood which suggest that some type of immune reaction is occurring.

While Vietnam veterans are not dying at a greater rate than other veterans or the population at large, they are still more likely to die from certain causes of death. These include a group of causes such as motor vehicle accidents and homicide that are lumped together as "external causes of death." Overall, however, Vietnam veterans in general do not appear to experience more diseases or to be more likely to die of any specific disease than other veterans or the U.S. population as a whole.

Most studies of cancer mortality among Vietnam veterans have shown them to be at little or no increased risk, but a few studies have reported increased risks for certain types of cancer in those who served in Vietnam. There is a problem with deriving clear–cut conclusions from such studies in which very few veterans actually contract these cancers, so that a 50% increase in incidence may in fact describe six individuals with the specific cancer in the veterans versus four among the controls, a difference which may not always be meaningful. For example, an epidemiologic study that was published by scientists at the Veterans Administration 1988 found significantly increased mortality from two types of cancer, non–Hodgkin's lymphomas and lung cancer, in U.S. Marine veterans of Vietnam but not in U.S. Army veterans. Subsequently, in the 1991 follow–up publication from the same source, it was the Army veterans who were shown to have an increased death rate from cancers of the lung and larynx, while the increases previously found among Marine veterans appeared to reflect the very low incidence of these cancers in the non–Vietnam veterans with whom they were compared. If they were compared with the general U.S. population there was no excess. Another study conducted on behalf of the U.S. Centers for Disease Control found that Vietnam veterans were at 50% greater risk of developing non–Hodgkin's lymphoma than were veterans who did not serve in Vietnam. However, this increased risk could not be tied to any of the factors such as military region, unit, or dates of service, which might indicate that they were exposed to Agent Orange. Risks for five other cancers covered in this study were not increased.

Similar conclusions were evident in the complete report on the 1987 follow–up of the Operation Ranch Hand personnel who worked with Agent Orange daily, compared with a control group of veterans. In this study of 995 Air Force veterans, few differences between these groups were seen in objective measures of health status. The only one of these that was of clinical importance was a significantly increased incidence of basal cell carcinoma (a type of cancer of the skin) among the Ranch Hand veterans, a difference which had also been noted in the two previous studies of their health status. This type of skin cancer is known to be related to exposure to the sun, but the excess of such cancers among the Ranch Hand group as a whole could not be accounted for by known differences in exposure to the sun, neither was it associated with their blood dioxin levels. With respect to other types of cancer, no differences could be determined between the Ranch Hand and comparison groups. However, blood TCDD levels were related to the incidence of benign, non–cancerous tumors 75% of which were lipomas.

These recently reported studies fit into the same patterns established in earlier ones, such as that undertaken on members of the U.S. Army Chemical Corps who had been involved in other missions involving herbicide application, such as clearing vegetation from military installations in Vietnam. This group of veterans also showed no overall trends in the relatively few cancers they developed.

**4. Cancer**

The question of a possible association between cancer and exposure to phenoxy herbicides and their dioxin contaminants, which has received no consistent answer from the studies with veterans, has met a



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similarly ambivalent response in the civilian area. There has been a large number of studies of workers who may have been exposed to these compounds during their manufacture or in the course of their application in agriculture, forestry, and highway and railroad maintenance. Over the past 10 years, more than 50 publications in the scientific literature have described over 30 epidemiologic investigations of all types, including proportionate mortality, historical cohort studies, and case control studies. These studies have been conducted in many countries in addition to the United States, and have in some cases been international in scope. They have shown no consistent evidence of an association between herbicide exposure and the risk of cancer, either in general, or of any specific type.

Attempts to explain the apparent inconsistencies among these studies have been hampered by the numerous differences between them in terms of how they were carried out, and by the existence of many potential interfering factors. As an example of the latter, in assessing possible associations between herbicide exposure and cancer in agricultural workers, it is notable that while farmers as a group are at lower risk of dying of cancer than the general population, they appear to be at a higher risk for cancers of the lymphatic system, particularly non–Hodgkin's lymphoma. While at first sight this might imply a relationship to herbicide exposure, several studies have not found any such association with the types or amounts of herbicide used by those farmers. Here we may be seeing the effects of the many other factors which may be unique to farmers, such as exposure to a wide range of other agricultural chemicals and plant and animal pathogens, or even as yet unsuspected features of diet and lifestyle in a rural environment.

Several studies were published during 1991 in which possible associations between cancer and occupational exposure to dioxin were examined. The most significant of these was conducted by the National Institute for Occupational Safety and Health (NIOSH), and has been in progress for a number of years as part of the NIOSH Dioxin Registry. This study, published in early 1991 presented the results of a cohort mortality study of 5,172 workers at 12 chemical plants in the United States, who were exposed to dioxins while employed in the manufacture of chlorinated phenols or phenoxy herbicides. The NIOSH investigators identified the cause of death in 1,037 of the 1,052 who had died, and found that death rates within this group were what might be expected for the general U.S. male population. When considering specific causes of death, they found fewer deaths from diseases of the digestive system (specifically cirrhosis of the liver) and significantly more deaths from accidental causes than would be expected. The number of cancer deaths in the cohort also was slightly but significantly above what would be expected. This excess cancer risk was greatest in those workers who had been exposed to dioxins for one year or more, and whose first exposure occurred at least 20 years previously. In this group the mortality ratio was 145 as percent of control. Overall excess mortality was not due to a marked increase in any particular form of cancer, a finding that is rather unusual for chemical carcinogens, which typically show some organ specificity. Instead, mortality rates for a number of cancers, such as soft tissue sarcomas and respiratory cancers, were slightly greater than expected, but only the rate for cancers of "other and unspecified" sites was significantly elevated. This category was simply an arbitrary grouping of a number of cancers that do not fit other categories, and which are individually rather rare. It is difficult to ascribe significance to changes in such a nebulous category. A limitation in the study design was that it did not take account of the effect of smoking habits or the presence of other chemicals in the workplace.

A multi–site study carried out under the aegis of the International Agency for Research on Cancer, involved 18,910 production workers and herbicide sprayers from ten countries. Through a combination of factory records, work histories, questionnaires, and recorded data from sprayings, it was found this large group showed a doubled risk of soft tissue sarcoma, relative to cause–specific national death rates. There



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were also small increases in testicular, thyroid and nasal cancers, but the numbers were too small to be meaningful. Unfortunately, this study presents a number of problems. First, the deaths from soft tissue sarcoma, four in all, took place exclusively for the time period 10 to 19 years after first exposure. In addition, two of these deaths occurred after less than one, and the other two after 10 to 19 years of exposure. This clustered pattern is what might be expected for random, non–significant variation in the distribution of a rare disease. Second, not only are national death rates based on less accurate reporting of causes of death than medical records, but their use in comparisons may be misleading, because they do not reflect specific risk factors which are associated with other chemicals and workplace conditions to which these workers are exposed. For these reasons, the conclusions of this study are not very convincing; a longer follow–up may strengthen the study, but will not eliminate the problem of the control comparison.

A study of mortality among workers at a herbicide plant in Germany where the products had been heavily contaminated with dioxin prior to 1954, showed increases in overall cancer mortality compared with both German national statistics and a comparison group of workers in the gas industry. Rates were highest for those with 20 or more years of employment, and women showed an increase in breast cancer. Two major problems with this study were the use of mortality data from national statistics and death certificates for the control groups, compared with more accurate medical records in the study group, and the 80% higher rate of smoking among the herbicide workers than the general population. Both factors could severely affect the findings.

In a region of northern Italy in which heavy spraying with phenoxy herbicides had occurred over several decades, there was a higher incidence of lymphomas of all types. This increased incidence also was related to higher measured soil levels of these herbicides in the areas where the subjects lived. Unfortunately, no attempt was made to look at the occupations of the study subjects or their length of residence in the particular area. Men did show a higher incidence than women, however, suggesting that occupation might be a factor. Also in Italy, further follow–up of those involved in the industrial accident at Seveso in 1976, which released large amounts of dioxin, showed that even among individuals who were most heavily exposed on the basis of their blood TCDD values and areas of residence, there were no statistically significant increments in cancer incidence.

The inconclusive nature of the studies attempting to associate exposure to dioxins with cancer in humans stands in stark contrast to the results of studies in experimental animals, where TCDD has been found to be a carcinogen in many strains and species. No additional animal studies of the production of cancers by conventional long–term administration over the course of eighteen months to two years were published in 1991. There was however, an important reevaluation of 1978 work on the production of liver cancer in rodents, based on the fact that since that time the criteria used by pathologists to define what is or is not liver cancer have changed. The 1978 data are very important because they serve currently as the basis on which such agencies as the Food and Drug Administration and the Environmental Protection Agency calculate the hazard that dioxin presents to human health. Using the new criteria, it was found that the risk to humans may be between ten and one hundred times less than had been calculated earlier. This does not mean that it is no longer considered to be a carcinogen, however. Another advance seen in 1991 papers, has been the use of tests that are based on biological indicators of precancerous changes that occur before a tumor appears, and which can evaluate carcinogenic potency more rapidly, and with the use of fewer animals, than conventional methods.





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**5. Genetic effects**

Extensive testing of TCDD and related compounds over the last 10–20 years in various strains of bacteria, in animal and human cells in culture, and in whole experimental animals, has produced no convincing evidence that these compounds cause genetic mutations. Despite some conflicting findings, the smaller amount of information available suggests that the same is true of phenoxy herbicides. On the other hand, some studies in experimental animals have suggested that TCDD can cause damage, other than mutations, in chromosomes. There is no reliable evidence of genetic damage or changes in chromosomes from studies of humans exposed to phenoxy herbicides or dioxins.

No studies implicating either phenoxy herbicides or dioxins in producing genetic damage in humans were published in 1991. Two studies of TCDD, one in the bacterial Ames' test, and the other in an animal cell culture, confirmed that TCDD is inactive in producing mutations at the highest concentrations at which it would dissolve. Another study with animal cells found that the phenoxy herbicide 2,4–D did cause mutations at high concentrations.

**6. Reproductive effects**

The cumulative body of research undertaken to date provides a few definitive answers to the question of whether exposure to phenoxy herbicides or dioxin causes adverse reproductive effects. It is fairly certain that delayed development of young children can occur when women are exposed to TCDD and related compounds before or during pregnancy. An example of this is a study published in 1991 of 128 children born in Taiwan to women who had been exposed to high levels of various polychlorinated compounds contaminating the cooking oil which they had been using. Developmental delays, and speech problems were much more frequent in these children than in a comparison group, and persisted over a prolonged period. There was, however, no evidence of the frank physical abnormalities that have been well documented in experimental animals exposed to these compounds.

Further instances of such physical findings appeared in 1991 reports describing the production of cleft palates and a kidney abnormality called hydronephrosis in the offspring of mice exposed to TCDD and similar substances having bromine substituted for chlorine. Even when normal newborn mice were exposed to TCDD through their mothers' milk, abnormal kidney development occurred. Interference with development also was demonstrated when embryonic tissue from the palate region was exposed to TCDD in vitro. An interesting result here was that tissue from humans or from rats was 200 times less sensitive than that from mice, which might provide an explanation of why the physical abnormalities, which are so prevalent in mice, have not been clearly demonstrated to occur in humans. It is true that a number of studies have been described in the Review over the past few years in which the authors concluded that there is a correlation between a large number of adverse reproductive consequences, including spontaneous abortions and birth defects, and exposure of civilian Vietnamese women to herbicides during the war in that country. All such studies have suffered from deficiencies that included lack of an appropriate historical basis or control groups with which to compare the incidence rates, and the absence of unequivocal evidence of exposure to Agent Orange.

Two recent studies have reported damage to the testicles, one in phenoxy herbicide sprayers using 2,4–D, and the other in rats exposed to TCDD. The damage led to diminution in sperm count and increases



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in abnormal or inactive sperm. However, another study undertaken in male rats exposed to TCDD disclosed no significant effects of this testicular damage upon the number or health of the offspring. The authors concluded that the data did not demonstrate any "biologically significant paternally–mediated developmental toxicity." Previous volumes of this Review found no evidence of an association between spontaneous abortions and a history of military service in Vietnam by the father, beyond a slightly, but not statistically significant, increased risk of congenital anomalies in one study of children fathered by such men. The ongoing Ranch Hand study has given no evidence of such adverse effects.

**7. Effects on the immune system**

The available evidence indicates that the phenoxy herbicides do not affect the immune system. Dioxins, however, are another matter. They have clearly been shown to alter the immune system in experimental animals, but studies of humans exposed to these substances have not disclosed significant effects. In humans, the Air Force Health Study, for example, did find changes in blood proteins suggesting that some mild chronic inflammation was at work, but white blood cells, the core of the immune system, were unaffected. Some abnormal reactions to skin tests did not appear to be related to concentrations of TCDD in the blood. Another study with patients suffering from AIDS indicated that those who had the highest amounts of TCDD in their blood also experienced many more other types of infection, termed opportunistic infections, than did patients with lower levels. This suggests that dioxin was making their immune system even worse, but the fact that these patients had an immune defect from the underlying AIDS to begin with, makes interpretation of the results difficult. Another recent study on white cells taken from either humans or monkeys showed that TCDD changed the proportions of various subset types of these cells, but despite this, monkeys given TCDD showed no signs that their immune system was defective.

An effect of TCDD, related to the immune system, which has been known for a long time, is that it causes the thymus gland to shrink and cease functioning. Papers published in 1991 indicate that this effect is not due to an action of dioxin on the active immune cells that make up much of the weight of the gland, but rather to damage to the supporting structure. Once the latter was repaired, fresh cells returned from the bone marrow and the thymus recovered.

**8. Other effects**

While it is clear that the potential human health effects of most concern are cancer, adverse reproductive effects, and alterations in the immune system, there have been some recent publications dealing with other potential adverse effects both in humans and in animals. Chief among these have been reports of effects on the nervous system. Ranch Hand personnel showed evidence of some changes in their coordination and gait that could be correlated with levels of TCDD measured in their blood. Similarly, among the children of the Taiwanese women, discussed above, who had consumed contaminated cooking oil, there was evidence of a lag in the development of their coordination skills.

In animals, the most conspicuous result of a single large dose of TCDD is that they stop eating, and in susceptible strains, waste away till they die. A 1991 study suggests that this refusal to eat results from a disturbance in the balance of substances in the brain which control the sensations of hunger and satiety.

Dogs are rather sensitive to phenoxy herbicides, and a study appearing in 1991 reported on the changes in brain waves and muscle strength of dogs exposed to 2,4–D.

Another area of toxicity restricted to humans is the skin disorder known as chloracne. This is very characteristic to exposure to dioxin, and a follow–up of those exposed to TCDD in the accident that occurred at Seveso in Italy, showed that development of chloracne was tied closely to high blood levels of TCDD. Among other toxic symptoms of dioxin exposure that were reported during 1991, were effects on the liver, manifested as alterations in fat metabolism, and some interference in blood coagulation.

**9. Dioxins in human tissues**

A topic of continued active research interest is the relationship between concentrations of TCDD in blood, body fat, or breast milk, and past exposure to dioxins or phenoxy herbicide preparations that contained dioxins. This activity has been made possible by the development of sensitive methods for analysis of TCDD that can detect levels of this and related substances in the parts per trillion range. Elevated levels of TCDD in blood or fat tissue samples from Air Force veterans who participated in Operations Ranch Hand in Vietnam, workers exposed to dioxins in 12 different chemical manufacturing plants in the United States, and workers who were exposed to dioxins as byproducts of a manufacturing process in a German chemical company more than twenty years after exposure. In one case published in 1991, TCDD and a related compound were measured in the blood of a chemist who had made these substances 34 years previously! This technology has also shown that dioxin can cross the placenta and enter a growing fetus, or pass in the breast milk from mother to child.

Despite this sensitivity, some caution is needed in relying on these measurements as indicators of past exposure to dioxins and related compounds. There must clearly be a great deal of variation among individuals as to how much dioxin they absorb and how quickly they eliminate it from their bodies. While the finding of high average concentrations of TCDD in the blood may serve to identify groups of people who experienced unusually heavy exposure in the past, levels no higher than those in the general population do not necessarily indicate that those individuals did not undergo at least moderate exposure.

**10. Basic research on the mechanism of dioxin toxicity**

As has been true for a number of years, a large proportion of the scientific literature published during 1991 has described basic research on TCDD and closely related compounds. Most of these studies are of little direct relevance to potential human health effects. They have, however, served to outline in greater detail the means by which these substances produce their toxic effects, and in this way have laid the ground work for a better understanding of the true extent of the hazard they present for human health.

Studies published in 1991 confirmed that most of the effects of dioxin arise from its interaction with a particular component (known as the Ah receptor) in the cell, which helps to transport it to the cell nucleus and attach it to special sites on the cell's DNA. It can then turn on various processes within the cell that lead to the adverse changes. A few effects of dioxin, especially those related to the immune effect, may not use this particular receptor, but it is not yet clear how this happens.

Another area of basic research that received considerable attention during 1991 as in the past few years, was the antiestrogenic and antiandrogenic activity, that is, the effects on female and male hormone action, of TCDD in a number of experimental models. The antiestrogenic action seems to depend on direct effects on tissues of the breast and uterus, whereas androgens are antagonized indirectly through effects on hormones from the pituitary gland in the brain.

Basic research has also implicated some involvement of dioxin in the action of Vitamin A, but there is no clear picture as yet of how this antagonism occurs. It may be because the Ah receptor to which dioxin attaches is related in structure to the receptor for the vitamin. Doubtless many other basic research findings will be made over the next few years which will finally elucidate the different mechanisms by which this "environmental hormone", as dioxin has been termed, exerts all its varied actions.

**11. Summary and conclusions**

Clearly, the most important research results relevant to the potential human health effects of phenoxy herbicides and dioxins to become available during 1991 have confirmed and extended those reported in 1990, in which there was a small but significant increase in the risk of cancer among men who were occupationally exposed to relatively large amounts of dioxins more than 20 years ago. These data were to some extent tied to blood dioxin levels, and could be said to reflect the likelihood that dioxins promote cancer, rather than initiate it.

In contrast to studies of dioxin–exposed workers, those carried out among Vietnam veterans, were either negative or equivocal. These studies found no increased risk of cancer except for sun–related skin cancers among Air Force personnel who participated in Operation Ranch Hand, and these could not be associated with dioxin levels. Benign tumors did show an increased incidence.

Human studies which were published during 1991 provided no convincing evidence for the existence of an association between exposure of males to phenoxy herbicides or dioxins and adverse reproductive outcomes. Exposure of females to related chlorinated furans and PCBs, however, did lead to slowed development of their children. In mice, frank malformations such as cleft palate were produced by TCDD and many related compounds, but studies with human tissue suggested that humans are less sensitive to this action.

It is clear that many questions remain regarding the potential human health effect of phenoxy herbicides and their dioxin impurities. This is especially true of the immune system and hormone regulation. In addition, further basic studies are needed, not merely for the theoretical satisfaction of elucidating the detailed mechanism of action, but more importantly, to help define the relative sensitivity of human tissues, and thus resolve the ongoing debate on how harmful dioxin is to human health.

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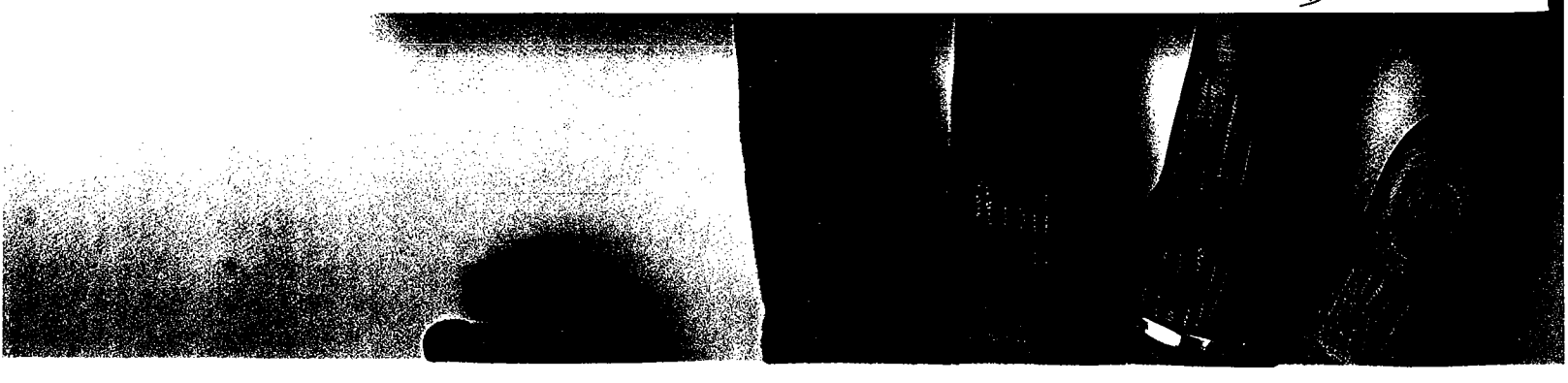
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Department of Veterans Affairs

# Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins No. 7 – (Volumes XV and XVI)

Veterans Health Services
and Research Administration

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# SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS NO. 7 – (Volumes XV and XVI)

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## PREFACE

This synopsis is the seventh in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. Synopsis No. 1 of Volumes I and IV was published in July 1985, Synopsis No. 2 of Volumes V and VI was published in October 1985, Synopsis No. 3 of Volumes VII and VIII was published in October 1986, Synopsis No. 4 of Volumes IX and X was published in July 1987, Synopsis No. 5 of Volumes XI and XII was published in September 1988, and Synopsis No. 6 of Volumes XIII and XIV was published in October 1989.

This current synopsis, a review of Volumes XV and XVI, continues the effort of the Department of Veterans Affairs to provide for the general public a summary in laymen's terms, of the scientific literature published during 1989 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

Environmental Medicine Office

Department of Veterans Affairs

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## 1. Introduction

In May 1990, Clement Associates, Inc. a research firm in Fairfax, Virginia, completed a review of the literature published during 1989 on the health effects of Agent Orange and related compounds. A critical review and an annotated bibliography of this literature have been published as Volumes XV and XVI of the ongoing Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins. This synopsis summarizes the key new information that became available during 1989.

Phenoxy herbicides are a group of structurally related chemicals that have been used in agriculture and forestry to kill weeds in cultivated crops, to kill unwanted tree species in coniferous forests, and to clear vegetation from road beds and fence lines. Historically, the phenoxy herbicides that have been most frequently used in the United States are 2,4–D and 2,4,5–T. The latter has not been used in the United States for a number of years, and its use has been banned in most countries around the world. Another phenoxy herbicide, MCPA, has had extensive use in Scandinavian countries. Several herbicidal preparations were used by the U.S. Air Force in Vietnam from 1963 to 1971. A major purpose of this operation (known as Operation Ranch Hand) was to remove leaves from trees in heavily forested areas of Vietnam in order to be able to see enemy troop movements and supply operations. While several herbicidal preparations were used in this operation , Agent Orange, a mixture of equal parts of 2,4–D and 2,4,5–T was, by far, the one use most frequently.

Commercial phenoxy herbicide preparations manufactured from the 1940s until the early 1970s contained small quantities of contaminating impurities known as chlorinated dibenzo–p–dioxins. The terms "dioxins" or "dioxin" have frequently been used as shorthand for this family of chemical compounds. The exact dioxin compounds and the amounts of them that were present in phenoxy herbicide preparations varied from preparation to preparation and perhaps even from batch to batch. Commercial preparations of 2,4,5–T contained small amounts of one of these dioxins, 2,3,7,8–tetrachlorodibenzo–p–dioxin (TCDD); this contaminant was present in Agent Orange in Vietnam. The effects of TCDD have been extensively studied in experimental animals, and it is believed to be the most toxic member of the dioxin family of compounds. While 2,4–D contained small quantities of dioxins, TCDD was not one of them. When it was recognized that phenoxy herbicides were contaminated with dioxins, manufacturing processes were changed to reduce or eliminate dioxin contamination. Some other herbicidal preparations that were used in Vietnam contained cacodylic acid and/or picloram. These preparations were used in much small quantities, however, and they were not contaminated with dioxins.

## 2. Description of the literature published in 1989

Just under 400 scientific papers about the health effects of phenoxy herbicides, dioxins, and other herbicides used in Vietnam were published during 1989. This is an increase over the



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number of papers published in each of the three preceding years. While some of this increase can be attributed to more research activity, most of it can be attributed to the fact that the proceedings of two International Symposia on Chlorinated Dioxins and Related Compounds that were held in 1987 and 1988 were published in 1989. Much of the information contained in the symposia presentations was contained in articles published in other journals. Thus, the increased number of citations in the bibliography is not indicative of a proportionate increase in unique scientific information.

As judged by the number of publications addressing these issues, several topics are attracting undiminished and even increased scientific attention. These include epidemiologic studies of long–term health effects (especially cancer) from exposure to phenoxy herbicides and/or dioxins in various groups of people including Vietnam veterans, agricultural and forestry workers, and chemical manufacturing workers. Other areas of interest are the mechanism by which TCDD and related dioxins cause adverse effects such as cancer and birth defects in animals and the interrelationships between concentrations of dioxins in blood and fat, exposure to phenoxy herbicides and/or dioxins, and resulting health effects.

### 3. Studies of the general health of Vietnam veterans

Two studies that examined a number of possible adverse health effects among Vietnam veterans were published in 1989. One of these was an update of an ongoing study of causes of death among men who were involved in Operation Ranch Hand (the herbicide application program) in Vietnam. The Air Force has identified a group of 1,247 men who were assigned to some aspect of this operation. By the end of 1987, 74 of these men had died. The relative frequency of death by specific cause within this group was compared to the relative frequencies of causes of deaths for 1,039 men who had died in a comparison group of 19,101 men who had similar assignments in the Air Force in Vietnam but were not involved in the application of herbicides. At that time the death rate in the Ranch Hand group was not different from that in the comparison group, but there has been a trend toward a higher death rate in this group in recent years. Closer examination indicates that this trend is seen mostly among flying officers and may reflect an unusually low death rate for this subgroup prior to 1986. The only specific cause of death that was more frequent in Ranch Hand personnel than in the comparison group was digestive disease. Of the six deaths attributed to digestive diseases among Ranch Hand personnel, five were diagnosed as alcoholic liver disease. Therefore, it is unlikely that the increased number of deaths from digestive diseases seen in the Ranch Hand group was caused by exposure to herbicides.

In a study conducted by the Armed Forces Institute of Pathology (AFIP), pathology specimens taken from Vietnam veterans at Veterans Administration hospitals throughout the United States were collected and examined by pathologists who were unaware of either the original diagnosis or the military service history of the persons from whom the specimens were taken. A total of



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1,828 cases were diagnosed in this study. Of these, 1,053 were veterans who had served in Vietnam, and the remainder were veterans of the same era who had not served in Vietnam. The frequencies of diagnoses were compared between these two groups. Two skin conditions, epidermal inclusion cysts and dermatitides, were diagnosed more frequently in Vietnam veterans than in non–Vietnam veterans. Both of these conditions are relatively common, are not life–threatening, and cannot be considered to be serious health problems. Two benign tumors, dermatofibroma and seborrheic kertosis, were more common in Vietnam veterans, but these also are fairly common and not serious. There was no excess of cancer among Vietnam veterans, although there were slightly more basal cell carcinomas and lymphomas in this group. These increases were not statistically significant. There were no other differences between Vietnam veterans and non–Vietnam veterans in the frequencies of specific diagnoses.

Together, these studies did not indicate any important differences in the long–term health status of Vietnam veterans. The Ranch Hand study is designed to identify long–term effects attributable to herbicide exposure, but because of the small number of deaths in the study group through 1987, only dramatic differences between Ranch Hand personnel and the comparison group in terms of causes of death would be evident. The AFIP study was designed to relate diagnoses to military service in Vietnam; no attempt was made to investigate possible connections to herbicide exposure. Whether or not the minor differences between Vietnam and non–Vietnam veterans seen in this study are attributable to herbicide exposure is a matter for speculation.

## 4. Cancer

Two studies of cancer among individuals who served in Vietnam were published during 1989. One of these, the Ranch Hand study, was described in Section 3 above. Twelve men in the Ranch Hand cohort had died of cancer as of the end of 1987. This is slightly fewer than expected based on the incidence of cancer deaths in the comparison group. None of the twelve cancers was a lymphoma or a soft tissue sarcoma. While this study suggests that there is no connection between Agent Orange exposure and death from cancer, small differences in cancer mortality in the two groups may become apparent as more deaths occur in both groups.

Another study of cancer in Vietnam veterans was published in early 1990; because of its importance, it was included in this volume of the review. This study, known as the Selected Cancers Study, was conducted as part of the Vietnam Veterans Health Studies by the U.S. Centers for Disease Control (USCDC). It was designed to see if there was any connection between military service in Vietnam and the later diagnosis of any of six forms of cancer that other studies had suggested might be associated with exposure to phenoxy herbicides and/or dioxins. The six forms of cancer were non–Hodgkin's lymphoma (a cancer of the lymphatic system), Hodgkin's disease (another type of cancer of the lymphatic system), sarcomas (including soft tissue sarcomas), nasal cancer (cancer of the nose), nasopharyngeal cancer



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(cancer in the nose and throat), and liver cancer. This study was not designed to see if there was a connection between these forms of cancer and exposure to Agent Orange. The USCDC had concluded two years earlier that there was no reliable way to determine Agent Orange exposure among Vietnam veterans.

This study was a case–control study, meaning that men who were between the ages of 15 and 39 in 1968 and were diagnosed between 1985 and 1989 as having these types of cancer were compared to men of the same age who did not have any of these types of cancer but were as similar as possible in other respects. If the men with the cancer were more likely to have served in Vietnam than the men without cancer, there is an apparent association between that form of cancer and military service in Vietnam. As case–control studies go, this study was quite large. There were 1,157 cases of non–Hodgkin's lymphoma, 310 cases of Hodgkin's disease, 342 cases of sarcoma, 62 cases of nasal cancer, 89 cases of nasopharyngeal cancer, and 130 cases of liver cancer. These were compared to 1,776 controls.

For five of the cancers studied, men with the cancers were no more likely to have served in Vietnam than men without. However, men with non–Hodgkin's lymphoma were more likely to have served in Vietnam than the controls. USCDC found no evidence, however, that the increased risk of non–Hodgkin's lymphoma was related to exposure to Agent Orange. The risk of non–Hodgkin's lymphomas was highest among Navy veterans who served on ships off the coast of Vietnam and slightly lower in troops who were stationed in the III Corps region where Agent Orange was most heavily used than in troops stationed in other areas of Vietnam. Only one of the 99 Vietnam veterans who had non–Hodgkin's lymphoma reported that he had handled herbicides in Vietnam, and none of the 99 was involved in the application of herbicides. In fact, USCDC was unable to identify any specific aspect of the Vietnam experience that might explain the increased risk of non–Hodgkin's lymphoma that was seen in this study. It is interesting to note that a study of cancer mortality among Vietnam veterans that was published by the Veterans Administration in 1987 found an increased mortality due to non–Hodgkin's lymphoma among Vietnam Marine veterans compared to Marine veterans who did not serve in Vietnam. This difference was not seen in Army veterans. Thus, two independent studies suggest that there is a small but significant relationship between some aspect of military service in or near Vietnam and non–Hodgkin's lymphoma. It is highly unlikely that the aspect of the Vietnam experience is exposure to herbicides (Agent Orange). It is also possible that the difference in cancer risk is attributable to some undiscovered difference, not related to military service, between men who served in Vietnam and those who did not.

There have been a number of studies over the past ten years looking at possible associations between cancer and exposure to phenoxy herbicides during there use in agriculture and forestry. Some studies conducted in Scandinavia and the midwestern United States have suggested that there is an association between exposure to phenoxy herbicides and non–Hodgkin's lymphoma. The midwestern studies, one of which was published in 1989, suggest that the association is with 2,4–D, a phenoxy herbicide that is not contaminated with TCDD. The Scandinavian studies



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have also shown an association between phenoxy herbicide exposure and soft tissue sarcoma. No other studies including those in the midwestern United States have replicated the soft tissue sarcoma findings of the Scandinavian studies. Moreover, studies of the relationship between non–Hodgkin's lymphoma and herbicide exposure in New Zealand and western Washington State have failed to find an association. The authors of these latter two studies both published articles during 1989 in which they reported the results of reanalysis of their data and still found no evidence of an association.

Three new studies of cancer in relation for occupations in which there is potential exposure to phenoxy herbicides were published in 1989. In a study of licensed and pesticide applicators in three agricultural provinces of northern Italy,the authors found excess risks of lymphatic cancers and of cancers of the skin. A case–control study of non–Hodgkin's lymphoma among white males in Hancock County, Ohio, showed an increased risk of this form of cancer associated with the occupation of farming, but because of the small number of cases in this study the finding was not statistically significant. Finally a study of highway maintenance workers in Minnesota found a trend toward an increased risk of cancers of the lymphatic system with duration of employment; this increased risk was statistically significant among men with 30–39 years of employment. There was no analysis of non–Hodgkin's lymphoma separate from other lymphatic cancers in this study. In only one of these three studies, the one in northern Italy, was there an attempt to ascertain herbicide exposure. The criterion for exposure in that study was the possession of a license to apply pesticides. Individuals with a pesticide applicator's license certainly differed from those without a license in more ways than exposure to herbicides. In the Ohio and Minnesota studies, there were no direct or indirect measures of herbicide exposure. These studies are of interest in that they continue to add to a large and growing body of evidence that there is an association between some aspect of agriculture and lymphatic cancers, and specifically non–Hodgkin's lymphoma. At the present time, attempts to identify the reason for this association have not been successful.

Previously published reports describing studies of causes of death among workers who were exposed to dioxins during the manufacture of phenoxy herbicides and related compounds at the Dow Chemical Company plant in Midland, Michigan have indicated no association between exposure to dioxin and cancer. The results of an additional two years of follow–up of this group of workers were published during 1989. The total cohort of dioxin–exposed workers comprises 2,192 people. As of the end of 1984, there were 406 deaths in this group compared to 445 expected on the basis of mortality statistics for the U.S. population as a whole. There were 95 cancer deaths compared to 92 expected. The authors concluded that there was no clear evidence of a causal association between any cause of mortality and potential occupational exposure to dioxins. However, there were 8 deaths caused by stomach cancer in this cohort compared to 4.2 expected. Furthermore, there was a statistically significant trend toward an increased risk of stomach cancer with increased intensity and duration of exposure to dioxins. Taken by itself, this finding may not be noteworthy. However, two other studies have shown an increased risk of stomach cancer in workers who were exposed to dioxins and/or phenoxy herbicides, two studies (one of which was conducted in this same Dow cohort), have shown an increased risk of non–cancer stomach disease in workers exposed to dioxins, and animal studies have indicated

that ingestion of dioxins causes significant effects in the stomach. Taken together these results suggest that cancer and other diseases of the stomach should be studied in populations that have been exposed to dioxins. The results of a large mortality study among all workers in the United States who have been exposed to dioxins has not yet been published.

Scientists in Italy published the results of a study of causes of death among nearly 200,000 residents of 11 villages in the vicinity of a chemical plant, where a reactor accident in 1976 resulted in the release of a cloud that contained high concentrations of dioxins, among other chemicals. Causes of death were analyzed in relation to place of residence at the time of the accident, with the entire study area being divided into four zones based on levels of dioxin contamination measured one month after the accident. While some increased risk of death from cardiovascular disease, cancers of the lymphatic system, and cancers of the gallbladder and bile ducts appeared to be associated with residence in the more contaminated areas of these towns, it is unlikely that these findings were indicative of a cause–and–effect relationship because of the short time (10 years) that has elapsed since the accident, inconsistencies in the timing of excess deaths by cause, and uncertainties regarding the reliability of exposure estimates based solely on place of residence. This study serves mainly to provide justification for further study of residents of this area.

5. Genetic effects

The weight of the scientific evidence gathered over a period of years from experiments in animals and in cultured cells indicates that neither the phenoxy herbicides nor their dioxin impurities cause gene mutations. There is no evidence that these compounds cause gene alterations that can be inherited by subsequent generations and become manifest as an abnormality or disease in the offspring. No articles were published during 1989 that would change this point of view. On the other hand, there is some evidence from experiments with animals that TCDD and perhaps some related dioxins may cause damage other than mutations to chromosomes or the DNA in them. No studies of the effects of dioxins on human chromosomes or DNA were published in 1989. Several studies indicating the TCDD may increase a form of chromosomal damage known as sister chromatid exchanges in experimental animals were published. At the present time, the significance of these findings for human health is not clear.

6. Reproductive effects

Over the years there have been isolated reports that exposure to phenoxy herbicides and/or their dioxin contaminants may interfere with reproduction or lead to birth defects. However, the overwhelming majority of studies designed to detect such effects have shown no association between phenoxy herbicide or dioxin exposure and adverse reproductive effects. Studies in

experimental animals, on the other hand, indicate that TCDD and some closely related compounds have the potential to interfere with reproduction at relatively high exposures, and at lower doses, cause birth defects in the offspring of exposed females. There is no evidence that exposure of male animals to dioxins causes defects in the offspring of unexposed females to which they are mated.

One group of studies that have suggested adverse reproductive effects in humans who may have been exposed to phenoxy herbicides are those conducted by scientists in Vietnam among civilian and military personnel who may have been exposed to Agent Orange during the U.S. military action in that country. Several of these studies were published in 1989. The authors reported a number of adverse reproductive effects including spontaneous abortions, stillbirths, and major birth defects in groups of people who were exposed to Agent Orange. It is difficult, if not impossible, to assess the validity of these studies. Because of the long–term political and military upheaval in that country, the keeping of health statistics and medical records has been haphazard. The type of baseline information on reproductive outcomes that is so important for conducting meaningful epidemiologic studies is not available. Data on the background incidence of adverse reproductive outcomes in the Vietnamese population in general are inconsistent. Furthermore, all of the published reports lack information on the specific methods used to select the study population and ascertain exposure and reproductive outcomes. The potential for bias and uncontrolled factors to influence the results of these studies is quite high.

The results of a case–control study of spontaneous abortions in relation to military service by the father in Vietnam were published in 1989. Spontaneous abortions in the first 27 weeks of gestation may reflect mutations that are induced in the germ cells of the male parent prior to conception. In this study, the military service history of the husbands of 201 women in the Boston area who had spontaneous abortions was compared to that of the husbands of 1,119 women who had normal pregnancies and deliveries during the same time period. Husbands of the women who had spontaneous abortions were slightly less likely to have served in Vietnam than men who fathered normal pregnancies, suggesting that there was no association between military service of the father in Vietnam and spontaneous abortion. No attempt was made in this study to ascertain herbicide exposure of the fathers.

A study of reproductive outcomes among people who may have been exposed to dioxins and related compounds as a result of an electrical transformer fire in Binghamton, New York, found no increased risk for spontaneous abortion, stillbirth, or birth defects. The number of people included in this study was small, and for many of them there was little evidence that they were actually exposed.

The experimental animal studies that were published during 1989 were primarily studies of the mechanism(s) by which dioxins cause birth defects in mice. Some of these studies indicated that TCDD alters the estrogen receptor in several tissues and that it may interfere with reproduction as a indirect result of interfering with the normal mechanisms by which sex

hormones regulate the function of the reproductive organs. A series of studies suggested that a commercial mixture of the herbicides 2,4–D and picloram caused birth defects in mice either when the fathers were treated prior to mating or when the mothers were treated during pregnancy. The doses of herbicide used in this experiment were high and caused toxic effects in the parents. It is possible that the defects were an indirect result of the toxic effects on the parents. Overall the new information on reproductive effects of phenoxy herbicides and/or dioxins did not significantly change the conclusions based on the overall body of evidence prior to 1989.

7. **Other effects**

Studies in experimental animals have indicated that TCDD and closely related compounds change the way that the immune system responds to foreign materials in the body. In mice, very low doses of TCDD suppress the defense mechanism against a variety of foreign materials including allergens, disease–causing organisms, and cancer cells. There is no evidence that phenoxy herbicides affect the immune system. Very few epidemiologic studies of humans who were potentially exposed to phenoxy herbicides and/or dioxins have included a careful evaluation of the status or function of the immune mechanism. Over the past several years, however, evaluation of immune status has been included in several such studies. Studies of Ranch Hand personnel have failed to indicate any differences in immune status between Ranch Hand personnel and the comparison group.

In 1986 a series of publications described studies of a group of people who resided in areas of Missouri that were contaminated with relatively high levels of dioxins when chemical wastes from a phenoxy herbicide manufacturing plant were mixed with oil and used to control dust on unpaved roads. The initial studies of this group of people found that they were less likely to exhibit an allergic response when exposed to a group of materials that often provoke such a response. These people also had subtle differences in the relative numbers of specific types of white blood cells that are thought to be indicators of immune status. Subsequent studies have indicated that the methods used to evaluate the response to allergens in the first study were flawed, and a repeat of the study failed to show a difference between exposed and unexposed people. Since that time, blood samples collected from most of the people in the original study group were analyzed for their dioxin content. A new health study was conducted in which health status was evaluated in terms of dioxin concentration in the blood. The results of this study were published in 1989. This study did not show any indication of an impaired allergic response to the test substances. It did, however, continue to show the subtle differences in white cell types seen in the earlier study. These differences were correlated with dioxin concentration in the blood. These subtle differences were not accompanied by any signs or symptoms of altered immune function. Unfortunately, immunologists do not yet know whether these subtle differences reflect any actual differences in the function of the immune system.

In another study among dioxin–exposed residents of a mobile home park in Missouri, scientists found that concentrations of a hormone associated with the thymus were different in



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the blood of residents than in the blood of an unexposed control group. The thymus is the organ where the specialized white blood cells that play a role in many immune functions are formed. The scientists found no evidence of altered immune function in this study. Together these studies and the animal studies that were reported during 1989 did little to resolve the question of whether dioxins have the potential to alter immune function in humans. The ways in which the human immune system functions are extremely complex and poorly understood at the present time. It may be some time in the future before the human health significance of subtle alterations in cell populations and altered immune function in experimental animals is demonstrated.

A study designed to assess the relative psychological status of Vietnam veterans who reported that they were exposed to herbicides in Vietnam found significant differences in several measures of psychological well–being when compared to Vietnam veterans who reported that they were not exposed. The poorer psychological status of veterans who reported being exposed could not be accounted for by differences in upbringing, educational level, or demographics. The authors of this study made no attempt to determine actual herbicide exposure in Vietnam by objective methods.

Studies were published during 1989 that indicated that when female monkeys were fed diets containing quite low concentrations of TCDD, their offspring exhibited subtle differences in the ability to learn. These learning differences correlated more closely with the amount of TCDD in body tissues than with the amount of TCDD in the mother's diet. The significance of these studies is that very small amounts of dioxins can produce subtle effects on learning behavior that would be difficult to detect and that some, if not all, of the health effects of dioxins may be determined by the amount of dioxin in the body rather than the daily intake. While these two indicators of exposure are related, they may differ from individual to individual based on how the body absorbs and eliminates the dioxins to which it is exposed.

### 8. Dioxins in human tissues

One area of scientific inquiry that accounted for some of the increase in literature that was published in 1989 was the measurement of TCDD and related dioxins in human tissues. This area of investigation has become increasingly active since the methodology to measure very small concentrations of dioxins in human blood and fat was developed four or five years ago. If levels of dioxins in human tissues can be correlated with past exposure to dioxins or dioxin–containing chemicals, on the one hand, and with adverse health effects, on the other, the measurement of these levels becomes an extremely important tool for the conduct of epidemiologic studies were published during 1989. Dioxins were determined in blood and fat samples of Vietnam veterans, individuals who were exposed to dioxins during the manufacture of chemicals containing dioxins, civilian populations exposed to dioxins as a result of environmental contamination, and the general population.

Taken together, the results of these studies indicate that, in general, humans have detectable concentrations of dioxins in their blood and fat. The source of these compounds is not entirely clear, but dioxins in the diet, especially in animal fat, may represent the major source. Studies of people with abnormally high dioxin exposures in the past indicate that elevated concentrations of dioxin in either the blood or the fat is a reliable indicator of past exposure. Once in the body, dioxin is eliminated very slowly. In the absence of additional exposure it is estimated that it takes approximately seven years for the body to eliminate half of the dioxin that it has stored. Thus, among people who were relatively heavily exposed, it is possible to detect elevated dioxin levels in blood or fat 15–30 years after the exposure. Studies published within the last year or two have identified several groups of people with significantly elevated concentrations of dioxin in their tissues. These include workers who were exposed to dioxins during the manufacture of phenoxy herbicides and related compounds, people who were exposed to dioxins as a result of the accident in Seveso, Italy, in 1976, some of the people who live in a dioxin–contaminated area of Missouri, people who consumed cooking oil that was contaminated with dioxins and related compounds in two separate incidents in Japan and Taiwan, and a few Vietnam veterans who were relatively heavily exposed to herbicides in Vietnam. Studies of dioxin levels of Vietnamese who may have been exposed to Agent Orange during the war give inconsistent results but are generally supportive of elevated tissue levels among people who may have been heavily exposed. In general, Vietnam veterans do not have higher concentrations of dioxins in their tissues than non–Vietnam veterans. This suggests that exposures of most U.S. military personnel in Vietnam were not great and that adequate time has passed for elevated body burdens to decrease to background levels.

Several health effect studies published in the last year attempted to correlate observed effects with tissue body burdens of dioxins. Among these were a study of health effects among people in Missouri and a study of the health effects in monkeys born to mothers who had been treated with dioxins. It is anticipated that more studies will be designed to relate health status to dioxin body burden in the future. Also, measurements of dioxins in tissue may be used to identify populations for epidemiologic study. This should help to overcome the problems with many epidemiologic studies in the past where people with little or no exposure were included in the "exposed" group.

## 9. Summary and conclusions

The number of articles about potential health effects of phenoxy herbicides and /or dioxins published in the scientific literature during 1989 was greater than in each of the preceding several years. Much of this increase was attributable to the publication of the proceedings of two symposia, and there was a fair amount of duplication and overlap. Increases were seen, however, in the number of articles published about concentrations of dioxin in human tissue and about the mechanism(s) by which dioxin and related compounds affect the body.

By and large the results of research published during 1989 were consistent with the general body of information that had been developed prior to 1989. In other words, no new health



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effects were identified, and no breakthroughs were made in resolving apparent inconsistencies among several human health effects studies or in understanding why effects of dioxin seen in experimental animals have not been observed in humans who have been exposed to dioxins.

One of the more noteworthy findings in this year was the association between military service in Vietnam and an elevated risk of non–Hodgkin's lymphoma. This is the second independent study that has suggested the possible existence of such an association. While these studies suggest an association, they provide no evidence that the increased risk is related to exposure to herbicides and, in fact, the study conducted by the USCDC suggests that it probably is not. Five other types of cancer did not appear to be associated with military service in Vietnam. Several studies of non–Hodgkin's lymphoma published in 1989 and earlier suggest that this type of cancer is associated with some aspect of agricultural employment. Whether or not this aspect includes exposure to herbicides is unresolved at present and needs to be the focus of continued investigation in the future.

Another result that might prove to be of importance was the observation of a trend toward an increased risk of stomach cancer within a cohort of workers who were exposed to dioxins while employed at the Dow Chemical Company in Midland, Michigan. While this observation may not be of great significance by itself, it becomes significant when coupled with the results of other epidemiologic and experimental evidence that suggests that the stomach may be an important target for the effects of dioxins in primates.

Several studies of reproductive outcomes among Vietnamese civilians and military veterans reported an association between exposure to Agent Orange and spontaneous abortions, stillbirths, and birth defects. The validity of these conclusions is questionable because of methodological weakness. A study in the United States of a possible association between spontaneous abortion and military service of the father in Vietnam indicated that there was no such association. Several studies of humans exposed to environmental dioxin contamination in Missouri suggested an association between dioxin exposure and subtle changes in the proportions of some blood cells that have a role in the immune system, but there was no evidence of impaired immune function or clinical disease in these individuals.

Research has indicated that concentrations of dioxins in the blood or fat are reliable indicators of relatively heavy past exposure to dioxins or to phenoxy herbicides contaminated with dioxins. The correlation may prove extremely useful for identifying populations for epidemiologic studies and for relating health risks to body burdens. This finding is not useful for identifying health effects among U.S. military veterans who may have been exposed to Agent Orange in Vietnam, however, because only a few heavily exposed individuals have concentrations of dioxins in their fat or blood that are significantly different from the general U.S. population.

Department of
Veterans Affairs

# Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins

## Volume XIX
## Analysis of Recent Literature on Health Effects
## and
## Volume XX
## Annotated Bibliography of Recent Literature on Health Effects

Veterans Health Services
and Research Administration

VA Department of Veterans Affairs

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Veterans Health Administration

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# REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

## Volume XIX: Analysis of Recent Literature on Health Effects Published in 1991

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## FOREWORD

Public Law 96-151, enacted December 20, 1979, mandated the Veterans Administration to conduct "a comprehensive review and scientific analysis" of the worldwide literature on Agent Orange and other phenoxy herbicides. This mandate was in response to an increasing awareness among veterans, the Congress, and the public of the potential long-term health consequences of exposure to these herbicides and their dioxin contaminant. In October 1981, the Veterans Administration published a two-volume "*Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*." Because of continued active research, a two-volume update covering the literature through December 1983 was published in 1984. The *Review* has been updated each year since that time. The present two-volume update covers literature that became available during 1991.

This report was prepared by Information Ventures, Incorporated. It is an independent assessment of the current state of knowledge about the health effects of phenoxy herbicides, their contaminating polychlorinated dibenzo-*p*-dioxin impurities, and two other herbicides (picloram and cacodylic acid) that were used in Vietnam. The publication of this document by the Department of Veterans Affairs (VA) does not signify that the contents necessarily reflect the views and policies of the VA.

The project director for Information Ventures and principal author of this update to the *Review* was William A. Creasey, D.Phil. Phyllis Guinivan, Ph.D. was co-author. Consulting advice was provided by Michael A. Gallo, Ph.D., William F. Greenlee, Ph.D., David E. Lilienfeld, M.D., M.P.H., M.A.C.E., and Alan P. Poland, M.D.

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# I. INTRODUCTION

This report consists of a bibliography and critical review of the scientific literature that became available during 1991 on the health effects of the herbicides (including contaminants) that were used as defoliants during the Vietnam conflict. It comprises Volumes XIX and XX of an ongoing series of publications entitled "*Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*." Volumes I and II of this series were prepared by JRB Associates and published by the Veterans Administration in October 1981. Volumes III and IV, covering literature published from 1981 through 1983, were prepared by Clement Associates, Inc., and published by the Veterans Administration in June 1984. Subsequent volumes also were prepared by Clement Associates and published by the Veterans Administration: Volumes V and VI, covering literature that became available in 1984, were published in 1985; Volumes VII and VIII, covering literature that became available in 1985, were published in 1986; Volumes IX and X covering literature that became available in 1986, were published in 1987; Volumes XI and XII, covering literature that became available in 1987, were published in 1988; Volumes XIII and XIV, covering the literature that became available in 1988, were published in 1989; Volumes XV and XVI, covering the literature that became available in 1989, were published in 1990; and Volumes XVII and XVIII, covering the literature that became available in 1990, were published in 1991. In this update, Information Ventures, Inc., has identified and reviewed the scientific literature that became available during 1991 relevant to the potential adverse health effects of exposure to these herbicides and their contaminating impurities.

An attempt has been made to identify all scientific literature (including unpublished material) relevant to the potential adverse health effects of the herbicidal preparation commonly referred to as Agent Orange, its active ingredients, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and their esters, as well as the polychlorinated dibenzo-*p*-dioxins (primarily 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD) known to be present as contaminating impurities in some herbicidal preparations, and the herbicides, picloram and cacodylic acid. The scope of this review extends



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beyond health effects in humans to encompass studies of the biological effects of these compounds in animals or *in vitro* systems, their basic mechanisms of action, and their pharmacokinetic disposition. However, literature dealing exclusively with their chemistry, analysis, or environmental issues is not included.

In order to identify relevant literature, Information Ventures utilized searches of on-line databases, screening of primary journals and various ancillary sources. Searches of on-line databases covered the MEDLINE database of the MEDLARS on-line information systems of the National Library of Medicine, BIOSIS, CA, EMBASE, Japan Technology, and the Life Sciences, NTIS, PASCAL, and SCISEARCH files of DIALOG.

Since there is a significant time delay between publication of scientific reports and their entry into on-line databases, it was necessary to screen the primary scientific literature for optimal coverage of research that became available during 1991. Personnel from Information Ventures routinely screened over 600 scientific journals, both in our library and at the libraries of five local Medical Schools, and retrieved articles within the scope of this *Review*. In addition, the biweekly issues of *CA Selects: Carcinogens, Mutagens, and Teratogens*, and *CA Selects: Herbicides*, published by Chemical Abstracts Service, Columbus, Ohio, were screened in order to identify articles in journals not covered by the primary screen. Finally, information was obtained regarding unpublished reports, or material not in the open literature, from scientific meetings and from interaction with Information Ventures' consultants and other scientists actively engaged in research on the health effects of herbicides and dioxins.



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## II. SUMMARY AND CONCLUSIONS

The annotated bibliography that accompanies this review contains 340 citations to literature relevant to the human health effects of the herbicides used in Vietnam. This represents an increase from the previous year, undoubtedly due in large measure to the growing effort to elucidate the mechanism of action of chlorinated dibenzo-*p*-dioxins such as TCDD and related compounds. In addition, a significant number of review articles, abstracts and editorials are included to reflect the widespread interest in and controversy surrounding these substances.

### A. General Health Studies of Vietnam Veterans

Two studies of the general health status of Vietnam veterans, or of veterans who had served in the vicinity, were published in 1991. The first of these was a second report on the 1987 follow-up of U.S. Air Force personnel who were involved in the herbicide application program in Vietnam (Operation Ranch Hand). A notable feature of the 1987 follow-up had been the inclusion of accurate measurements of serum dioxin, made possible by recent technological advances. These were integrated into the 1991 report, in which clinical findings in the Ranch Hand cohort and the comparison group were correlated with current and estimated initial TCDD serum levels, using three models with differing pharmacokinetic assumptions. It was evident that the Ranch Hand cohort was indeed heterogeneous with respect to the extent of exposure to Agent Orange, in terms of both the military ranks and the individuals composing it. When dioxin levels were used as a basis for comparison, it was found that among Ranch Handers, both higher percentage body fat and increased erythrocyte sedimentation rates were positively correlated with higher current or initial TCDD levels. Since there was also a relationship between deduced initial dioxin levels on the one hand, and elevated IgA, leukocyte and platelet counts on the other, it appears that there is a long-term subtle inflammatory response among these subjects. This is in agreement with reports of earlier follow-ups. Cardiovascular, renal, hepatic, dermatologic, neurologic and psychological findings were negative or inconclusive with respect to any association with dioxin. There was some



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suggestion that dioxin may accelerate the development of a diabetic or prediabetic state. The incidence of benign and malignant neoplasms, and serum TCDD levels are discussed below.

In a study based on monozygotic twins that addressed the question of service in and around Vietnam, rather than exposure to Agent Orange *per se*, there were increases in self-reported hearing problems, skin problems and stomach conditions with the combat index, a composite measure of involvement in the conflict.

Health studies reported during 1991 have contributed no new findings to those of earlier reports, which provided no indications of any marked differences in disease incidence or mortality resulting from service in Vietnam, or from exposure to the herbicides used there, although there was some increase in deaths from external causes. Indications of a subtle inflammatory response, and an association with a historical diagnosis of chloracne, have been the only consistent findings for the Ranch Hand cohort as a whole. The use of serum and adipose tissue levels of TCDD permits greater discrimination in analyzing data, but the limited sizes of the study populations limit the statistical power to detect any differences that might be small but significant.

## B. Cancer

A large number of studies relevant to the potential carcinogenicity of dioxins appeared in 1991. They included seven reports that looked at the incidence of neoplasms in Vietnam veterans, and five occupational health studies of civilian populations. In addition to these primary publications, there were several in-depth reviews and a meta-analysis of earlier Swedish data.

In a report on the 1987 Air Force Health Study follow-up, in which correlations with measured TCDD levels were sought, an elevated incidence of basal cell carcinomas and sun-related cancers, previously ascribed to the Ranch Hand cohort as a whole, could not be associated with dioxin exposure as reflected in intragroup variations in serum dioxin levels. There was, however, a correlation between such levels and the incidence of benign neoplasms (75% were lipomas), for which the adjusted relative risk ratio for those with current dioxin levels greater than 33.3 ppt was 2.13.



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Three case-control reports appeared on cancer incidence encountered in the Centers for Disease Control's Vietnam Experience Study. This comparison of randomly-selected groups of Army Vietnam and non-Vietnam veterans, also included a group of controls, identified by random digit dialing in the areas where veterans with cancer lived, who were frequency-matched by age to the cases. There was no evidence of any association between service in Vietnam and the incidence of non-Hodgkin's lymphoma, soft tissue tumors and other sarcomas, Hodgkin's disease, nasopharyngeal carcinoma, and primary liver cancer. Although serum or tissue dioxin levels were not measured, there was no evidence of association of these tumors with surrogate measures of possible exposure to Agent Orange, such as rank, combat role, military branch or military region of Vietnam in which service occurred. The design of this study had sufficient power to detect a doubling of risk for all soft tissue tumors and sarcomas as well as for all types of lymphomas. The Department of Veterans Affairs proportionate mortality study of Army and Marine Vietnam-era veterans (Watanabe *et al.* 1991) reported excessive deaths from laryngeal cancer among Army veterans, but in the case of Marine veterans, elevated proportionate mortality ratios for lung cancer and non-Hodgkin's lymphoma were due to deficits among the non-Vietnam comparison group. In addition to the usual limitations of proportionate mortality studies, this study provided no information on the smoking and drinking habits of the study groups, factors of critical importance in considering the occurrence of laryngeal and lung cancers.

Among other studies of veterans that were published in 1991, one was based on findings that military working dogs who served and died in Vietnam exhibited elevated frequencies of testicular dysfunction and tumors. Patients of the age group that would have included those liable for service in Vietnam, and who had been admitted to Washington, DC, area hospitals with testicular cancer, were compared with a group of patients with non-genitourinary cancers. It was found that there was an approximately two-fold increase in risk for testicular cancer in Vietnam veterans, with the largest increase in subjects aged below 35 years. A study of 4,600 women Vietnam veterans indicated that standardized mortality ratios were elevated in veteran nurses for pancreatic and uterine cancers compared with U.S. women in general, but only a small number of deaths



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were involved. Finally, a study based on the Massachusetts Cancer Registry, disclosed an elevated odds ratio for mortality from soft tissue sarcomas, but not from non-Hodgkin's lymphomas. However, since this study provided no demographic data or details of military service, it is of limited value.

The largest and best executed of the civilian occupational studies was that of Fingerhut *et al.*(1991) who analyzed data obtained from 5,172 male workers at 12 plants in the U.S. that produced chemicals contaminated with dioxin. The data also included measurements of serum TCDD levels in 253 members of the surviving cohort. Mortality from all forms of cancer was elevated to a slight but statistically significant extent, with the largest increase (standardized mortality ratio of 145) in the subcohort with ≥ 1 year of exposure and ≥ 20 years of latency. Among individual tumor types, small increases in soft tissue sarcomas and respiratory system cancers were seen in this most highly exposed subcohort. The study did not exclude possible contributions from smoking or exposure to other chemicals in the workplace, but did address many other concerns that can be raised regarding studies carried out at multiple sites. Another multi-site study was undertaken by the International Agency for Research on Cancer on 18,910 production workers and herbicide sprayers from ten countries. There was an apparent overall two-fold increase in the risk for soft tissue sarcomas, which was not, however, statistically significant. Slight increases in the risk for other cancers involved numbers too small to serve as the basis for definitive conclusions.

A mortality study of workers employed at a herbicide plant in Germany where the products had been contaminated with dioxin prior to 1954, showed increases in overall cancer mortality as compared with German national statistics and a cohort of workers in the gas industry. The increases were more pronounced in those with 20 or more years of employment, and women showed an increase in death from breast cancer. The significance of the study was diminished by the use of mortality data from death certificates for controls, rather than the more accurate medical records used for the cases, and by confounding due to a more than 80% higher prevalence of smoking among the subjects compared with the general population.



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Two studies carried out in Italy were related to environmental exposures. In an area of northern Italy in which heavy spraying with phenoxy herbicides had taken place over several decades, the mortality rates for Hodgkin's and non-Hodgkin's lymphomas were elevated. There was a correlation with living in areas which had higher measured soil levels of the herbicides 2,4-D and 2,4,5-T. The authors did not attempt to stratify for length of residence or for occupation, but since rates were higher for men than for women, some contribution from occupational factors is probable. No conclusions could be drawn regarding mortality from soft tissue sarcomas. The Seveso incident, in which an industrial accident released a large amount of dioxin over a several square mile area in 1976, has been one of the best documented from the point of view of soil and human tissue levels of TCDD. Even among the most contaminated group, only small, non-significant increases in soft tissue sarcomas, leukemia and melanoma have been noted in males, and of biliary cancer in females. Among the latter, however, an almost statistically-significant decline in breast cancer has been registered.

The chief value of animal carcinogenesis studies is their relevance to defining the risk of dioxins to human populations. There is an extensive data base of results from animal studies indicating that TCDD and related dioxins are multi-site, complete carcinogens for a number of species and strains. Official recommendations for limiting exposure to these compounds rely primarily on linearized extrapolation from data for induction of liver cancer in rodents, which was originally obtained over the period 1978 - 1982. Two reevaluations of these older experiments, and of the models used to estimate human risks, based on updated histopathologic criteria, have appeared during 1991. They suggested, in general, that the human risk may be between 10 and 100 times less than that presently accepted by regulatory agencies in the U.S. However, further study is needed to define this risk more exactly. Another advance achieved through animal studies, and emphasized in 1991 publications, has been the establishment of assays based on surrogate markers of carcinogenesis, biochemical and biological changes that precede overt cancer development, and thus afford a more rapid method for evaluation of carcinogenic potential, and one requiring fewer animals.



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In summary, the human data, taken in conjunction with findings made in animals, is indicative of a moderate carcinogenic risk to humans, associated with the highest levels of exposure to which humans are likely to be subjected occupationally or environmentally. There is no clear evidence that Vietnam veterans were in general exposed to these higher levels.

## C. Genetic Effects

No new studies implicating phenoxy herbicides or dioxins as causative agents in producing genetic effects in humans became available during 1991. Experiments associated with a study of the mutagenic potential of fish contaminated with a variety of polychlorinated compounds, showed that pure TCDD is non-mutagenic at levels up to the toxicity limit for *Salmonella typhimurium* in the Ames test. In a study that used a mouse lymphoma forward mutation assay, TCDD was inactive up to its solubility limit of 1 $\mu$g/ml. These data further confirm the large body of earlier findings indicating that TCDD is essentially inactive as a genotoxin. On the other hand, the phenoxy herbicide 2,4-D was found to be both mutagenic and cytotoxic for V79 hamster cells in culture. Earlier literature does report scattered findings of modest genotoxicity associated with this herbicide.

## D. Reproductive and Teratological Effects

In a study of organ cultures of human and rodent palatal shelves, it was evident that TCDD interfered with differentiation, but that humans and rats required concentrations 200 times higher than those effective in mouse tissue. Both TCDD and 2,4-D were reported to produce testicular damage and abnormal spermatogenesis in rats and humans, respectively, but there was no evidence of paternally-mediated developmental toxicity in rats administered TCDD. Finally, one report added to the evidence for teratogenicity in mice by showing that TCDD and tetrabrominated dioxins and furans produced cleft palate and hydronephrosis. Interestingly, cleft palate was not induced by TCDD in embryos that had been made exencephalic by exposure to cadmium chloride.



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## E. Immunological Sequelae

While there is a significant body of literature suggesting that TCDD and related compounds produce a variety of actions on the immune system in animals, evidence that this occurs in humans is equivocal. In the recent report on the Air Force Health Study, for example, the only immunological parameter that could be related to serum dioxin was an increased IgA level. Abnormal delayed hypersensitivity skin test data seen in the Ranch Hand cohort as a whole did not correlate with dioxin levels. However, another study found that when human and non-human primate lymphocytes were cultured in the presence of TCDD there was a pronounced decrease in the CD4 subset, a finding seen also in monkeys who were given this compound. These changes in lymphocyte subsets did not appear to lead to immunosuppression, but in one study with AIDS patients, those with the highest body dioxin burdens also were more susceptible to opportunistic infections, a finding suggestive of some type of immune deficit.

Thymic involution is a well known result of dioxin intoxication whose mechanism is only now beginning to be clarified. Three studies carried out in rodents established that thymic involution is an indirect effect, since changes in lymphocyte subsets did not occur rapidly, nor to the extent that would have been expected if this were the primary site of action. It appeared that involution resulted from reversible damage to the epithelial component of the thymus, and that this change in the cellular microenvironment in turn led to impairment of lymphocyte differentiation. Once the epithelial damage was repaired, there was an influx of progenitor elements from the bone marrow, leading to full recovery of thymic architecture and function. An interesting finding made in a study that compared TCDD high-responder and low-responder mouse strains, was that thymic involution following acute exposure was mediated by the Ah receptor, whereas with a subchronic regimen some other mechanism appeared to be involved.

While the results of two studies in rodents suggested that any effects of TCDD on B cells were secondary to alterations in T cell function, several others showed that this agent may act directly on B cells. As with thymic involution, studies on TCDD-induced immunodepression indicated that acute dioxin effects were mediated by the Ah receptor, while those associated with subchronic exposure to lower doses were not. The nature



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of such alternate mechanisms is as yet unknown, but one early biochemical effect of exposure to TCDD which has been reported was increased tyrosine kinase activity, the timing and magnitude of which were correlated with inhibition of antibody synthesis.

## F. Neurobehavioral Effects and Appetite Suppression

Earlier human and experimental animal data have shown that heavy exposure to TCDD can give rise to neuropathies. In the recent report from the Air Force Health Study, a significant correlation was demonstrated between current and extrapolated initial levels of serum dioxin and abnormalities in the CNS index, a composite of coordination, tremor and gait. In the portion of the report devoted to psychological assessment, results of the tests employed were somewhat at variance, but overall there was no convincing evidence of a significant psychological deficit ascribable to exposure to Agent Orange and its associated dioxins in these Vietnam veterans. In a follow-up of children of women in Taiwan who had consumed cooking oil contaminated with polychlorinated biphenyls and benzofurans, there was evidence of significant delays using standard criteria for developmental status.

A highly characteristic result of dioxin intoxication in animals is hypophagia and wasting, a phenomenon which shows extreme variations in species and strain sensitivity. Strain differences in one study were shown to reflect recovery from anorexia in the resistant but not the sensitive rat strain, and some intestinal factor was involved in the development of hypophagia. Other reports, however, are compatible with central effects involving alterations in hypothalamic histamine and/or $\beta$-endorphin.

Dogs are relatively more sensitive to 2,4-D than many other mammals, and a three-part study published in 1991 defined the dose-response relationship for development of electroencephalographic changes and myotonia in this species. It was found that dogs running loose on a plot heavily treated with 2,4-D did not develop any neuromuscular abnormalities.



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## G. Other Toxic Effects

A characteristic symptom of heavy exposure to dioxin in humans is the appearance of chloracne. This relationship has been strengthened by the demonstration of a clear correlation between elevated serum TCDD levels and this dermatological condition, in the recent follow-up of the subjects involved in the Seveso incident in Italy. Some degree of hepatotoxicity occurs both in humans and in animals, with its principle manifestation being altered lipid metabolism. Other toxic effects that were reported on during 1991, included an anticoagulant effect based on thromboxane-mediated inhibition of platelet aggregation, and a hypergastrinemia seen in rats in the dioxin-induced hypophagic state.

## H. Tissue Residues and Pharmacokinetics

This has been an active area of research in the literature reported during 1991. Perhaps most important has been the extension of serum TCDD measurements in the Ranch Hand cohort, and the correlation of these levels with military rank and occupational classifications. There has been some controversy regarding the validity of conclusions about exposure to Agent Orange based on measurements of serum concentrations made many years after the fact; alternative pharmacokinetic models for humans have also been suggested. However, several recent studies have indicated that such factors as increasing body fat do not have the major repercussion that might be expected on the disposition of TCDD, which over most of its time course can best be expressed by single compartment kinetics. Other data from recent studies of occupational and environmental exposure to polychlorinated dioxins, benzofurans and biphenyls are indicative of the long-term retention of these compounds. These data support those obtained in veterans in indicating that even after many years, the prolonged half-life of these compounds means that high current serum and adipose tissue levels reflect earlier heavy exposure. Moderate or low exposures, however, may not be reflected in increased levels.

This year has seen continued activity with regard to the transport of TCDD and related compounds transplacentally, and more especially through excretion in breast milk, with its clear implications for the health of infants. This is emphasized by studies in rats,



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where the amounts of TCDD secreted in milk or transported across the placenta were sufficient to induce hydronephrosis in nursing pups.

## I. Basic Studies

The large body of literature on basic studies that became available during 1991 has served to further document the importance of the role played by the Ah receptor in mediating the toxic effects of dioxin. This primary interaction serves as the basis for intervention in many other systems, most notably xenobiotic metabolism, steroidogenesis and lipid metabolism. However, there is evidence for the existence of other sites of dioxin intervention that are independent of the Ah receptor, especially in relation to immunologic effects . Although TCDD induces a vitamin A-deficient state, this does not appear to be a primary mechanism for dioxin toxicity. Basic studies of dioxin toxicity are playing, and will continue to play an important role in establishing the sensitivity of humans to this agent. This is an essential step in defining the hazard presented by dioxin and the most appropriate recommendations for its regulatory control.



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## III. HEALTH EFFECTS OF PHENOXY HERBICIDES AND CONTAMINANTS

### A. General Health Studies of Vietnam Veterans

1. The Ranch Hand Study

The United States Air Force has been conducting an ongoing prospective epidemiologic study of the cohort of Air Force personnel assigned to the herbicide application program in Vietnam between 1962 and 1971, inclusive. This program was known as Operation Ranch Hand, and during its execution, 10 to 12 million gallons of Agent Orange, containing an estimated 368 pounds of the contaminant dioxin TCDD, were sprayed in various areas of Vietnam (Gough 1991). In this "Ranch Hand" study, mortality and general health status of members of the study cohort have been compared to those of Air Force personnel who served in Vietnam during the same period, but lacked the opportunity for exposure to herbicides because of different duty assignments. The first mortality results of this cohort were published in 1983 and reviewed in Volume III of this *Review* in 1984. The mortality portion of the study has been updated twice since that time, and these updates were covered in Volumes IX and XV of this *Review*, published in 1987 and 1990. The most recent of these two updates also was published as a journal article by Michalek *et al.* (1990). The cohort of Ranch Hand personnel (called "Ranch Handers") was characterized by a greater incidence of external causes of death, such as accidents or homicides, a finding also noted in the recently-updated Army and Marine Vietnam-era Veterans Study (proportionate mortality ratio of 1.16 for homicides) from the Department of Veterans Affairs (Watanabe *et al.* 1991), and a study of women Vietnam veterans (relative risk for accidents 1.33) compared with non-Vietnam veterans (Thomas *et al.* 1991).

The results of the baseline general health status (morbidity) study of this cohort were published in 1984 and reviewed in Volume V of this *Review*. The first follow-up of the general health status portion of the study was published in 1987, and the findings were discussed in Volume XI of this *Review* in 1988. There was little difference between the cohort and the comparison group in terms of overall general health, except for a consistently elevated incidence of basal cell carcinoma (skin cancer) in the Ranch



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Handers. The self-perception of health had been worse in Ranch Handers in the first follow-up; this cohort also had a more favorable proportion of body fat but a higher proportion of abnormal erythrocyte sedimentation rates than did the comparisons.

The second follow-up of the general health status portion of this study was released and published as a journal article (Wolfe *et al.* 1990) in 1990, and discussed at length in Volume XVII of this *Review*. Over the intervening years, there had been 33 deaths from among the original cohort of 1,208 subjects, and another 13 individuals had been identified and enrolled for a 1987 total of 1,188. Participation in the second follow-up was 84% (995 individuals) of whom 944 had participated in the baseline study. A concern expressed by the reviewers was that the incomplete participation in the study in both follow-ups introduced a possible bias, and this, together with the inclusion as Ranch Handers of individuals who had experienced little or no abnormal herbicide exposure, detracted from the power of the study to detect differences in health status between the exposed members of the cohort and controls. The variability in exposure to dioxin among the members of the Ranch Hand cohort was documented by current serum TCDD measurements. Clinical findings were very similar to those noted at the first follow-up. For example, more members of the Ranch Hand group had experienced chloracne, but at the time of follow-up there were no observable dermatologic lesions compatible with a history of that condition. As in the first follow-up, there were significantly more Ranch Hand individuals with abnormal erythrocyte sedimentation rates, but other health parameters showed no preponderance of abnormalities in the exposed cohort. However, compared with the earlier follow-up, there was a greater than 50% decline in the proportion of veterans who reported their health status as fair or poor.

A major feature of this second follow-up was the inclusion of accurate measurements of serum dioxin levels; the complete data have since been published in a report (Roegner *et al.* 1991). The findings on serum levels are discussed in Chapter V, but here we are concerned with correlations between those levels and observed health status (except for cancer which is discussed in Section III B). The lipophilic nature of TCDD and its very limited metabolism combine to give the compound a prolonged biological half-life, of the order of 7 years. This permits the determination of dioxin in



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serum and adipose tissue many years after exposure to abnormal levels, using the extremely sensitive assay systems that are now available. In this way, such determinations provide an independent marker of significant past exposure to dioxins, and thus a way of stratifying the Ranch Hand cohort. Accordingly, this report attempted to associate clinical findings with measured dioxin levels. Three statistical models were used in evaluating any possible associations:

- Model 1, estimated initial TCDD levels using Ranch Hand participants only;
- Model 2, current dioxin levels and time since military service in Vietnam in Ranch Hand participants only;
- Model 3, categories of current dioxin levels using both Ranch Hand and Comparison cohorts.

These models differed in their assumptions and utility. Model 1 assumed that there had been first-order elimination of dioxin at a constant decay rate, whereas model 2 made no such assumptions about the kinetics by which body burdens decreased. These two models were applied under either the minimal (only those Ranch Hand participants with more than 10 ppt serum dioxin, n = 521) or the maximal (all Ranch Handers with current levels above 5 ppt, n = 742) assumptions. Model 3 used all participants in both Ranch Hand and Comparison cohorts, and related health consequences to current dioxin levels only. This multi-model approach helped to increase the discrimination of the analyses.

Ranch Handers had higher levels of body fat and increased erythrocyte sedimentation rates, both of which parameters exhibited significant positive relationships with current and estimated initial serum levels of TCDD. The continued elevation in sedimentation rates over this long period implies the existence of a subtle chronic inflammatory response, a conclusion supported by a correlation between deduced initial dioxin levels and elevated IgA (although other immunoglobulins did not show this relationship), and by increased leukocyte and platelet counts in Ranch Handers with the



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highest dioxin levels. However, earlier conclusions regarding abnormal skin-test reactions in the Ranch Hand cohort, were not supported by analysis based on a relationship to dioxin levels.

The findings of percent body fat are consistent with an observed positive association between dioxin levels on the one hand, and serum triglycerides and high density lipoprotein cholesterol, on the other. However, it could be argued that the correlation reflects the larger storage compartment for dioxin provided by the greater amount of body fat, thus leading to more prolonged retention, rather than a stimulatory effect of TCDD on lipid formation. This question will only be resolved by further follow-up and basic studies. These lipid changes may have led to reductions in vital lung capacity in the high current dioxin category, but the abnormalities in spirometric results observed, although significant statistically, were not clinically important.

A new finding resulting from analysis of the health data in terms of serum TCDD concentrations related to the incidence of diabetes. Ranch Handers were classified on the basis of 2-hour postprandial glucose levels as normal (<140 mg/dl), impaired (≥140 to <200 mg/dl), or diabetic (≥200 mg/dl, or medical history of diabetes). Stratified in this way, there was a strong positive correlation ($p$ = 0.001) with current (13.5, 14.8 and 21.9 ppt for the three groups, respectively) and initial (112.8, 123.7 and 169.9 ppt, respectively, under the maximal assumption) serum dioxin levels. Under the minimal assumption, the correlation with initial dioxin levels (174.4, 176.2 and 221.9 ppt) was marginally significant ($p$ = 0.095), as it was also for the comparison cohort (3.4, 4.0 and 4.5 ppt; $p$ = 0.028). These correlations are interesting, but do not necessarily infer a causal relationship between dioxin and the development of diabetes. The same survey noted a significant correlation between both initial and current dioxin levels and increase in body fat, as we have mentioned above, and Ranch Handers classified as obese (>25% body fat) also had significantly ($p$ <0.001) higher current (22.4 versus 12.9 ppt for normal/lean) and initial (161.1 versus 110.2 ppt, under the maximal assumption) dioxin concentrations in their sera. Obesity is a known risk factor for the development of late-onset diabetes, so that the dioxin relationship to diabetes could merely reflect a common association with body fat. It is apparent that this important health aspect of the Ranch Hand Study merits



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further detailed examination, and ideally should be accompanied with correlative studies in experimental systems. Diabetes has not been described in experimental animals exposed to TCDD, but the disturbances in the satiety response, and the enzymatic evidence of impaired gluconeogenesis, which are described on pages 62-64 and 114, respectively, could be of possible relevance. It is possible that such changes might serve to accelerate the manifestation of developing, but not yet clinically overt, disease.

All three dioxin concentration models supported the existence of a positive association between testicular size and serum dioxin levels. There was a significant negative correlation between dioxin levels and serum testosterone when no allowance was made for body fat. However, it is possible that the lipid changes discussed above impinged upon this finding, since when the latter were factored in, there was no significant relationship between dioxin and abnormally low testosterone levels.

Cardiovascular findings were inconclusive. Thus, although there was a significantly increased risk of essential hypertension in Ranch Handers with high current TCDD levels (>33.3 ppt) relative to background comparisons (≤10 ppt), and their adjusted mean continuous levels of diastolic and systolic blood pressures were higher also (without considering body fat), the fraction of participants exhibiting abnormally high blood pressures showed no correlation with dioxin. Furthermore, the adjusted relative risk of verified heart disease was less than 1 in Ranch Handers with high current dioxin levels. Other attempts at correlation with dioxin levels in the areas of renal or hepatic function, dermatologic or neurologic findings, and psychological status (Symptom Check List-90-Revised and the Millon Clinical Multiaxial Inventory) led to null or inconsistent results.

2. Other Studies

A study that addressed the question of service in and around Vietnam, rather than exposure to Agent Orange *per se*, was reported by Eisen *et al.* (1991). It is relevant to this *Review*, because it is difficult to dissociate the effects of exposure to Agent Orange in Vietnam from those attributable to the health hazards of the location alone, or the sequelae of military combat. This study, based on mail and/or telephone interviews, surveyed the impact of military service in Southeast Asia on 13 categories of health



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problems among 2,260 male-male monozygotic twin pairs. The reliability of this epidemiologic approach was validated in a preliminary trial of 150 Connecticut-born twin pairs. A combat index, based on 18 specific activities, such as serving as a "tunnel rat" or being in a unit patrol that was ambushed, was employed to evaluate the degree of combat exposure. This index ranged from 0 for no Southeast Asian exposure to >7 for heavy combat in the area. The year of data collection was 1987. Among the twins, service in Southeast Asia was associated with an increased current incidence of self-reported hearing problems (odds ratio (OR) = 1.9, 95% confidence interval (CI) 1.3-2.7) and persistent skin problems (OR = 2.1, CI 1.4-3.2). The odds ratios for these problems increased as the combat index rose. Odds ratios for ever having hearing problems (OR = 1.8, CI 1.3-2.5), persistent skin problems (OR = 2.1, CI 1.5-3.0), or having been hospitalized for stomach conditions (OR = 2.6, CI 1.4-4.9), also were elevated. There were marginal elevations in the odds ratios for ever having stomach (OR = 1.4, CI 1.0-1.9) or urinary (OR = 1.5, CI 1.0-2.1) conditions. The design of the study, and the identification of monozygotic twins without prior knowledge of exposure or disease state, helped eliminate some potential confounders. In summary, the general physical health of veterans who served in Southeast Asia is similar to that of their twin siblings who did not, with two exceptions. Hearing impairment has been observed in military personnel under combat conditions in other theaters of action, and is most probably associated with loud noise, known to produce similar effects in various civilian occupations. The skin conditions experienced at such a long interval of time after combat, cannot readily be explained, but their existence could be a confounding factor in investigating claims of association of such conditions with exposure to Agent Orange.

Three other studies have been concerned with measurements of the serum lipid and adipose tissue contents of TCDD and related compound in veterans. These will be described in detail in Section V. Seven other reports have described the occurrence of various benign and malignant tumors in Vietnam veterans; these will be the subject for discussion in Section III B.



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## B. Cancer

The results of a number of epidemiologic studies became available during 1991, which described possible correlations between exposure to phenoxy herbicides and their contaminant dioxins, or at least of the opportunity for experiencing such exposure, with the development of neoplastic diseases. They include further updates of the U.S. Air Force's Ranch Hand Study and the Centers for Disease Control's Vietnam Experience Study, other articles describing observations in veterans, and some epidemiologic work in civilian populations. In addition, a significant amount of data was reported for studies carried out in experimental animals, which will be described because of its relevance to interpreting the human data.

### 1. Studies of Vietnam Veterans

Seven reports which became available during 1991 have looked at the general incidence of cancers and other neoplasms in Vietnam veterans, but only one specifically searched for a definitive correlation with exposure to Agent Orange. This was the Air Force Health Study correlating health status with measured and estimated dioxin levels, which was outlined in Section III A above. When dioxin levels were used as reference, the higher incidence of basal cell carcinoma and sun exposure-related skin neoplasms in general, described in both earlier follow-ups and the previous report of the 1987 survey, could not be substantiated. An increased incidence of basal cell carcinoma of sites other than the ear, face, head or neck was noted in the enlisted flyer category. However, this was thought to be an artifact, since the association was not seen in the enlisted ground crew who had higher serum dioxin levels. This question merits further study, not only in terms of future follow-up, but also with respect to the models used for estimating initial dioxin levels as discussed in Section V. Furthermore, the number of cancers involved is small, so the study may not have sufficient power to achieve statistical significance. The risk for development of systemic malignant neoplasms was not elevated. Ranch Hand participants did have a significantly higher incidence of benign neoplasms than the comparison cohort, and the effect was related to estimated initial levels, falling from 9.7% at high, to 5.7% at medium and 1.6% at low levels. The adjusted relative risk for those



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with the highest current dioxin levels (>33.3 ppt) was 2.13. Lipomas comprised 75% of Ranch Hand and 70% of comparison group benign neoplasms (Roegner *et al.* 1991).

Watanabe *et al.* (1991) published an update (through 1984 for a total of 62,068 veterans) of the Department of Veterans Affairs' proportionate mortality study of Army and Marine Vietnam-era veterans. They reported significant excesses of deaths from laryngeal and lung cancer among the Army veterans, with calculated proportionate mortality ratios (PMRs) of 1.53 and 1.08, respectively. However, among Marine Vietnam veterans, apparently elevated PMRs for lung cancer and non-Hodgkin's lymphoma, resulted from deficits in the non-Vietnam comparison group. A survey carried out as an extension of routine surveillance of the Massachusetts Cancer Registry for cases diagnosed between 1982 and 1988 (Clapp *et al.* 1991), disclosed an elevated odds ratio (OR) for mortality from soft tissue sarcomas among Vietnam veterans (OR = 3.08, 95% confidence interval (CI) of 1.07-8.73), but no significant increase for non-Hodgkin's lymphoma, a malignancy considered to be associated with exposure to dioxins on the basis of earlier studies by the National Cancer Institute and by Swedish workers. However, since the Massachusetts study involved no interviews, questionnaires or other interaction with the study participants, and no information was obtained regarding the timing or duration of military service or any other demographic data, its value is quite limited. In a study of 4,600 women Vietnam veterans, standardized mortality ratios (SMRs) for cancers of the pancreas (five deaths) and uterine corpus (four deaths) were elevated, at 3.27 and 4.05, respectively, in Vietnam veteran nurses compared with U.S. women in general (Thomas *et al.* 1991).

The specific topic of non-Hodgkin's lymphoma was addressed in three reports. O'Brien *et al.* (1991), as part of the Centers for Disease Control's Vietnam Experience Study (VES), used data from a randomly-selected group of 9,324 Army Vietnam veterans and 8,989 non-Vietnam veterans. Of these two groups, 246 Vietnam veterans and 200 controls had died between discharge from active duty and the close of the mortality study (December 31, 1983). Telephone interviews, medical records and review of such records by a panel of physicians, were used to establish causes of death and diagnosis of current disease. Seven Vietnam veterans and 1 non-Vietnam veteran developed non-Hodgkin's



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lymphoma, a difference that was significant (p = 0.07). However, none of the cases had military job titles suggesting that they were exposed to herbicides during their tour of duty in Vietnam. Also as part of the VES study, the Selected Cancers Cooperative Study Group utilized the population-based cancer registries for five metropolitan areas and three states for a case-control study restricted to men born between 1929 and 1953. A total of 1,157 non-Hodgkin's lymphoma patients were frequency-matched by age to 1,776 controls who were identified by random-digit dialing from these regions. The risk of developing non-Hodgkin's lymphoma was elevated in Vietnam veterans (OR = 1.47, CI = 1.1-2.0) compared to those men with no Vietnam service; these veterans were also at higher risk than other veterans, contemporary veterans who had not served in Vietnam, and those individuals with no military service. The relative risk increased with length of time in Vietnam, but showed no correlation with factors such as military region, unit, or dates of service that could be associated with exposure to Agent Orange (Selected Cancers Cooperative Study Group 1990a). A hospital-based, case-control study of 201 Vietnam-era veterans treated for non-Hodgkin's lymphoma between 1969 and 1985, disclosed no increased risk of non-Hodgkin's lymphoma relative to a group of 358 Vietnam-era patents with a diagnosis other than lymphoma (OR = 1.03, CI = 0.7-1.50). Neither was there any correlation with surrogate measures of potential exposure to Agent Orange, such as specific military branch, combat role or region of Vietnam in which the subjects served (Dalager *et al.* 1991).

Soft-tissue sarcomas have also been claimed to be associated with exposure to dioxins. As part of the VES study, and using the matching procedures indicated for non-Hodgkin's lymphoma, 342 men with soft tissue and other sarcomas were compared with 1776 controls (Selected Cancers Cooperative Study Group 1990b). The study design had the power (97%) to detect a relative risk of 2.0 for all sarcomas. Relative risks for these tumors were not increased, either for total sarcomas (OR = 1.0, CI = 0.6-1.6), or for soft tissue sarcomas only (n = 254, OR = 0.9, CI = 0.5-1.6). There was no evidence of overrepresentation of specific histologic subtypes of sarcoma, or of increased risk to those whose military service included activities that might have exposed them to Agent Orange.



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In a third segment of the VES study, the incidence of four other cancers was studied, using the same Cancer Registry-based, case-control matching procedure (Selected Cancers Cooperative Study Group 1990c). The cancers studied were Hodgkin's disease (310); nasal carcinoma (48); nasopharyngeal carcinoma (80); and primary liver cancer (130). All were matched to 1,776 controls. Risks relative to controls, and to other veterans or men who never served, were: 1.1 (Hodgkin's); 0.7 (nasal); 0.5 (nasopharyngeal); and 1.2 (liver). None of these risks differed statistically from unity, but only in the case of Hodgkin's disease, was the power of the study (96%) sufficient to detect a doubling of the risk; for other tumors the ability to detect a similar difference ranged from 38% to 75%.

Based on findings that military working dogs, who served and died in Vietnam, exhibited significantly elevated incidences of testicular dysfunction and testicular tumors, data from a previously reported case-control study of human testicular cancer were reexamined by Tarone *et al.* (1991). Subjects aged 18-42 years, newly diagnosed with testicular cancer during the period January 1, 1976 to June 30, 1981, and referred to Washington DC-area hospitals, were compared with patients newly diagnosed with cancers of non-genitourinary sites. A standardized questionnaire was employed, and exclusions made for cryptorchidism, low birth weight, non-Hodgkin's lymphoma, and birth prior to 1955, in order to reduce problems from confounding factors, for example, the known association of crytorchidism with testicular cancer. The ORs for Vietnam service were 2.6 for cases diagnosed before age 35, 3.0 for those diagnosed between 30 and 34 years, and 1.1 for subjects diagnosed after 35 years of age. For Vietnam service the OR was 1.8 (CI = 0.6-5.1) for seminomas, and 2.4 (CI = 1.1-5.4) for nonseminomas. This approximately two-fold increase in risk was similar to that described in dogs, as was the relatively greater risk for younger subjects. It is well to bear in mind when considering both the dog and the human data that many confounding factors could have been at work in addition to herbicides. They include infectious agents and parasites endemic to Vietnam, the use of chemotherapy, including tetracyclines which are known to cause testicular dysfunction, to treat those infections, and the effects of stress itself.



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The INSERM North-South Network for Environmental Epidemiology in Vietnam is conducting three studies in Vietnam regarding wartime exposure to Agent Orange, and the subsequent development of non-Hodgkin's lymphoma, molar pregnancy and choriocarcinoma, and primary liver cancer, using a case-control design (Abenhaim *et al.* 1991). These studies, while not involving former U.S. military personnel, will provide data that might help to shed light on some of the inconsistencies in the studies with veterans.

2. Other Studies of Human Subjects

Most of the reports dealing with cancer in humans not involved in the Vietnam conflict have dealt with occupational exposures. Perhaps the largest compendium of such data was provided by Fingerhut and her coworkers (Fingerhut *et al.* 1991), who analyzed data from 5,172 male workers at 12 plants in the U.S. that produced chemicals contaminated with TCDD. This study is part of the National Institute of Occupational Safety and Health's (NIOSH) Dioxin Registry. Occupational exposure was based upon job description, supplemented with measurements of serum TCDD in 253 members of the surviving cohort; mortality data was derived from death certificates. Of the subjects entered into the study, 202 were included in the overall mortality analysis, but excluded from analyses based on duration of exposure because these data were unavailable. Mortality from all forms of cancer combined was raised to a slight but statistically significant extent (standardized mortality ratio, SMR, of 115, CI = 102-130), and to a greater degree in the subcohort (n = 1,520) with ≥ 1 year of exposure and ≥ 20 years of latency (SMR = 146, CI = 121-176). There was no elevation in the incidence of Hodgkin's disease, non-Hodgkin's lymphoma, stomach, liver and nasal cancers, diseases that have been reported to be associated with dioxin toxicity. However, there was a slight, but not significant, increase in deaths from soft tissue sarcoma (SMR = 338, CI = 92-865, four deaths). There was a significant increase for this latter disease only if those workers with ≥ 1 year exposure and ≥ 20 years of latency were considered (SMR 922, CI = 190-2,695, three deaths); respiratory system cancers also were increased in this group (SMR = 142, CI = 103-192). This study did not exclude the contribution of factors such as smoking or exposure to other chemicals in the work place, and two deaths were



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misclassified in the soft tissue sarcoma group. Furthermore, objections can be raised to combining data obtained at so many sites, a practice somewhat resembling meta-analysis, although in this case the authors did not merely combine the results of separate studies, but rather identified the individual subjects, coded and analyzed data under a common protocol, and reviewed the procedures used at each work site, procedures which negate most of the problems of meta-analysis. If there is any conclusion to be drawn, it is surely that the study indicated a relatively low order of cancer risk from occupational exposure to TCDD. Nevertheless, it provoked considerable discussion, and its data were used by others as conclusive support for both the standard linear model used by the EPA for cancer risk assessment (Goldman *et al.* 1991), and for the receptor-based, practical effect threshold model (Carlo *et al.* 1991) that is a currently-favored alternative.

Another study of a large multi-site nature was carried out by the International Agency for Research on Cancer (IARC), and involved 18,910 production workers or herbicide sprayers from ten countries (Saracci *et al.* 1991). Estimates of exposure were obtained by a combination of questionnaires, recorded durations and frequency of spraying, factory records, and work histories; cause-specific national death rates were used as reference for each country's contribution. There was a two-fold increase in overall risk of soft tissue sarcoma (SMR = 196, CI = 53-502), which lacked statistical significance, however. The increase was concentrated so as to become statistically significant only for the time period 10-19 years after first exposure, both for the total cohort (SMR = 606, CI = 165-1,552), and for the subgroup of sprayers (SMR = 882, CI = 182-2,579). There appeared to be small increases in the risks for testicular, nasal, thyroid and other endocrine-related cancers, but the numbers were too small to draw any definitive conclusions. Peto (1991) has questioned the conclusions that were drawn from the data of the IARC study, pointing out that there were four deaths from soft-tissue sarcoma in the group classified as 10-19 years since first exposure, but none for those associated with any other time interval. Similarly, two of these deaths occurred after less than one, and the other two after 10-19 years of exposure. This clustered distribution pattern does not support any specific statistical conclusions regarding subgroups. A

separate description of part of the British contribution to this IARC study was published by Coggon *et al.* (1991). Among a total of 2,239 men at four chemical manufacturers, there were two deaths from non-Hodgkin's lymphoma with 0.87 expected, and a further living case with this disease, a non-significant excess of lung cancer (19 deaths with 14.2 expected) possibly due to confounding factors or chance, but no cases of soft tissue sarcoma or Hodgkin's disease.

The Swedish group which has carried out a number of studies of the association between dioxins and soft tissue sarcomas over the past 15 years, published a meta-analysis of four of their studies (Hardell *et al.* 1991), using the criteria of the Fingerhut study (Fingerhut *et al.* 1991). There were two stratifications, first between subjects with less than one and more than one year of exposure, and second between those with 5-19 years and 20 or more years of latency. There were 352 cases and 865 controls in the study. A significant trend for increased incidence with increased exposure to dioxins was noted (Chi squared test = 18.2, *p*, 0.001). Volume XVII of the *Review* presented a detailed analysis of the most recent of the Swedish studies, in which it was pointed out that there had been a steady decline in the apparent risk from 5.3 in the first study (Hardell and Sandstrom 1979) to 1.34 in the more recent publications (Eriksson *et al.* 1990; Hardell and Eriksson 1988). The most marked association was with chlorophenols rather than phenoxy herbicides, and there also were inconsistencies in the use of normal or cancer case controls. In general, the risk ratios were smaller when cancer cases were used as controls, and it was speculated that recall bias was operative here. In view of such objections, and the limitations of meta-analysis, this most recent study from the Swedish group cannot be said to clarify the issue.

Other studies have been restricted to single plants or occurrences. A mortality study of 1,184 men and 399 women employed between 1954 and 1984 at a chemical plant in Germany that produced herbicides, and involved products contaminated with TCDD, was described by Manz *et al.* (1991). Dioxin production was curtailed at the plant after an outbreak of chloracne in 1954. SMRs were calculated using as references the national mortality statistics for West Germany, and deaths among a cohort of gas workers. As of 1989, there had been 313 deaths among men and 54 among women, of



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which 93 and 20, respectively, resulted from malignancies. Total cancer SMRs for men were 1.24 (CI 1.00-1.52) versus national data, and 1.39 (CI 1.10-1.75) compared with gas workers. These risks for cancer deaths rose to 1.87 and 1.82 against the two references, respectively, for those men with 20 or more years of employment, and to 1.61 and 1.87 for men hired before 1955. For men employed in areas with the highest probability of TCDD exposure, SMRs were 1.42 and 1.78 compared with national and gas worker figures. Adipose tissue levels of TCDD were measured in only 48 individuals, with figures of 296 ± 479 and 83 ± 73 ng/kg for the two classes of high and lower exposure. Of the men, 39.6% worked in high exposure locations compared with 7% of women. Among women there was no increased overall risk of cancer mortality, but mortality from breast cancer was raised (SMR = 2.15). There are a number of concerns regarding this study. National mortality data is based on death certificates, whereas deaths among the study population were documented by medical records which are likely to provide more accurate causes of death. Other concerns, raised by Triebig (1991), relate to the failure to document which of the subjects experienced chloracne, a good indicator of heavy dioxin exposure, determinations of TCDD in such a small, possibly unrepresentative, fraction of the study population, and the unusually high percentage of smokers among the chemical workers (73%) compared with the general male population of Germany (40%). This latter factor could confound comparisons with national statistics, and also could affect the results through a process of multiplicative interaction with carcinogens such as benzene and asbestos, which were present at the site.

One study evaluated the relationship between mortality from lymphomas and soft tissue sarcomas, and environmental exposure to phenoxy herbicides in the provinces of Novara and Vercelli in northern Italy (Vineis *et al.* 1991). These areas are noted for cultivation of rice, and phenoxy herbicides have been used heavily there since 1950. A survey of four local hospitals, and others to which residents of the two provinces would have been admitted, identified 43 cases of Hodgkin's disease, 141 of non-Hodgkin's lymphoma and 30 cases of soft tissue sarcoma in men; for women the corresponding figures were 20, 112 and 19 cases. Age-adjusted, standardized incidence rates were calculated with the world population as reference. Determinations of the soil and water



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concentration of 2,4-D and the propionic ester of 2,4,5-T (2,4,5-TP), carried out in several areas of each province in 1974 and 1975, were used to define two categories of exposure: A, in which these compounds were detected by at least one measurement; and B, the areas where greatest contamination of water was recorded (2.4-D, 0.07-0.46 ppm; 2,4,5-TP, 0.10-0.19 ppm). Annual incidence rates (with 95% confidence intervals) for non-Hodgkin's lymphomas were elevated for men aged 17-74 years from 8.8 per 100,000 (CI = 7.4-10.4) for the region as a whole to 11.7 (CI = 6.5-19.3) for those living in category A areas, and to 18.2 (CI = 11.1-28.0) in area B. For women the corresponding figures were: 5.8 (CI = 4.7-7.0); 6.2 (CI = 2.8-11.8); and 7.4 (CI = 3.5-13.6). The rate ratio for men in category B areas was 2.2 (CI = 1.4-3.5). Annual incidence rates for Hodgkin's disease were 3.3 (CI = 2.4-4.4) in men and 1.5 (CI = 0.9-2.3) in women; for soft tissue sarcomas the corresponding rates were 1.8 (CI = 1.2-2.6) and 0.9 (CI = 0.5-1.4). Numbers for these latter two tumor types were too small to permit any conclusions to be drawn. The study is of potential value because it included objective measurements of environmental herbicides. However, no attempt was made to dissect out the contribution from occupational elements, such as the contribution to overall mortality of those subjects who were herbicide sprayers, neither was there any stratification for length of residence in the area. Furthermore, although on its face value this study suggests that phenoxy herbicides themselves are associated with non-Hodgkin's lymphomas, the measurements made may in actual fact reflect the activity of any accompanying dioxin contaminant, which was not determined.

Bertazzi (1991) has reviewed the latest status of the follow-up of subjects exposed to dioxins during the Seveso incident in Italy on July 10, 1976, when rupture of a safety valve in a plant producing trichlorophenol, released a cloud that deposited its contents over a several square mile area. TCDD was a prominent component of the deposited material. This episode is discussed further in Section V in connection with studies of tissue levels of TCDD. In the period ending 1986, cancer mortality findings for both males and females in Zone B, where dioxin levels were high but the population remained, were essentially negative, with ORs below unity. However, there were non-significant increases for soft tissue sarcoma (but only two cases), leukemia and melanoma among males. In



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females, there was an increase in biliary cancer, and a noticeable decrease in breast cancer incidence that approached statistical significance. This latter finding should be viewed in the context of the antiestrogenic action of dioxins, discussed in Section VI. It is necessary to emphasize that the breakdown into specific diseases left very few tumors in each category, making statistical evaluation unreliable. Further follow-up of this population is important, because this incident represents, perhaps, the best opportunity to correlate disease prevalence with actual measurements of environmental and tissue TCDD levels, and thus provide definitive estimates of the hazards from dioxins.

Several reviews and commentaries on the epidemiologic evidence for an association with cancer became available during 1991. The NIOSH study has been criticized for inclusion of data obtained by both "new" and "old" procedures, leading to internal inconsistencies (Collins *et al*. 1992). This claim has been refuted by Fingerhut *et al*. (1992), and on balance it would appear that the overall uniform review of data that took place in the preparation of the NIOSH report made it essentially a "new" study. Two reviews have examined the whole area. Gough (Gough 1991) has recently discussed the conflicting claims of health effects from occupational exposure to dioxin. He reviewed the inconsistent results of epidemiologic studies linking several cancers and exposure to dioxins, and pointed out that nearly all the positive associations relate to herbicide applicators. Workers in chemical plants, who have generally shown higher serum and adipose tissue levels of TCDD and a greater incidence of chloracne, both indicators of heavy exposure to dioxin, have not shown the expected major increase in cancer incidence. Tollefson (Tollefson 1991), examining the problem from the point of view of the 1,600-fold range in acceptable TCDD intakes set by regulatory agencies in the U.S., Canada and Europe, stressed that this reflected the degree of uncertainty in the scientific data. He considered the best studies were those in which actual exposures are emphasized, backed where possible by adipose tissue and serum levels. He felt that the studies of the participants in the NIOSH Dioxin Registry and the Seveso incident follow-up offer the best prospect of future definition of the human carcinogenic risk from dioxin. Taken together with the animal data, current information suggests that at most the



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calculated increased risk from TCDD exposure is moderate, bearing in mind high prevalent background cancer rates.

3. Studies in Animals

Dioxins, and especially TCDD, the one which has been studied most intensively, are generally recognized as trans-species, trans-strain, trans-sex, multi-site complete carcinogens. In the U.S. National Toxicology Program (NTP), TCDD is listed as an agent causing cancer in both mice and rats (Huff *et al.* 1991a); see also the analysis by Ashby and Tennant (1991). The original basis for this classification may be found in the feed study of Sprague-Dawley rats by Kociba *et al.* (1978) and the NTP's gavage study of rats and mice (National Toxicology Program 1982), both of which described the induction of liver tumors. Although subsequent work has extended these observations to other species, tumors, and routes of administration, these original studies have been widely applied as the standards for estimating human cancer risks from exposure to TCDD. The evidence from studies in experimental animals for the carcinogenicity of TCDD and related compounds has been reviewed recently by Huff *et al.* (1991b). Experimental data now indicates that TCDD produces neoplasms of the lung, oral and nasal cavities, thyroid, adrenal gland and liver in rats, of the liver, subcutaneous tissue, thyroid and thymus gland in mice, and in hamsters it induces squamous cell carcinomas of the facial skin. This review also included a detailed presentation of the Kociba and NTP studies. The Kociba study has also received attention and reevaluation, because of the significant changes that have taken place in the histopathological criteria used for classifying proliferative lesions of the liver since 1978. Two reevaluations were published in 1991 by the same investigating group, both based on reexamination of the original slides by an independent board of pathologists (the Pathology Working Group, which published its findings in 1990) using the current NTP criteria for hepatic lesions. Among their findings were two-thirds fewer malignant tumors in female rats, and the redefinition of many adenomas as hyperplasias. In the first of these reevaluations, the no-observed-adverse-effect level for hepatocellular carcinomas was calculated as 0.01 rather than 0.001 $\mu$g/kg/day, as determined in the original study. This new estimate was applied to the task of deriving

risk-specific doses (RsDs) for humans, using body weight rather than surface area as the basis for scaling rodent data to humans because of the implications of a receptor-based mode of action. For the standard linearized multistage model, the RsD for a $10^{-6}$ upper bound (95% confidence) lifetime incremental cancer risk was calculated as 370 fg/kg/day for carcinomas, and 100 fg/kg/day for all hepatic tumors combined. These risks are 16-fold lower than those calculated from the original Kociba data (Keenan *et al.* 1991). In the second paper, the data were reviewed using a stochastic two-stage, biologically-based model of carcinogenesis, the Moolgavkar-Venzon-Knudson model, rather than the linearized multistage model (Paustenbach *et al.* 1991). When this model was applied to data which had been adjusted to current pathologic criteria, the RsD for hepatocellular carcinoma soared to 25,000 fg/kg/day, although it remained at a comparable figure of 80 fg/kg/day for hepatocellular carcinomas and adenomas combined. When applied to the unadjusted Kociba findings, this model predicted RsDs for hepatocellular carcinoma and of carcinomas plus adenomas of 150 and 10 fg/kg/day, respectively, close to the values of 130 and 35 based on the linearized multistage model. These reanalyses do provide a toxicologic basis for reevaluating the estimates of carcinogenic risk to humans used by regulatory agencies, but do not negate the carcinogenic potential of dioxins.

Several of the reports that became available during 1991 in the area of dioxin carcinogenicity described studies using various surrogate measures or intermediate endpoints of carcinogenesis. Such markers are widely recognized as being closely associated with eventual malignant transformation, and offer the significant advantage of permitting evaluation of carcinogenic potential in much less time than is required for conventional carcinogenesis studies. In these studies, TCDD served in most cases as a standard reference for promoting activity. For example, Massa *et al.* (1991) described a host-mediated *in vivo/in vitro* assay of peritoneal macrophage transformation to demonstrate the carcinogenicity of TCDD in mice. Macrophages were harvested from control and treated mice and cultured for 5-6 days on soft agar, after which time normal and transformed cells could be distinguished. Carcinogenic potential was expressed as an index based on the frequency of clone sizes of defined classes; the test was positive at least at the 5% significance level by the *t*-test. TCDD alone exhibited a concentration-



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dependent carcinogenic potential, while a cocarcinogenic effect in combination with phenytoin, was only seen when the two compounds were applied together. Dragan *et al.* (1991) described an initiation-promotion assay in rat liver that followed the activity of four enzymes (placental glutathione-*S*-transferase (PGST); γ-glutamyltranspeptidase (GGT); canalicular ATPase; and glucose-6-phosphatase) in altered hepatic foci. TCDD was an effective promoter when used with diethylnitrosamine, and 100% of the altered foci were scored by the combination of PGST and GGT together. A number of polychlorinated dibenzo-*p*-dioxins and dibenzofurans were compared in an altered hepatic foci assay, to determine their relative promoting activity in combination with the initiator diethylnitrosamine when administered to Sprague-Dawley rats (Waern *et al.* 1991). While the pentachlorodioxin analog was of similar activity to TCDD, the furans had only a tenth of the activity, but showed more prolonged tissue retention. Lucier *et al.* (1991) studied the female sex-dependence of hepatocarcinogenicity in Sprague-Dawley rats, by following altered hepatic foci in a two stage model with initiation by diethylnitrosamine. The percentage of the liver occupied by GGT-positive foci was 0.37 in normal versus 0.08 in ovariectomized rats; similar data were obtained for PGST-positive foci. In addition, proliferative indices obtained by the bromodeoxyuridine technique, indicated that cell division was enhanced by carcinogen treatment of normal, but not of ovariectomized rats. These differences were seen in the absence of any effect of ovariectomy on the distribution of TCDD, or its Ah receptor-dependent induction of cytochrome P450. This latter finding adds emphasis to the caution expressed by Silbergeld (1991) that more information is needed about the intervention of dioxins in such functions as gene expression, immune surveillance and endocrine regulation, before a complete and definitive reevaluation of the overall risk assessment for these compounds can be made.

Finally, in connection with the major herbicidal components of Agent Orange, a case-control study of canine malignant lymphomas in dogs, associated the occurrence of the tumor with the use of 2,4-D by their owners (Hayes *et al.* 1991). A total of 491 cases were compared with 466 nontumor and 479 tumor controls, and the odds ratio (OR) was significantly elevated to 1.3 in those whose owners applied the herbicide, or employed a lawn service to do so, more frequently. The OR was about 2 in dogs whose



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owners carried out four or more applications of 2,4-D themselves every year. Another report, also described in Section IV, indicated that exposure to Tordon 202C, a mixture of 200 g of 2,4-D and 12 g of picloram per liter, raised the incidence but not the size of adenomas in female CD-1 mice induced with urethan (Adams *et al.* 1991). The data in these two reports support claims of a carcinogenic effect of 2,4-D made on the basis of agricultural exposure studies in humans, although in the earlier of the human studies a contribution to the overall effect from the higher levels of contaminating dioxins then prevalent is highly likely. In marked contrast to 2,4-D, chronic administration of 2,4,5-T to MRC-Wistar rats (600 mg/kg diet) was not carcinogenic, neither did it affect in any way the carcinogenicity of diethylnitrosamine (Mirvish *et al.* 1991).



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## C. Genetic Effects

No studies specifically associating phenoxy herbicides or their dioxin contaminants with human genotoxicity became available during 1991. One report described statistically significant elevations in the incidences of chromosome aberrations and sister chromatid exchanges in lymphocytes from 32 healthy individuals working in the flower industry, who were exposed to 48 insecticides, fungicides and herbicides, including 2,4-D, and 32 patients with bladder cancer and similar occupational exposure, compared with 31 normal controls (DeFerrari *et al.* 1991). However, without information on the actual individual usage of the various compounds by the subjects, this study, while of interest from the point of view of occupational hazard assessment, is of no value for the purposes of this *Review*.

While there have been some conflicting claims in the literature regarding the mutagenicity of TCDD , the bulk of the evidence does not support such an activity (Fahrig 1991). This forms the basis for the negative listing given to the compound by the U.S. National Toxicology Program (Huff *et al.* 1991). Two studies reported in 1991 lend further support to this conclusion. In the course of assessing the mutagenic potential of fish from the Pigeon River, Tennessee, which are contaminated with TCDD and other compounds, Blevins (1991) reported that pure TCDD was not mutagenic for strains TA97, TA98 and TA100 in the *Salmonella typhimurium* assay at the highest non-toxic level of 825 ng/ml of top agar; above this concentration it was highly toxic for all three strains. Acidic extracts of the fish were mutagenic, but since the maximum level of TCDD in the fish was 117 $\mu$g/kg of wet weight, it was evident that other contaminants, individually or in combination, were responsible for this activity. In the L5178Y tk+/tk- mouse-lymphoma cell forward mutation assay, in which the cells were exposed to TCDD at 1 $\mu$g/kg (the solubility limit) for 4 hours, and then cultured for 2 days before plating in soft agar with or without trifluorothymidine (3 $\mu$g/ml), the dioxin exhibited no toxic or mutagenic effects. This was true in the presence or absence of an enzyme activation system (McGregor *et al.* 1991).

In contrast to the apparent absence of mutagenic activity in the case of TCDD, the phenoxy herbicide 2,4-D showed both mutagenic and cytotoxic effects on V79 hamster



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fibroblast cells in culture at concentrations of 10 $\mu$g/ml and greater. Structural changes in the chromosomes and chromatin, as well as altered cell cycle characteristics and mitotic activity were evident in shallot root tip cells in culture exposed to 2,4-D (Pavlica *et al.* 1991).



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## D. Reproductive and Teratological Effects

Earlier volumes of the *Review* have documented the work undertaken to evaluate both the reproductive effects and the teratologic potential of the dioxins and related compounds. Most of the studies which have been carried out in humans have been subject to methodological problems such as recall bias, and various confounding factors which have served to prevent the studies from reaching definitive conclusions. Among the experimental systems that have been used to evaluate this activity have been the induction of cleft palate and hydronephrosis in mice at doses that are not overtly toxic to the dams or offspring. A few scattered studies concerning the reproductive toxicity and teratologic effects of 2,4-dichlorophenoxyacetic acid (2,4-D) and dioxin became available during 1991. Couture *et al.* (1990) reviewed studies related to this topic, and discussed the issues of species and organ specificity, and the possible mechanisms responsible for the observed teratologic effects.

### 1. Human studies

Lerda and Rizzi (1991) studied the reproductive function of 32 male farm sprayers who were occupationally exposed to 2,4-D. The level of exposure was estimated by measuring the concentration of 2,4-D in urine samples (mean level 9.02 mg/l). Sperm samples obtained from exposed and control subjects were analyzed for asthenospermia, necrospermia, and teratospermia. Exposed workers exhibited a significant degree of asthenospermia (49.0 millions/ml), necrospermia (37.1% alive), lowered motility (24.8% motile) and teratospermia (72.9% abnormal). Corresponding values for the control group were 101.6 millions/ml, 82.9% alive, 70.4% motile and 33.4% abnormal, respectively. Following a three month interval, asthenospermia, mobility and necrospermia had improved in the exposed group, but teratospermia persisted. The authors concluded that 2,4-D at these exposure levels damaged the germinal epithelium resulting in altered spermatogenesis.

The effects of TCDD on human, mouse and rat embryonic palatal shelves in organ culture were studied by Abbott and Birnbaum (1991). Palates were cultured in the presence of various levels of TCDD to determine points at which cytotoxicity and altered

differentiation of medial palatal cells occurred. Cytotoxicity, as detected by transmission electron microscopy, was observed at $10^{-10}$ M TCDD in mouse tissue, but at $10^{-7}$ M in rat and human cultures. Similarly, it was found that altered differentiation of medial palatal cells occurred at $5 \times 10^{-11}$ M TCDD in mouse, but at $10^{-8}$ M in rat and human preparations. The data suggest that the sensitivity of humans to TCDD is similar to that of rats, and that high levels of TCDD would be necessary to alter human palatal shelf differentiation. This study also examined the effects of exposure to TCDD on EGF, TGF-$\beta$1, TGF-$\beta$2 and TGF-$\alpha$ receptors. At higher TCDD doses, medial epithelial levels of EGF were increased, nasal epithelial levels of TGF-$\beta$1 and TGF-$\beta$2 were decreased and TGF-$\alpha$ was decreased in all epithelial regions. TCDD-induced changes in growth factor expression may be at least partially responsible for alterations in normal palatogenesis.

2. Animal studies

The effect of TCDD on rat testes was studied by Rune *et al.* (1991). Rat testes were injected with a single dose of TCDD (0.3-25 $\mu$g/kg body weight) and examined seven days later by light and electron microscopy. Exposed testes exhibited decreased intercellular contacts, sloughing of premature spermatids, and increase in necrotic germ cells. Cytoplasmic vacuolization, with increases in lipid droplets and phagolysosomes was also observed in exposed Sertoli cells. No spermatogenic stage-specific sensitivity to TCDD was found. TCDD produced a decrease in 3 $\beta$- and 17 $\beta$-hydroxysteroid dehydrogenase activity at 1 $\mu$g/kg body weight, and morphological changes in the germinal epithelium at 3 $\mu$g/kg body weight.

Chahoud *et al.* (1991) examined whether paternal exposure to TCDD could produce abnormalities in the progeny. Male rats were exposed to TCDD weekly for 10 weeks prior to mating, and 12 weeks during the actual mating period. No change was noted in the number of implantations, the number of fetuses per litter, the resorption rate or fetal weights. No gross abnormalities were observed. However, a slightly increased rate of still births was discovered, and incomplete ossification of fingers and ossa zygomatica was observed in the offspring. The authors concluded that the data do not demonstrate any "biologically significant paternally-mediated developmental toxicity". On

the other hand, maternal exposure to TCDD (acute doses of 0.3 or 12 μg/kg by gavage on gestation day 6) induced hydronephrosis in the offspring of C57BL/6N mice (Couture-Haws *et al.* 1991). Total incidence of the lesions was 69.50 ± 9.90% at the low, and 72.18 ± 6.11% at the high TCDD doses. Administration of the dioxin to lactating dams led to essentially the same incidence of hydronephrosis in the nurselings (70.15 ± 7.77 and 64.70 ± 8.32%, respectively), and exacerbated the condition persisting from prior exposure *in utero*, giving values of 79.52 ± 7.98 and 88.64 ± 5.30%, for the double exposure at the high and low dosages, respectively.

The teratogenic effects of brominated dioxins (TBDD) and furans (TBDF) were studied by Birnbaum *et al.* (1991). Pregnant mice were injected with 0-4,000 μg/kg of the individual TBDD or TBDF congeners. Maternal liver weight increased at all dose levels without evidence of toxicity, and brominated dioxins and furans produced hydronephrosis at doses below those at which they induced cleft palate. The incidence of cleft palate fit a curve with a common slope for all four brominated compounds and TCDD, indicating that a common mechanism of action was involved in all cases. Increased fetal mortality was observed at 500 μg TBDF/kg. The authors concluded that bromination decreased the teratogenic activity of TBDD relative to TCDD but increased the potency of TBDF relative to TCDF. Therefore, the brominated compounds produce the same teratogenic alterations as their chlorinated congeners but with altered potency. Yasuda *et al.* (1991) discovered that exencephalic mouse fetuses were resistant to cleft palate induction by TCDD. Pregnant mice were given one of two dosage regimens of $CdCl_2$ in order to produce exencephalic embryos. Dams were then given 40 μg TCDD/kg on Day 12.5, and fetuses were examined on Day 18.5. At one dose regimen, 76% of live fetuses were exencephalic and did not develop cleft palate. All remaining live fetuses without exencephaly had cleft palate. The other dose regimen produced similar results, demonstrating resistance to TCDD-induced cleft palate in exencephalic mice.

Reproductive toxicity related to environmental exposure to TCDD was studied in several different species. Mink and otter populations were reduced relative to their proximity to contaminated water sources in the Great Lakes region (Wren 1991). This reduction was attributed to consumption of contaminated fish by mink and otters.



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Additional research is needed to strengthen the association between chemicals and reductions in these animal population. Bishop *et al.* (1991) studied the effects of dioxins, furans, PCBs and other organochlorine pesticides on turtle eggs. Eggs were examined for hatching success and the presence of deformities. The eggs obtained from highly contaminated locales contained higher pesticide residues and were more poorly developed than those obtained from less polluted areas. Additional controlled studies are needed to confirm these observations.

The effects of Baltic herring oil and Icelandic cod liver oil on embryos of the Japanese medaka were studied by Cooper *et al.* (1991). A commercial Icelandic cod liver oil and fish oil derived from wild Baltic herring collected from the Gulf of Bothnia, Sweden, were analyzed for specific dioxin and furan isomers. Both types of oil contained similar isomers, but the herring oil contained almost twice the concentration of dioxins and furans as the Icelandic cod liver oil. This was attributed to the higher level of pollution in the Gulf of Bothnia. The oils were tested for embryotoxicity in Japanese medaka using an embryo larval assay. Oil derived from Baltic herring produced hemorrhage, cardiac effects, tissue necrosis and lethality (30-90%) in exposed medaka. These lesions were not observed in embryos exposed to the Icelandic cod liver oil or control corn oil. The author cautioned that the use of contaminated fish oils in hatchery feed may be responsible for the poor viability of Swedish hatchery salmon. This theory is supported by the presence of lesions in hatchery-reared fish which resemble those observed in medaka following exposure to dioxin/furan-contaminated oil.

Recent articles by Ames and Gold (1991) and Myers and Colborn (1991) may be consulted for a review and discussion of the risk posed by dioxin with regard to reproductive toxicity and teratology.



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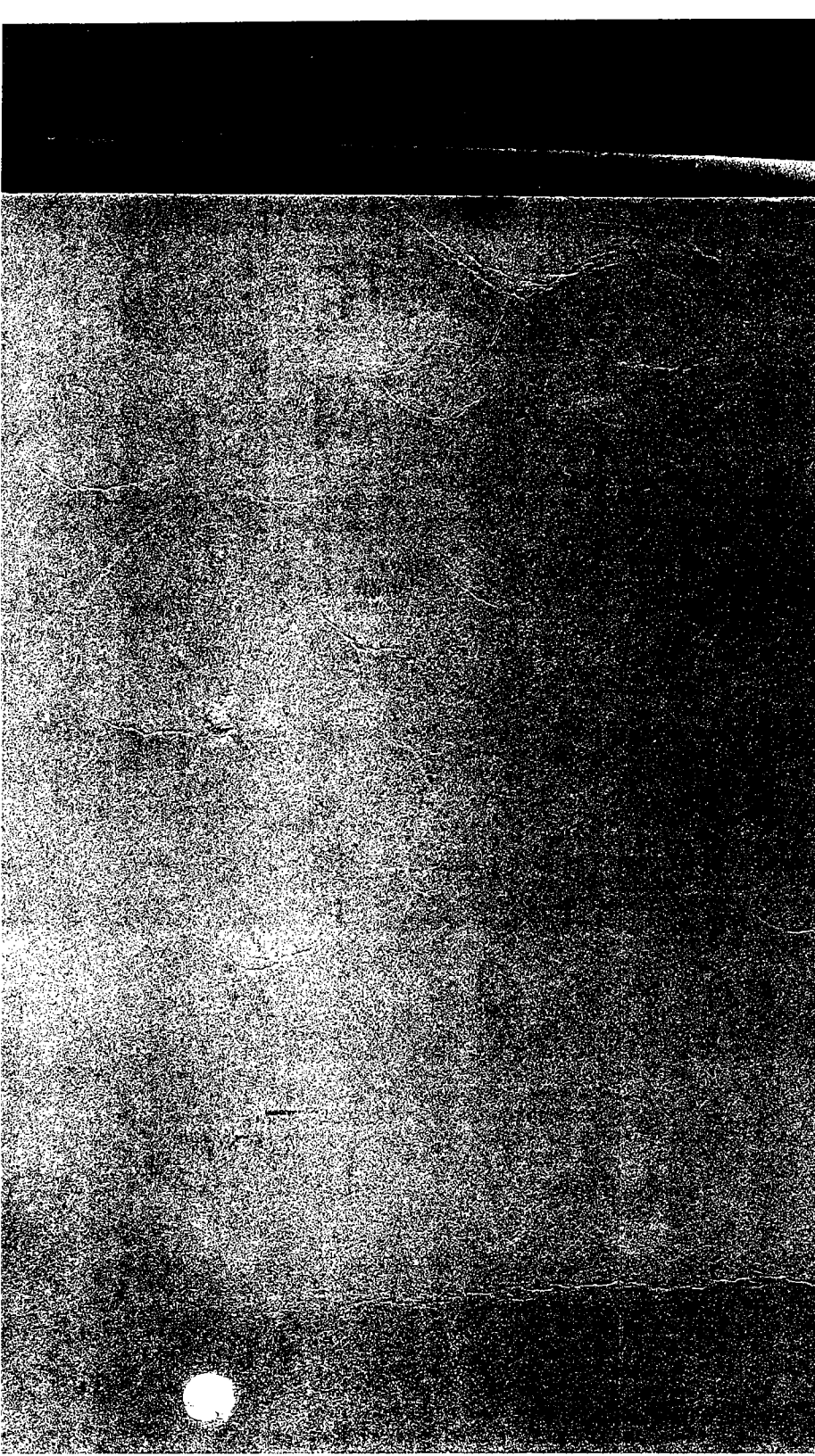
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## E. Immunological Sequelae

There is a general consensus that 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) impacts on the functioning of the immune system. Studies have consistently demonstrated that low levels of TCDD affect various lymphocytic subsets. However, it is difficult to compare directly the various study results due to the diversity of immunological protocols employed. Changes in specific study parameters may produce conflicting results. These parameters include the species employed, age at the time of exposure, presentation of the antigen relative to TCDD exposure (before, after, or simultaneous), and the level and duration of exposure. Two reviews were published in 1991 which discuss the role of TCDD in immunosuppression. Holsapple *et al.* (1991b) reviewed alterations in the immune system produced by exposure to dioxin, including effects on specific indicators of immune function, innate and acquired immunity, lymphocytic homing, and immune function in exposed human populations. In a separate article, Holsapple *et al.* (1991a) reviewed the potential mechanisms for TCDD-induced immunosuppression, including the role of the Ah receptor, phosphorylation, calcium and hormones.

### 1. Human and Primate Studies

The 1987 Air Force Health Study (Roegner *et al.* 1991) found no clinically significant alterations of immune status related to current or initial dioxin levels in Ranch Hands. There was, however, a significant association between the initial dioxin level and increased IgA levels in Ranch Hands. Also, in the current report, a composite skin-test analysis did not demonstrate any dioxin-related effect on delayed hypersensitivity skin-test responses (DHR). The authors speculated that the abnormal DHR results reported in the initial analysis of the 1987 follow-up may have been unrelated to dioxin.

Neubert *et al.* (1991b) studied the effects of TCDD on lymphocytes isolated from humans and from a non-human primate (*Callithrix jacchus*, marmoset monkey). When lymphocytes from either species were cultured in the presence of TCDD and mitogen, a pronounced decrease in the CD4 (helper/inducer) and CD20+ (B1) lymphocytic subsets was observed. The percentage of CD8+ (cytotoxic/suppressor) cells was increased in most experiments, but the CD4+CD45+ (suppressor/inducer) population was apparently



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not significantly affected. This study is notable in that it describes the lowest TCDD concentration, 2.5 fg/ml, yet reported to produce a biological effect. Similar results were obtained in studies with human whole blood, but much higher concentrations of TCDD (250 fg/ml) were required to produce an effect, and the suppressor/inducer population was reduced. Similar results were reported by Neubert *et al.* (1991a) when monkeys were treated *in vivo* with a single dose of TCDD. However, Neubert noted that a multiple dose regimen produced conflicting results in the CD4 subset at high versus low exposure levels. He cautioned that observations at higher doses should not be extrapolated to very low exposures. Hong (1991) studied the effects of prolonged TCDD exposure on rhesus monkeys and their offspring. A decrease in helper (C4+) cells and an increase in cytotoxic cells were observed in the mothers, but lymphocytic populations were unaltered in the offspring. None of the animals exhibited any clinical evidence of immune suppression.

Waithe *et al.* (1991) characterized a high-affinity Ah receptor in a human B-lymphoblastoid cell line (BCR-5). A complete regulatory mechanism for the Ah-receptor - mediated induction of cytochrome P450IA1 was demonstrated in this cell line. The maximum concentration of Ah-receptor in the cytosol was 200 fmol/mg protein. This concentration, which is greater than other studies have described for peripheral leukocytes, may be correlated with the blastoid nature of this particular cell line. This enhanced concentration of receptors in blastoid cells lends support to the theory that dioxins primarily effect precursor or immature lymphocytes (Holsapple *et al.* 1991b). Lorenzen and Okey (1991) described the presence of a functional Ah receptor in human tonsils and suggested that tonsil might be an appropriate model for mechanistic studies of aromatic hydrocarbon-induced immunotoxicity.

Two studies were published in 1991 that examined the potential association between dioxins/furans and HIV infection. Schecter *et al.* (1991) examined the dioxin levels in pooled blood samples from five groups of individuals. These groups included male homosexual AIDS patients with opportunistic infections (n = 100), male homosexual AIDS patients with Kaposi's sarcoma (n = 100), asymptomatic HIV-1 positive male homosexual patients (n = 100), asymptomatic HIV-1 positive intravenous drug users (n



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= 50), and blood bank controls (n = 100). Toxicity equivalents (TEQ), a measure of the total toxicity of various PCDD and PCDF congeners, were determined for each group according to the International Dioxin Toxic Equivalent Factors method. The total TEQs for HIV-1 positive asymptomatic intravenous drug users and for the Kaposi's sarcoma group did not differ significantly from the control group. The total TEQ for HIV-1 positive asymptomatic homosexual patients (33.3) was significantly less than that of the control group (42). However, AIDS patients with opportunistic infections had a total TEQ of 52.2, a statistically significant elevation compared to the total TEQ of the control population. The authors speculate that HIV-1 positive individuals with a higher dioxin body burden may be more susceptible to opportunistic infections than those with low to normal dioxin levels. This increased susceptibility may be the result of TCDD-induced immune suppression. Definitive studies of individual patients using age-, race- and sex-matched controls are needed to confirm these preliminary findings. The role of TCDD as a possible activator of HIV infection was studied by Pokrovsky *et al.* (1991). The effects of 10-150 Nm TCDD on HIV reproduction in lymphoid cell cultures was examined. TCDD did not produce toxic effects on MT-4 cells at this concentration. However, HIV viral production, as evaluated by viral antigen determination and reverse transcriptase activity, was increased in MT-4 cells after exposure to TCDD. The phenomenon may be related to TCDD bound to the Ah receptor since removal of free TCDD did not alter the activation of HIV. The authors speculate that TCDD may alter HIV regulatory gene expression. The activation of viral production could also result from actions on transcription, processing, RNA stability, translation or protein stability.

2. Animal Studies

Early immunotoxicity studies demonstrated that thymic involution occurred as a consequence of TCDD exposure. The nature of thymic involution has been a source of some controversy. Some investigators have suggested that TCDD directly affects thymic lymphocytes, while others believe that it is the thymic epithelia which sustain damage. Several 1991 studies addressed this issue.

Korte *et al.* (1991b) injected pregnant rats with TCDD (0.3 μg/kg body weight) and demonstrated that *in utero* exposure to TCDD caused thymic involution in offspring. Andersson *et al.* (1991) studied the effects of coplanar polychlorinated biphenyls and TCDD on thymus organ cultures from fetal mice. Lymphoid development was inhibited in the presence of these compounds. These workers also found a decreased number of lymphoid cells in thymuses isolated from chicks which had been injected with TCDD *in ovo.*

Lundberg (1991) injected mice with 50 μg/kg body weight of TCDD and examined the thymuses on days 1,2,4 and 8 after exposure. Cell proliferation within the thymus was decreased by 50% and cell number by 20%, on the second day of exposure. Proliferation increased on Day 3 but cell number continued to decrease throughout the 8-day observation period. Lymphocytic subpopulation analysis revealed that the immature precursor lymphocytes CD4+CD8+ (double positive) and CD4-CD8- (double negative) cells continued to decrease for twenty days after exposure, but mature helper/inducer (CD4+) and suppressor/cytotoxic (CD8+) cells were only marginally affected by TCDD. The author suggested that TCDD may induce thymic atrophy by inhibiting cell proliferation and disturbing the lymphocytic selection/differentiation process. However, the author believed that a direct action of TCDD on thymocytes is unlikely, since cell number did not decrease immediately, and the CD4+ and CD8+ subsets were only marginally affected. Additional evidence that TCDD inhibits normal thymocyte maturation was presented by Holladay *et al.* (1991). Pregnant mice were treated with TCDD (1.5 or 3.0 μg/kg/day) on gestational days 6-14. TCDD-exposed offspring exhibited severe thymic atrophy and cellular depletion when examined pre- or post-natally. No change in cellular distribution was found, but distinctive alterations in thymocyte subsets were discovered. Immature thymocyte populations (CD4-8- and CD4-8+) were increased with TCDD-exposure, but thymocytes further along the differentiation pathway (CD4+8+) were decreased in number. Therefore, the authors suggest that TCDD interferes with normal thymocyte differentiation.

Van Loveren *et al.* (1991) demonstrated the reversibility of TCDD-induced thymic atrophy. Male rats were exposed to 50 μg of TCDD/kg body weight. The right thymus



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lobes from treated and control rats were transplanted to 9-week-old rats and the vascular connections were restored. The left thymus lobes were used to determine the number of lymphocytes present at the time of transplantation. The thymus tissue of untreated rats exhibited normal histology, but TCDD-treated animals had a severe depletion of cortical elements. Recipient animals were sacrificed twenty days after transplantation and the grafted thymus lobes were examined. A full restoration of thymic size and architecture had occurred in the interim, and the grafts exhibited normal cellular subset composition. The authors conclude that the epithelial component of the thymus sustained reversible TCDD-induced damage, and restoration of normal morphology was accompanied by an influx and expansion of new progenitor cells from the recipient's bone marrow. These three studies by Lundberg, Holladay and Van Loveren support the contention that TCDD inhibits lymphocyte differentiation indirectly by altering the cellular microenvironment.

The mechanisms responsible for TCDD-induced thymic involution are unclear. Morris *et al.* (1991d) designed a study to determine the role of the Ah receptor in thymic involution. They compared Ah-high-responder (B6C3F1) and Ah-low responder (DBA/2) strains of mice which were administered acute (4.2, 14 or 42 $\mu$g/kg by oral gavage) and subchronic (0.3, 1.0, or 3.0 $\mu$g/kg by oral gavage for 14 days) doses of TCDD. B6C3F1 mice exhibited an abrupt, dose-related decrease in thymus and spleen weights with acute exposure, whereas DBA/2 mice exhibited a decrease in thymus and spleen weights only at the highest acute dose of TCDD. This would tend to support an Ah-receptor-related mechanism for thymic involution. However, conflicting results were obtained when the subchronic dosage regimen was used. When both strains of mice were exposed to TCDD over a 14-day period, thymic involution in the Ah-low responder strain was greater than that exhibited by the Ah-high responder strain with either acute or subchronic dosing (68% versus 56% decrease after a total dose of 42 $\mu$g/kg). This suggests that multiple mechanisms may be involved in TCDD-induced thymic involution, and that the conditions of exposure may alter the toxic effects.

The effects of TCDD on peripheral lymphocytes were also examined by several investigators in 1991. Analysis of subpopulations of lymphocytes following TCDD exposure have produced a number of theories concerning the mechanism(s) responsible



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for TCDD-induced immunosuppression. Several investigators have found a deficit in the T-helper cell population as a consequence of TCDD exposure. Tomar and Kerkvliet (1991) evaluated the role of T-helper cells in the TCDD-induced suppression of the antibody response. Mice were primed with the T-cell-dependent antigen SRBC (sheep red blood cells) and simultaneously exposed to TCDD. When spleen cells from these mice were cultured with a hapten-antigen (TNP-SRBC), a reduced anti-hapten response was observed compared to controls. To confirm that T-helper cells were responsible for the decreased antibody response, unexposed B cells were incubated with T cells primed by simultaneous exposure to the carrier hapten and TCDD. The anti-hapten response was profoundly suppressed, and removal of the suppressor cell population did not increase this response. These results indicate a reduced T-helper activity in TCDD-primed T cells as opposed to the generation of suppressor cells.

Lundberg *et al.* (1991) used the popliteal lymph node assay to study the effects of TCDD on the immune response to the T-dependent antigen, ovalbumin. Ovalbumin was injected into the hind foot pads of mice 4 days after TCDD exposure. Exposed animals exhibited a decreased cell number in lymph nodes, a reduced population of antigen-specific B cells, and an impairment of T cell function in the DTH (delayed type hypersensitivity) assay. Isolated B cells retained the ability to produce antibody and their proliferation was not affected in response to an in vivo secondary immunization. Antigen-presenting cells (APC) were also relatively unaffected. The results of this and the previous study suggests that TCDD exposure alters T cell function which then leads to impaired B cell activation. The popliteal lymph node assay was also used by Korte *et al.* (1991a) to study TCDD-induced immunosuppression in rats. No immunosuppressive response to human RBC antigen was demonstrable with TCDD exposures of up to 600 ng/kg body weight. The authors suggested that this assay is not sensitive enough to detect small immunotoxic effects and that it produces a wide variability in the data. This conflicts with the clear response described in the previous study by Lundberg *et al.* (1991). These two studies differed, however, in several experimental parameters, such as the species used (mice, rats), the time interval between antigen exposure and assay (4 days, 7 days), and the level of exposure (50 $\mu$g/kg vs. 0.06-600 ng/kg). Couture *et al.* (1990) reviewed



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differences in sensitivity to TCDD with respect to developmental toxicity and pointed out that rats are 200-fold less sensitive to the toxic effects of TCDD than mice. Perhaps a differential species sensitivity to TCDD could account for the lack of response observed in rats with this assay, and therefore for the disparate results between the two studies.

Morris and Holsapple (1991a) have also examined the TCDD-induced suppression of the T-dependent antibody response to SRBC. Their results suggest a mechanism which differs from that proposed in the previous studies, one involving the direct activation by TCDD of resting B cells. Spleen-derived resting B cells, which had not been previously exposed to antigen, were exposed to TCDD *in vitro*. An increase in total IgM occurred on day 7, but it was noted that only certain lots of serum could support this *in vitro* B cell activation. In a comparable study, SRBC-sensitized and unsensitized mice were exposed to TCDD for 5 days. Isolated splenic B cells from unsensitized mice again exhibited a serum-dependent proliferation. SRBC-sensitized mice had a complete loss of their splenic B cell population, indicating movement of these cells to the blastogenic stage. T-helper cells were apparently not required, since B cells could be activated by TCDD without antigen sensitization. The activation was dependent on the presence of serum *in vitro*, and appeared to be intensified by the presence of antigen *in vivo*. The evidence implicates the direct activation of B cells by TCDD.

In an extension of this work, Morris and Holsapple (1991b) demonstrated that, in the absence of serum, $\gamma$-IFN (gamma interferon) could potentiate the proliferation of resting B cells and IL-2 (interleukin 2) inhibited this co-stimulatory activity. TCDD, IL-2 and $\gamma$-IFN alone had no effect on B cell proliferation. These data demonstrate a direct interaction of these compounds with B cells, and supports the role of cytokines in modulating the immune response to TCDD. The modulation of B cell activation by serum factors was examined in additional studies by Morris *et al.* (1991c). TCDD mirrored the action of *Staphylococcus aureus* Cowan Strain I (SAC), a polyclonal B cell activator. Both TCDD and SAC suppressed the T-dependent antibody response to SRBC in a serum-dependent manner. In the absence of serum, TCDD and SAC produced an increase in B cell activation. The authors postulated that TCDD produces an "activation-like" signal for the B cell, and the presence or absence of serum indirectly modulates this action.



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Davis and Safe (1991) published additional evidence for the existence of multiple mechanisms in TCDD-induced immune suppression. α-Naphthoflavone is considered to have moderate affinity for the Ah receptor and to have weak agonist activity. TCDD, a strong Ah receptor agonist, and 1,3,7,8-TCDF (tetrachlorodibenzofuran), a weak Ah receptor agonist, have comparable immunosuppressive potencies. Cotreatment of mouse spleen cultures with 20 Mm TCDD and 10 μM α-naphthoflavone significantly inhibited the immunosuppressive activity of TCDD. A similar inhibition of immunosuppressive activity was observed by cotreatment of spleen cultures with 1,3,7,8-TCDF and α-naphthoflavone. α-Naphthoflavone was equally effective in modifying the immunosuppressive activity of both a strong (TCDD) and a weak (TCDF) Ah-receptor agonist. The evidence, therefore, does not support a role for the Ah receptor in mediating the immunosuppressive action of these compounds.

Morris *et al.* (1991d) and Holsapple *et al.* (1991c) have also recently published data which support the operation of multiple mechanisms in the immune suppression induced by dioxin. Ah-high-responder (B6C3F1) and low-responder (DBA/2) mice were treated with either acute or subchronic doses of TCDD. Subchronic exposure to TCDD (0.1, 0.3, 1.0, or 3.0 μg/kg/day for 14 days) of Ah-low-responder mice increased the suppression of humoral immunity 10-fold over that produced by acute exposures to the same cumulative TCDD dose. Thymic involution in the Ah-low-responders was also enhanced with subchronic exposure and exhibited a higher degree of atrophy than was observed in the Ah-high-responder line . This evidence suggests that whereas the Ah receptor may play a major role in the immunosuppression produced by a single exposure to high doses of TCDD, it plays only a minimal role in immunosuppression produced by subchronic exposure to much lower doses. TCDD may suppress humoral immunity through multiple mechanisms.

Clark *et al.* (1991) studied the role of tyrosine phosphorylation in TCDD-induced immunosuppression. Within minutes of TCDD exposure, an increase in membrane phosphorylation was observed. Two major, previously-identified, tyrosine-specific kinases (Mr 54,000 and 61,000 proteins) of murine B lymphocytes exhibited a TCDD-dose-dependent increase in autophosphorylation. TCDD also increased the tyrosine-specific



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phosphorylation of two additional proteins (Mr 78,000 and 90,000). Phosphorylation also occurred on tyrosine residues of a synthetic exogenous substrate as early as 5 minutes after TCDD exposure. The protein synthesis inhibitors puromycin and cycloheximide reduced tyrosine phosphorylation by 32% and 90%, respectively, and the transcriptional inhibitor actinomycin D inhibited the response by 98%. This suggests that tyrosine phosphorylation is mediated partially by transcriptional events, and that *de novo* synthesis of new protein may occur. The authors demonstrated that the TCDD dose-response for phosphorylation was identical to that for the inhibition of antibody synthesis. Tyrosine kinase activity has been linked to lymphocyte maturation in several studies (Bombick *et al*. 1987; 1988). The cloning of the *hck* gene, which apparently codes for a tyrosine kinase associated with hematopoietic cell differentiation, supports the role of tyrosine kinases in lymphocytic differentiation (Quintrell *et al*. 1987; Ziegler *et al*. 1987). Previous reports have also linked TCDD to other activities which are associated with tyrosine kinase activity, such as the down-regulation of EGF receptors and an early increase in hepatic tyrosine-specific kinase activity.

In light of the complex findings of the studies described in this Section, continued investigation of TCDD-induced immune suppression, with emphasis on the possible role of multiple dose-dependent mechanisms, is certainly warranted. In attempting to extrapolate the findings in experimental animals to humans, several points must be considered. First, the type of effects that predominate, which involve both B and T cell function, as well as altered lymphocyte maturation, are likely to lead to generalized immunosuppression rather than lesions in a specific function. Ranch Handers and other exposed human populations should be followed up with this in mind. Second, there appear to be major differences in species sensitivity to TCDD, and it is not yet clear which animal model best approximates to humans. Finally, the apparent existence of different mechanisms operating under conditions of acute and chronic exposure, may mean that immune effects differ according to the type of exposure received. Chronic occupational exposures may yield a different pattern or intensity of effects from that observed after an acute episode such as the Seveso incident.



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## F. Neurobehavioral Effects and Appetite Suppression

A limited amount of new data on the neurobehavioral effects of the subject herbicides and TCDD became available during 1991. Although some follow-up information was published on Vietnam veterans and on the civilian group who suffered Yucheng disease in Taiwan, most reports dealt with the problems of appetite suppression and myotonia in animals.

### 1. Human Studies

The Air Force Health Study report by Roegner *et al.* (1991) sought to relate any neurobehavioral changes in the Ranch Hand cohort to current and estimated initial TCDD levels, on the basis of three models, details of which may be found in Section III A. Neurological assessment of the veterans was based on physical examination of cranial nerve function, peripheral neurologic status and central coordination processes. In contrast to earlier studies of Ranch Hand personnel, there was no evidence of any association between dioxin and increased incidence of benign essential tremor. Also, no significant findings were made with respect to peripheral neuropathies, although both animal and human occupational data has established that heavy exposure to TCDD can give rise to such disorders, as for example in the Seveso incident in Italy in 1976, when TCDD was released in quantity (Bertazzi 1991). On the other hand, in agreement with previous reports, there was a significant association between dioxin and the results of the CNS index, a composite of coordination, tremor and gait, on the basis of model 3 (only current dioxin levels in Ranch Handers and the cohort of comparisons). The adjusted model 1 (initial dioxin estimated by first order kinetics, Ranch Handers only) data were significant for the CNS index, and marginally significant for coordination alone; when the maximal assumption was used (all Ranch Handers with TCDD levels > 5 ppt) the CNS index results were only marginally significant.

Psychological assessment of the veterans relied on reported sleep disorders, verified psychological disorders, and two clinical psychology tests: the Symptom Check List-90-Revised (SCL-90-R) and the Millon Clinical Multiaxial Inventory (MCMI). SCL-90-R is a list of 90 physical and mental symptoms that provide a measure of health-related



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concerns, anxiety, depression and emotional discomfort, while the MCMI supplements this assessment in the areas of depression, anxiety and hypochondriasis, but in addition, also provides a screen for personality patterns and disorders, and the major psychiatric syndromes. The unadjusted SCL-90-R variables often were associated significantly with dioxin, but when an adjustment for covariates was made they generally became non-significant. This was particularly true of the education covariate, which was correlated with dioxin levels because of the relationship of each with military rank and occupation; as will be described in Section V, rank was correlated with dioxin. Of the 20 MCMI results, 9 were significant under the minimal or maximal assumptions for initial TCDD levels; schizoid, avoidant, dependent, schizotypal, somatoform, psychotic thinking and psychotic depression scores showed a positive association, and histrionic and narcissistic scores a negative. This association held for most variables using model 2 analysis of Ranch Handers whose service in Vietnam had taken place more than 18.6 years before, while for model 3, Ranch Handers in the high current dioxin group had higher mean schizoid and schizotypal, and lower mean histrionic scores than Comparisons with background TCDD. Interpretation of these results is difficult because of the conflict between the verified psychological disorder questionnaire and the SCL-90-R, with their essentially negative findings, on the one hand, and the MCMI scores, with many correlations, on the other. It is significant that dioxin correlated with the fewest MCMI scores on the basis of model 3, which makes no assumptions about either initial levels or the pharmacokinetics of TCDD, but only includes current levels of dioxin in the total Ranch Hand and Comparison cohorts; this probably represents the most rigorous test of any association. Furthermore, the authors of the report felt that substantial overlap in the construction of the test scales might contribute to many of the MCMI findings. Overall it would not appear that there is convincing evidence of a significant psychological deficit among veterans resulting from Vietnam-era exposure to dioxin.

In 1979, there was an episode of poisoning (Yucheng disease) involving over 2,000 people in Taiwan, associated with the consumption between May and October of that year of cooking oil contaminated with PCBs and their PCDF breakdown products. Further details of this event, and of studies undertaken to monitor the exposed population, may



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be found in Section V of this report, and in earlier volumes of the *Review*. Yu *et al.* (1987) studied 128 children born to women involved in this episode, and who thus had been exposed to the compounds either transplacentally or through contaminated breast milk. This survey was carried out in 1985, 6 years after the initial episode, and involved interviews with parents, neurological examinations for the categories of prewalkers and walkers (Perinatal Collaborative Study criteria of the U.S. National Institute of Neurological Diseases and Blindness), and standard cognitive tests. In order to remove the variability created by comparing groups of children of differing ages and developmental status, the developmental scores were adjusted by adding or subtracting to all scores of a given test, a constant chosen so as bring the means of the control group, over all time points, to 100. This was done, for example, for the Bayley scores and the WISC full and Stanford-Binet Iqs. Exposed children reached 32 of the 33 items used as milestones in the interviews with parents, at a later time than controls, with the differences reaching statistical significance in 9 at $p < 0.05$ and in a further 6 at $p < 0.1$. Neurologic evaluations indicated that exposed children were uniformly delayed at milestones occurring at 18 months of age or more, but not at earlier times. There was an overall impression of developmental or psychomotor delay in 12% of the exposed versus 2% of the control children, and of speech problems in 7% and 3% in these groups, respectively. Bayley mental development and psychomotor development indices were both delayed significantly compared with controls ($p < 0.05$). On an individual basis, delays tended to be more pronounced for physically smaller children, in those who had evidenced some physical signs of intoxication, and in those with a history of problems with nail growth. Those delayed at initial evaluation also tended to be delayed at the 6-, 12- and 18-month follow-ups. Among the 36 children in whom PCB levels in the blood were determined, children with detectable concentrations tended to have lower developmental scores. Although they were not detected in the children, PCDFs which are more toxic, were measured in adults, and might have played a role in delayed development.



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2. Studies in Animals

Most of the studies carried out in animals have addressed the hypophagia and wasting syndrome characteristic of acute TCDD intoxication. One other characteristic is the extreme variation in sensitivity to dioxin, and Tuomisto and Pohjanvirta (1991a) have reviewed their series of studies which employed two rat strains of widely different sensitivity to study the regulation of food intake. Han/Wistar (H/W) rats tolerate doses up to 3,000 μg/kg, whereas 20 μg/kg is lethal to Long-Evans (L-E) rats, yet the two strains behave essentially similarly in terms of the pharmacokinetics of TCDD, Ah receptor binding, induction of P450 and associated hepatic enzymes, and other endocrinologic and biochemical changes. Hepatocyte swelling and vacuole formation, appearance of multinucleated cells, and infiltration of the liver by inflammatory cells, seen in L-E rats given a lethal dose of TCDD, were probably related to increased lipid peroxidation, made evident by the thiobarbituric acid method. With careful pair feeding, to correct for the tendency for TCDD-treated rats to scatter their feed, both control L-E and H/W rats exhibited similar signs of lipid peroxidation, and it was evident that the liver changes reflected the effects of starvation rather than of TCDD. The main difference between the strains was that after an initial period of anorexia following TCDD treatment, H/W rats started to eat in 1 to 2 weeks, whereas L-E rats did not eat again before they died. The data could reflect a biochemical lesion associated with gluconeogenesis, a topic which will be discussed in Section VI. TCDD also was more toxic in terms of hypophagia, when given by the intraventricular route, suggesting a central mediation of the effect. Although they recovered and recommenced feeding, even at 2 months after TCDD treatment, H/W rats displayed an absence of the 2-deoxyglucose feeding response, coupled with a hypersensitive satiety response to glucose, and more pronouncedly, to fructose.

The same group has further characterized the satiety signals in male H/W rats (Pohjanvirta *et al.* 1991). The animals received a high but non-lethal dose (1,000 μg/kg) of TCDD, which led to a sustained inhibition of body weight gain throughout the experiment. At various times between 2 and 90 days, feed intake was stimulated by depriving the animals of food for a 24-hour period. When starved TCDD- treated rats were allowed to drink 20% glucose or 0.25% saccharin solutions before access to feed,



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food consumption was reduced 50% in the glucose group. This effect was not seen in controls. Direct infusion of glucose solution into the stomach produced a longer suppression of feed intake in TCDD-treated than in control rats. In contrast, TCDD-treated rats were not hyperresponsive to intraperitoneal administration of sterile 30% glucose solution; earlier irreproducibility of the parenteral glucose effect was related to problems with tonicity of the solution. TCDD failed to affect significantly the suppressive effects of sulfated cholecystokinin octapeptide (CCK-8) or bombesin on feeding. Oral administration of corn oil also reduced feed intake, but the effect was only slightly greater in the TCDD-treated rats. These data indicate that some gastrointestinal factor(s) is responsible for the TCDD effect. Interestingly, in these studies the TCDD-treated animals consumed more saccharin than glucose solution, suggesting that an aversive response to a sweet taste was not responsible for the phenomenon. That such an aversive response could operate is suggested in a study by Daly (1991), who fed rats a diet supplemented with salmon from Lake Ontario which are significantly contaminated with PCBs, dioxins and other chlorinated organics. The exposed group showed a much larger contrast (depression) effect to offering a small food reward than did control animals, when they were switched from receiving 15- to 1-pellet rewards for running down an alley.

Several studies attempted to relate TCDD anorexia to changes in humoral factors. While they had shown earlier that brain serotonin levels were elevated in TCDD-intoxicated rats, Stahl *et al.* (1991) found that depletion of brain serotonin by up to 90%, as a result of intracerebroventricular injection of the neurotoxin 5,7-dihydroxytryptamine, did not affect the reductions in body weight and feed intake induced by TCDD. Maintenance of nutritional homeostasis has generally been ascribed to the hypothalamus, and Tuomisto *et al.* (1991b) used HPLC techniques to measure histamine concentrations in ten hypothalamic nuclei, the pineal and the cortex. The only region in which an effect of TCDD was evident was the median eminence, where histamine levels were significantly elevated ($p < 0.01$, *t*-test). Elevated histamine levels in the whole hypothalamus have been associated with decreased feed intake by the same workers, but the extreme localization of these findings in TCDD-treated rats makes it unlikely that they are involved in producing the hypophagia. Another hypothalamic system that has been associated



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with down regulation of feeding behavior is that involved in β-endorphin action. A single dose of TCDD (50 μg/kg, below the $LD_{50}$ of 60 μg/kg) given to Sprague-Dawley rats, induced hypophagia and weight loss, accompanied by values for hypothalamic β-endorphin that were 166%, 39% and 49% of control on days 1, 2 and 3, respectively. Total brain mu-receptor content rose from 53.3 ± 7.3 fmol/mg in control rats to 85.6 ± 3.5 fmol/mg at day 3 after TCDD treatment, an approximately 60% increase ($p < 0.05$); the value for food restricted animals at 52.0 ± 5.3 fmol/mg was unaffected. Also unaffected in both TCDD and diet restricted rats was the binding affinity of mu-receptor for β-endorphin. This serves as evidence that β-endorphin may play a role in TCDD hypophagia.

A three-part study of the toxicity of 2,4-D and 2-methoxy-3,6-dichlorobenzoic acid (dicamba) in dogs was reported from the veterinary group at the University of Illinois (Arnold *et al.* 1991a; Arnold *et al.* 1991b; Beasley *et al.* 1991). The toxicity of 2,4-D in dogs is generally considered to be moderate, with an acute oral $LD_{50}$ of 100 mg/kg, and gastrointestinal irritation, and muscular or neuromuscular weakness. The $LD_{50}$ for most mammals is in the range of 300 to 1,000 mg/kg, and the greater sensitivity of dogs may reflect limited renal organic anion transport. A dose escalation study, in which doses were spaced at least 1 month apart, showed that English Pointers given 2,4-D at 175 or 220 mg/kg developed both clinical and electromyographic (EMG) evidence of myotonia or pseudomyotonia. Subclinical evidence of myotonia was detected with the EMG at 86.7, 43.7 and 8.8 mg/kg, but not at 1.3 or 1 mg/kg. Dicamba appeared to be more toxic than 2,4-D, since 86.7 mg/kg of this herbicide gave both clinical and EMG changes similar to those given by the highest dose of 2,4-D. In a dog given 175 mg/kg of encapsulated 2,4-D, mild sedation and excessive slowing of the electroencephalogram (EEG) with loss of low voltage fast activity were seen at 24 hours, whereas at 220 mg/kg, EEG changes suggestive of irritation and mild seizure activity appeared at 7 hours, with return to normal by 24 hours. No EEG changes were seen at lower doses. In an attempt to determine if these physiological changes could be induced when the dogs ran free for 1 or 7 days on 2,4-D-treated lawns, three outdoor grass-plot enclosures were used, sprayed with the dimethylamine formulation of 2,4-D at maximum recommended, and 4-



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times maximum recommended levels, or with the vehicle alone. There was no evidence of electrocardiographic, EEG, EMG, clinical, hematologic or biochemical changes in the exposed dogs, nor could any gross pathologic or histologic effects be seen postmortem. However, at 24 hours, the measured serum levels of 2,4-D were within an order of magnitude of those found in dogs given the herbicide orally and exhibiting signs of myotonia.



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## G. Other Toxic Effects

### 1. Chloracne and Other Cutaneous Toxicity

Chloracne has long been associated with TCDD exposure, and is generally considered to be an indication of heavy exposure in occupational or environmental situations. This has been discussed in earlier volumes of the *Review*. More recently, this relationship has been put on a firmer footing by establishing correlations with serum dioxin levels. Examples of this are the Seveso incident in which an industrial accident led to widespread TCDD contamination, but chloracne occurred only in 10 subjects from the most heavily exposed group with serum TCDD levels between 828 and 56,000 pg/g lipid (Bertazzi 1991; Mocarelli *et al.* 1991), and a study in chemical workers, among whom chloracne was associated with elevated serum levels of TCDD (Neuberger *et al.* 1991). In the latter report, TCDD levels on the basis of serum lipid, ranged from 98 to 659 pg/g in nine workers with a history of chloracne compared with 8 to 28 pg/g in factory reference subjects without such a history, and 5 to 23 pg/g in external referents. The exposed workers had been involved in the production of 2,4,5-T and its raw material 2,4,5-trichlorophenol in 1971-1972, had experienced chloracne in the period 1972-1973, and had blood TCDD assays performed in 1990. The operation was closed down in 1973, extensive clean-up undertaken, and a new manufacturing process installed which did not involve formation of TCDD as a byproduct.

Normal mice do not exhibit cutaneous lesions after exposure to TCDD, but in hairless (hr/hr) mice a form of hyperkeratinization occurs, especially in the dermal epithelial cysts, and this effect is exacerbated by maintaining the animals on a Vitamin A-deficient diet (Puhvel *et al.* 1991). The interaction between TCDD and Vitamin A is considered in more detail in Section VI.

### 2. Hepatotoxicity

Evidence of subclinical hepatic damage associated with higher serum levels of TCDD has been described in the latest report of the Air Force Health Study (Roegner *et al.* 1991). This included positive associations between dioxin and serum cholesterol, high



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density lipoproteins and triglycerides, as well as serum alanine aminotransferase and γ-glutamyl transpeptidase activities.

A large number of reports became available during 1991 that described hepatic changes in animals treated with TCDD. Many of these changes represent normal processes of enzyme induction, or other metabolic effects that are more appropriate subjects for Section VI, which covers basic studies of the effects of dioxin. Some degree of hepatomegaly relative to body weight has been ascribed to treatment of rodents with TCDD (McKim *et al.* 1991; Shen *et al.* 1991) or 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (Koga *et al.* 1991) in several reports. In male Wistar rats, increased liver mass was accompanied by increased hepatic lipid content (McKim *et al.* 1991), but in mice strain differences were seen with respect to lipid accumulation. In TCDD-sensitive C57BL/6J mice, mild to moderate fat accumulation was seen in the absence of inflammatory or necrotic changes after 3 μg/kg, and mild inflammatory and necrotic effects with marked lipid infiltration occurred after 30 μg/kg of TCDD by the intraperitoneal route. In contrast, DBA mice showed evidence of inflammation and cellular necrosis after 30 μg/kg, and only slight fatty changes were seen when a dose of 600 μg/kg was reached (Shen *et al.* 1991). Both *in vivo* and *in vitro* exposure of rat hepatocytes to TCDD led to increased protein synthesis with the appearance of new protein bands on two-dimensional electrophoresis (Aoki *et al.* 1991). A study with rat 5L hepatoma cells, a derivate of the H4IIEC3 cell line, indicated that TCDD blocked the entry of the cells into S-phase without affecting progression throughout the rest of the cell cycle. This effect was seen within 4 to 8 hours, and led to a marked increase in cell volume, presumably due to the accumulation of cells in $G_1$ phase (Wiebel *et al.* 1991). Finally, in 19-day-old chick embryos, 2,4-D and more especially 2-methyl-4-chlorophenoxyacetic acid (MCPA), induced a biliary stasis that may have led to changes in drug metabolizing enzymes (Santagostino *et al.* 1991).

3. Other Toxicity

It has been known for several years that toxic doses of the chlorophenoxy herbicides can cause hemorrhage in various organs of animals that have been tested.



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It is interesting that these compounds present structural analogies to clofibrate (2-[*p*-chlorophenoxy]-2-methylpropionic acid), an antihyperlipidemic drug that is known to potentiate anticoagulant action by inhibiting platelet aggregation, and sulotroban, a derivative of phenoxyacetic acid that is a thromboxane $A_2$ ($TxA_2$) antagonist. Two papers from a group in Kuopio, Finland, have described the inhibition of human platelet aggregation by eight phenoxy herbicides (Elo *et al.* 1991; Ylitalo *et al.* 1991). The herbicides studied were: 2,4-D; 2,4,5-T; MCPA; 2-(2,4-dichlorophenoxy) propionic acid; 4-(2,4-dichlorophenoxy) butyric acid; 2-(2,4,5-trichlorophenoxy) propionic acid; 2-(4-chloro-2-methylphenoxy)propionic acid; and 4-(4-chloro-2-methylphenoxy) propionic acid (MCPB). Aggregation of the thrombocytes was induced by adrenalin, ADP, collagen, or the $TxA_2$ agonist U-46619 (Upjohn), and measured in a nine-channel spectrophotometer at 620 nm. A dose-dependent inhibition was demonstrated for these herbicides at concentrations between 0.02 and 2 mg/ml. No structure-activity relationship could be discerned since their activities were essentially similar. While this may appear to be a high concentration, it should be noted that blood levels in humans and animals with severe or fatal poisoning by these agents have been in the range of 0.4 to 1.0 mg/ml. When rabbits were injected subcutaneously with 2,4-D or MCPA at 100-150 mg/kg, the platelet-rich plasma prepared 2.5 hours later showed a 20-30% reduction in ADP-stimulated platelet aggregation compared with plasma obtained before injection. This inhibitory effect was lost in 20-23 hours. Inhibition by 2,4-D of aggregation induced by U-46619 was characterized by competitive kinetics, suggesting that the inhibition involved action at the $TxA_2$ receptor. Furthermore, 2,4-D or MCPB inhibited the production of $TxB_2$, as measured by a radioimmunoassay, during aggregation induced by U-46619 or by ADP and collagen, respectively. This suggests that the antiaggregation effect is mediated through interaction with the thromboxane system.

An effect on platelet aggregation, and thus on potential risk of bleeding, may not be unique to the phenoxy herbicides. In a study of TCDD levels in the breast milk of 14 Dutch mothers, Koppe *et al.* (1991) found that in the four infants with identified bleeding problems (two cases with intracranial bleeding within 48 hours of birth, and two in the fourth week), the mean concentration of TCDD in their mothers' breast milk (range 7.44



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to 16.82 ng/kg milk fat) was significantly higher ($p$ = 0.02 Wilcoxon test) than for the other ten. This relationship was not evident for 2,3,4,7,8- pentachlorodibenzofuran.

In a well-executed cross-sectional medical study of chronic respiratory conditions, 281 workers who had been exposed to TCDD more than 15 years earlier, while employed at firms producing trichlorophenol and 2,4,5-T in Newark, New Jersey and Verona, Missouri, were compared with 260 unexposed referents matched from within the individual neighborhoods by age, sex and ethnic group. Medical histories, physical examinations, serum TCDD assays, spirometric tests, and interviews regarding subjects' lifestyles and occupational histories were the bases for the study. Personnel involved in obtaining the information were blinded. Mean lipid-adjusted serum level of TCDD was 220 ppt for the study group compared with 7 ppt for the controls. Logistic and linear regression analyses, allowing for TCDD levels, were used to control for confounders that included past and current smoking and drinking status, height, other lung diseases, and dust exposure. No significant differences could be determined between the two groups with respect to risks for chronic bronchitis and chronic obstructive pulmonary disease. In addition, there was no association between exposure to TCDD and the spirometric parameters of lung function (Calvert *et al.* 1991).

Administration of TCDD to rats produces a hypergastrinemia that serves to protect the gastrointestinal mucosa against the atrophy that is produced in the hypophagic state. Since the antral mucosa is the source of much gastrin production, the response of this tissue to TCDD was studied in male Sprague-Dawley rats (Theobald *et al.* 1991). Fourteen days after an oral dose of TCDD (100 $\mu$g/kg), there were significant increases in antral wet weight and mucosal height, whereas pair-fed rats that experienced similar weight loss had antral atrophy. Antral G-cells (the gastrin-containing cells) showed no hyperplasia, however. A 7- to 10-fold increase in the serum gastrin concentrations, as determined by radioimmunoassay, was seen at this time, although not before, but levels of this hormone were unchanged in the controls. In contrast, antral concentrations both of gastrin and somatostatin decreased significantly about 1 week before hypergastrinemia was evident. Because of this difference in timing, the absence of G-cell proliferation, and the fact that the $ED_{50}$ values for the decrease in antral hormone levels were in the range



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of 19-29 μg/kg, compared with 46 μg/kg for hypergastrinemia, it is unlikely that the latter results from the changes in antral hormone levels.



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## IV. HEALTH EFFECTS OF OTHER HERBICIDAL ACTIVE INGREDIENTS

### A. Picloram

Picloram (4-amino-3,5,6-trichloropicolinic acid) was a major component of Agent White, one of the herbicides used in Vietnam, whose activity was due to a mixture of the triisopropylamine salts of picloram and 2,4-D. It is still commonly used on broadleaved plants, most frequently in association with 2,4-D as various formulations of Tordon. The compound has not been studied intensively, but reviews of earlier toxicologic studies may be found in Volumes I, III, V, VII, IX and XVII of the *Review* that were compiled between 1981 and 1990. The overall picture presented is of a mildly hepatotoxic compound, for which carcinogenicity and teratogenicity studies have yielded no conclusive results. It is absorbed readily from the gastrointestinal tract or through intact skin, but also is very rapidly excreted in the urine, essentially without metabolism or significant retention in the body. Two new studies involving picloram have appeared during 1991. In addition, a review and analysis by Ashby and Tennant (1991), listed picloram as an equivocal carcinogen in rats.

Adams *et al.* (1991) reported a study that involved exposure of female CD-1 mice to Tordon 202c, a commercial mixture containing 12 g of picloram and 200 g of 2,4-D per liter, at concentrations between 0 and 0.3% in the drinking water for 15 weeks. After 3 weeks of treatment, urethan (1.5 mg/g) was administered intraperitoneally, and the formation of pulmonary adenomas evaluated 12 weeks later. Tordon did not produce any visible signs of clinical toxicity, nor did it affect significantly measured weight gains or water consumption. It did, however, produce a dose-dependent increase in the multiplicity, but not the size of lung tumors. Since Tordon caused a decrease in urethan-induced sleeping time, it was concluded that the enhanced tumorigenesis did not result from impaired metabolism or excretion of urethan, but rather from suppression of immunological surveillance. No data were reported for the effects of each component of Tordon alone, but since the two herbicides were used in combination in Vietnam, this is not a significant defect for the purposes of this report.



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Channel catfish (*Ictalurus punctatus*) were exposed over the course of 10 days to picloram (2,5 mg/liter of aquarium water, corresponding to 25% of the 96-hour $LC_{50}$ concentration) and three concentrations of 2,4-D (22.5, 7.5 and 2.25 mg/l, corresponding to 25, 8.3 and 2.5% of the 96-hour $LC_{50}$ concentration), alone or in admixture. Fish developed decreased serum chloride concentrations and liver/body weight ratios, accompanied by increased ethoxyresorufin *O*-deethylase (EROD) in the liver, but only when exposed to a mixture of herbicides. Picloram, alone or with 2,4-D, produced an approximately 50% fall in hepatic lauroyl CoA oxidase (Gallagher and DiGiulio 1991). Since the rise in EROD was only 2.5-fold, it is likely that enzyme activation was responsible rather than induction, which typically results in a 15-fold or greater increase. The lauroyl CoA oxidase data indicated that picloram is not an inducer of peroxisomes. This research is compatible with previous observations of picloram's mild hepatotoxicity.

**B. Cacodylic Acid**

The limited available information on the toxicology of this agent has been presented in prior volumes of the *Review*. In summary, this substance produces a spectrum of acute toxic symptoms that includes gastrointestinal disorders, eye irritation and dermatitis. Studies in experimental systems have indicated that it has the potential for mutagenicity, clastogenicity and teratogenicity. Carcinogenicity has not been tested adequately, but it should be noted that this activity has been associated with other arsenic compounds. Only one abstract in a primary journal on cacodylic acid was identified in the literature that became available during 1991. It reported mitotic arrest and sister chromatid exchanges in V 79 Chinese hamster cells exposed to this compound (Kuroda *et al.* 1991).



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# V. TISSUE RESIDUES AND PHARMACOKINETICS OF CHLORINATED DIBENZO-*p*-DIOXINS AND RELATED COMPOUNDS

The polychlorinated dioxins (PCDDs) and related compounds are of a highly lipophilic nature, and therefore tend to become sequestrated into body fat depots from which they are released only very slowly. As a result, levels of these compounds in adipose tissue can serve to indicate the history of past exposure. For example, detectable levels of dioxins have been found in many individuals heavily exposed more than 20 years previously, and in one case, TCDD and greater amounts of its tetrabromo-analog, were measured by mass spectroscopic methods in the blood lipid fraction of a chemist exposed 34 years earlier while synthesizing these compounds (Schecter and Ryan 1991c). It has been shown that at least for the lower polychlorinated PCDDs and PCDFs such as TCDD, plasma or blood lipid levels are similar to those measured in adipose tissue lipids (Schecter *et al.* 1991b). Thus, blood is an appropriate source of samples for dioxin assays, one that is more accessible than adipose tissue. The extreme sensitivity of available analytical techniques permits detection of dioxins in the fg/g to pg/g, that is the parts per trillion (ppt) range. These techniques are being applied to various groups of exposed populations, to experimental animals, and to the study of the pharmacokinetics of these agents. It is probable that the linking of toxicologic findings to actual measurements of dioxin body burdens and kinetics will not only provide more meaningful interspecies comparisons, but also will help achieve much better risk assessment based on no-adverse-effect-concentrations (Neubert 1991).

## A. Studies of Vietnam Veterans

Previous volumes of this *Review* have presented evidence from studies of adipose tissue and serum levels of the major dioxin contaminant of Agent Orange, TCDD, which supported the conclusion that Vietnam veterans who had experienced the greatest exposure to Agent Orange had elevated serum levels of TCDD 15-20 years later. Other Vietnam veterans without such documented high exposure, generally had blood and tissue levels comparable to those in the general population or in non-Vietnam veterans.



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This correlation was seen, for example, in 888 serum samples from the Ranch Hand cohort of veterans who had participated in the U.S. Air Force's Operation Ranch Hand, and thus were associated with the actual aerial application of the herbicide. Flying and non-flying enlisted personnel exhibited much higher serum levels, 17.2 and 23.6 ppt, respectively, than did nonflying officers, pilots and navigators (range of 6.6 to 9.3 ppt). Matched control veterans (856 samples) not associated with Operation Ranch Hand, had low serum levels of TCDD (range of 3.9 to 4.7 ppt) that were not correlated with rank (Wolfe *et al.* 1990). A recent report (Roegner *et al.* 1991) has covered the serum dioxin levels and long-term health effects in personnel exposed to herbicides for the 1987 examination cycle under the Air Force Health Study. For the total group of 866 Ranch Hand personnel, the median TCDD level was 12.8 ppt serum lipid weight. Values for the median serum levels, and ranges for the three ranks of officer, enlisted flyer and enlisted groundcrew were, respectively: 7.8 ppt (0-42.6); 18.1 ppt (0-195.5); and 24.0 ppt (0-617.8). In the comparison group of 804 personnel, median serum levels were 4.2 ppt (range 0-54.8), with the breakdown by rank as follows: officer 4.7 ppt (0-18.5); enlisted flyer 4.0 ppt (0-12.8); and enlisted groundcrew 4.0 ppt (0-54.8).

Kang *et al.* (1991) addressed the question of whether Vietnam veterans, in general, received substantial exposure to dioxins while serving in Vietnam. This was a relatively small study that used adipose tissue samples obtained from the U.S. Environmental Protection Agency's archival collection of 8,000 specimens. TCDD levels were determined by high resolution gas chromatography coupled with double-focussing mass spectrometry. Samples from 36 Vietnam veterans were compared with groups of 79 non-Vietnam veterans and 80 civilians, matched for age and year of sample collection. Arithmetic mean levels and standard deviations for the three groups, respectively, were 13.4 ± 7.4, 12.5 ± 7.2, and 15.8 ± 14.5 pg/g total extractable lipid. These means did not differ significantly, and furthermore, there was no significant correlation between dioxin levels and four surrogate measures of exposure to Agent Orange, namely military branch, military occupation specialty code, military region, and time and distance from recorded herbicide spraying, apart from slight rises in levels in those who had been in combat status or within 3 days/2 km of sprayed areas. Since TCDD was the predominant



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polychlorinated dioxin contaminant of Agent Orange, the finding that there were no group differences in relative tissue levels of other polychlorinated congeners, suggests that sources other than Agent Orange, such as subsequent environmental or occupational exposure, may have contributed to the Vietnam veterans' overall TCDD levels. The higher levels of TCDD found in this study compared to others reported recently, were most likely due to the relatively earlier years of sample collection, with a mean of 1978 compared with the mid 80's or later for most other reports.

Reliance on blood or tissue levels, in samples collected 15-20 years or more after service in Vietnam, as a definitive indicator of whether or not veterans experienced high-level exposure to TCDD, is a logical step, based on the available data. This was certainly the conclusion of the Centers for Disease Control Veterans Health Studies (Centers for Disease Control 1988). However, there are questions about its validity. Albanese has raised concerns about the single compartment pharmacokinetic model used to estimate prior exposure, the neglect of weight gain (mainly in the form of lipid) and of tissue binding of TCDD, and possible selection bias (Albanese 1991). There is an approximate doubling of body fat in moving from the 20-24 to the 40-49 year-old age group, which would tend to lower serum TCDD levels by providing a larger depot storage compartment. He calculated that with time this would lead to a steady increase in the estimated half-life for TCDD as a result of altered body composition. Binding to specific or non-specific sites within tissues also will increase the apparent half-life of TCDD, and the relative importance of this factor will increase with time as body stores of unbound TCDD are depleted. The use of data derived only from subjects with unusually high levels, as in the report of Pirkle *et al.* (1989) which generated the commonly-used value of 7.1 years for the half-life of TCDD, introduces selection bias, since the sampling may have favored not only those heavily exposed, with resulting high initial levels, but also those who cleared body dioxin loads unusually slowly. Albanese concluded that the net result will be that extrapolation back to the time of exposure, using a probably overestimated half-life, derived from a single compartment model based on two measurements made 5 years apart, will lead to an underestimate of the exposures experienced 15-20 years before. These are powerful arguments, to which might be added the fact that it is on a pharmacokinetic basis



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questionable to infer single compartment kinetics from only two measurements made at extremely late times, with no information about the initial dose of TCDD received.

This issue calls for better definition of the pharmacokinetic pattern of TCDD in humans, but it is difficult to see how use of data from veterans of the group exhibiting lower levels of TCDD will help in this, considering the problems, both of relatively greater background noise in analytic procedures at low levels, and of the confounding effect of any possible subsequent chronic environmental exposures to TCDD, which would tend to produce a steady-state situation for dioxin body loads (Phillips 1989). Albanese recommended the use of a multi-compartment model instead of one based on a single compartment (Albanese 1991), and such a model for humans, involving seven body compartments, has been proposed by Kissel and Roberge (1988). However, lack of a range of sampled tissues, the paucity and limited collection times of those samples that are available, and low concentrations of TCDD, make it impossible to apply such complex models to data from Vietnam veterans. It is in any case questionable whether they are needed. Webster and Connett (1991) devised a new physiologically-based model with a system of nine simultaneous differential equations (compared with 11 in that of Kissel and Roberge). Using the same Ranch Hand data, a half-life of 7.9 years was arrived at, very close to the 7.1 years derived by Pirkle *et al.* (1989). They found that the system approximated a monophasic one (equivalent to a single compartment situation) after a few early transients. This reflects the predominant role of depot fat in determining the volume of distribution, the two orders of magnitude greater half-life of equilibration for this compartment, and the limited metabolism and low fecal excretion of TCDD.

Another concern has been addressed in a recent report from the ongoing Air Force Health Study, which focussed on the variability of TCDD half-life as a function of percent body fat (Michalek et al. 1992). Based on a repeated measures linear model, these authors found a marginally significant ($p = 0.09$) relationship between half-life and percentage body fat, but no significant ($p = 0.60$) change in half-life with relative changes in the percent body fat between 1982 and 1987.

In summary, studies reported during 1991 have generally supported earlier conclusions that blood and adipose tissue levels of TCDD can serve to indicate heavy



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exposure to Agent Orange, but lesser degrees of exposure may not be reflected in increased levels.

## B. Studies of Other Exposed Populations

Levels of PCDDs and PCDFs have been determined in a number of populations that were exposed to these agents occupationally, as a result of an episode of poisoning consequent to an industrial accident, or through environmental exposure.

A study of 281 chemical workers at plants in Newark, New Jersey, and Verona, Missouri, was undertaken to relate chronic bronchial disorders with exposure to dioxins. This study group, which had been exposed to TCDD over an approximately 2-year period 15 years earlier, while employed in the production of trichlorophenol and 2,4,5-T, was compared with 260 unexposed referents. The mean lipid-adjusted serum concentration of TCDD in the study group was 220 ppt compared with 7 ppt in the controls. The half-life-extrapolated mean initial serum levels were estimated as 1,896 ppt (range 2-32,400) for the exposed and 6 ppt (2-20) for the control populations (Calvert *et al.* 1991).

In a report from Austria, serum levels of TCDD were measured in nine production workers with a history of developing chloracne after exposure to PCDD's during the period 1971-1973. Serum levels were in the range of 98 to 659 pg/g blood lipid in 1990, compared with 8 to 28 pg/g for a group of 4 workers from the same plant without a history of TCDD exposure or chloracne, and 5 to 23 pg/g in 17 external referents (Neuberger *et al.* 1991). Schecter and Ryan (1991c) found 20 ppt of TCDD and 1100 ppt of the 2,3,7,8-tetrabromo- congener in the serum lipid of a chemist who was engaged in synthesis of these compounds 34 years earlier. In a study from New Zealand of 548 professional pesticide applicators who had utilized 2,4,5-T, Smith *et al.* (1992) measured blood serum levels of TCDD in 11 men, identified as having the greatest number of years and of months per year of pesticide application experience. They were matched with controls of similar ages who had no occupational exposure. Average levels of TCDD were 53.3 ± 16.1 and 5.6 ± 1.1 ppt in the applicators and controls, respectively. Serum levels of 6 other chlorinated dioxins and 9 chlorinated dibenzofurans were no higher in



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the study group than in the controls. Variations in TCDD levels between individual applicators was correlated ($r = 0.72$, $p = 0.03$) with duration of working exposure to 2,4,5-T. Since the level of the TCDD contaminant in the 2,4,5-T used in New Zealand fell 200-fold, from approximately 1 ppm to 5 ppb between 1971 and 1985, much of the serum dioxin is probably attributable to exposure many years previously. Knopp (1991) has monitored urinary excretion of 2,4-D by workers involved in spraying this herbicide. The highest urinary concentration recorded in a morning urine sample was 2.5 ppm, clearance half-life was 12 to 22 hours, and the calculated uptakes were 5.7 and 84.9 $\mu$g/kg.

There have been three major incidents of PCDD and PCDF poisoning that still generated research reports in 1991. These were the contamination of an area near Seveso, Italy, with 1.3 kg of TCDD in 1976, and the consumption of rice oil contaminated with PCDFs and PCBs in Japan (Yusho) in 1968, and in Taiwan (Yucheng disease) in 1979. Data from the Seveso incident are of particular value in that they include serum concentrations of TCDD measured within weeks of exposure, together with a 9-year clinical follow-up. In the study by Mocarelli *et al.* (1991), detectable levels of TCDD were only found in 20 serum samples, of which 19 were from those who stayed for any period of time in the most contaminated A zone, in which soil TCDD levels were in the range of 956 to 1,185 $\mu g/m^2$. The serum levels in zone A subjects varied from 828 to 56,000 ppt (lipid adjusted); none had undetectable levels. Of 10 subjects not associated with any of the three contaminated zones, only one was positive for serum TCDD with a value of 137 ppt. Chloracne types 3 and 4 developed only in 10 of the heavily contaminated subjects; in 3 of these, serum TCDD levels were at the lowest end of the range, but these individuals had experienced direct contact with TCDD, leading to a reaction similar to contact dermatitis. Clinical findings apart from the chloracne were unremarkable, with only slight or transient changes in laboratory tests. Continued clinical monitoring for cancer development is ongoing, but the findings to date do not support any firm conclusions (Bertazzi 1991).

Three reports concerned work related to the Yusho incident. In a comparison of 7 Yusho patients with 8 normal controls, levels of PCBs, PCDFs and PCDDs were measured in subcutaneous adipose tissue by high resolution gas chromatography and



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mass spectrometry in ion monitoring mode. Average values in TCDD equivalents were 17, 491 and 24 ppt for coplanar PCBs, PCDFs and PCDDs, respectively (Hirakawa *et al.* 1991). In scoring the total clinical findings over the period 1972 to 1988, and relating these scores to the coincident values for adipose tissue and blood levels of PCDFs, a strong correlation was seen for females ($r = 0.9885$). There were not enough male patients for statistical evaluation (Nakagawa and Takahashi 1991). An interesting study was performed in six Yusho patients who received the anion exchanger cholestyramine at a dose of 4 g three times daily for 6 months, leading to enhanced fecal excretion of various classes of polychlorinated compounds (Iida *et al.* 1991). This may represent sequestration of material excreted through the intestinal epithelium and/or secreted in the bile, making it unavailable for reabsorption.

Yu *et al.* (1991) reported on 128 children born to exposed women in Taiwan after the contaminated oil had been removed from the market; developmental delays were seen in many of these children. Measurable blood levels of PCBs were found in 34 of 74 mothers, and 20 of 36 children tested; no PCDFs were detected. PCB levels in children were: 4.5 ppb in breast-fed exposed, 0.53 ppb in breast-fed controls, 0.44 ppb in bottle-fed exposed and 0 in bottle-fed controls. Another study carried out on 3 exposed subjects between 1980 and 1989, however, found relatively high levels of penta-, hexa- and hepta- chlorodibenzofurans (initially at 15.4, 37.7 and 4.8 ppb), with half-lives of 2.14, 2.56 and 2.32 years, respectively. High blood concentrations of 8 PCB congeners were also documented; half-lives of those retained in the body were about twice as long as those of the PCDF congeners (Masuda *et al.* 1991). Human placentas from 5 exposed women were collected, beginning in 1983, four years after the incident (Lucier 1991). PCDFs were found in the Yucheng but not in the control placental samples; mean levels of the penta- and hexa-chlorinated derivatives were about 100 and 400 ppt, respectively. Control placentas had measurable levels of PCBs, evidence for the widespread environmental distribution of these compounds, but those in the exposed samples were between 5 and 96 times greater.

Although the organochlorine compounds are widespread throughout the environment, the overall contributions from all sources must vary, since a survey of the



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levels of these compounds in human adipose tissue samples from throughout the U.S. shows marked regional variations (Phillips and Birchard 1991). For PCDDs and PCDFs the highest ranked area was the East North Central, followed by the Mid Atlantic and East South Central. Polychlorinated compounds, including dioxins, enter humans when released through accidents, burning of materials, paper pulp processing, or when present as contaminants of herbicides; the most important route is the food chain. Through the food chain contaminants pass from soil or water to human populations. Fish, for example, are well known sources of these polychlorinated compounds, due to the prevalence of contamination in certain bodies of water. A recent report documented the levels of PCDDs and PCDFs in individuals eating fish from the Baltic Sea (Svensson *et al.* 1991). Ten dibenzofurans and 7 dioxins were assayed in plasma samples from three groups of Swedish men, one with high, almost daily fish intake (n = 11), a second with moderate intake (about once a week, n = 9), and a third with no fish intake (n = 9). Median levels of TCDD were 8.0 pg/g (range 2 - 13) for the high, 2.6 pg/g (range 1.2-4.2) for moderate, and 1.8 pg/g (range 1.0-2.5) for non-consuming groups, based on plasma lipid content.

Since dioxins are so closely associated with carcinogenesis, it is not surprising that attempts have been made to determine the levels of these compounds in patients with cancer. Muto *et al.* (1991) studied the distribution of PCDDs in the lung, liver, kidney, pancreas, spleen, gonads, gallbladder and muscle from each of 11 patients who had died of cancer. None of the PCDDs were at levels outside the ranges of those associated with unexposed populations in other studies reported in the literature. The dioxin present at the highest levels in all tissues examined was octachlorodibenzo-*p*-dioxin (39.9-344 pg/g), followed by the heptachloro- congener. TCDD was present at its highest level (0.8-3.2 pg/g) in the gonads.

Craig and Grzonka (1991) have developed an idealized, linear reaction kinetic model for TCDD body burden which takes as its primary parameters the TCDD transfer factor from soil to the human body, the background intake, the soil concentration and the body and soil elimination half-times. Values for the transfer factor were estimated from data derived from the Seveso incident in Italy (described above) and the Missouri incident



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in the U.S.A., which resulted from spraying horse arenas with TCDD-contaminated oil to control dust. The model determines a time scale over which the body burden acquired from a highly contaminated environmental exposure may exceed the levels due to other ubiquitous sources, and provides perspectives that permit decision making on source removal in connection with guidelines. It could be applied to mixed contamination with PCDDs and PCDFs, using TCDD equivalents.

### C. Studies of Dioxins in Milk

Absorption of polychlorinated organic compounds and their subsequent excretion in milk is an easily studied process, and one which could have profound impact on the health of human infants, exposed at a particularly vulnerable period in their development. This area continues to generate levels of research activity, both in humans and in animal systems, similar to those recorded in Volume XVII of the *Review*. A large international study documented the levels of a range of dioxins and dibenzofurans in human milk and blood in Cambodia, Germany, Thailand, the U.S.A., the former U.S.S.R., and Vietnam (Schecter *et al.* 1991a). In general, levels of the compounds studied were lower in milk than in blood, as measured on a lipid basis. As regards blood, these levels were lower in samples from Hanoi and other less industrialized countries. However, among the Vietnamese samples, TCDD concentrations were much higher in samples from Dong Nai Province (mean 12 ppt) where Agent Orange had been used, than in those from Hanoi (2.4 ppt, the detection limit) or Ho Chi Minh City (3.4 ppt). Milk samples also reflected industrialization, with dioxin levels highest in German samples, followed by those from the U.S., while samples from South Vietnam, where spraying with contaminated herbicides had occurred, were higher than those from North Vietnam; milk from relatively non-industrialized areas in Siberia and Cambodia had the lowest levels. In contrast, relatively high levels of DDT and its derivates were found in the milk samples from all regions of Vietnam, and also from Cambodia, Siberia and Thailand, reflecting widespread use of DDT in mosquito control operations. A Dutch study also has underlined the variations between breast milk samples collected from different countries (Koppe *et al.* 1991). In 14 Dutch mothers, milk levels in ng/kg milk fat ranged from 5.35 to 17.0 for TCDD and



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21.43 to 70.0 for 2,3,4,7,8-pentachlorodibenzofuran. The corresponding values for 5 Polish mothers were 2.58 to 4.59 for TCDD and 13.2 to 18.15 for the dibenzofuran, reflecting lower levels of environmental dioxins and related compounds in Poland.

A PCB fire in Quebec, Canada, in August 1988, presented the opportunity to study the levels of PCDDs and PCDFs in the milk of lactating women within the first three days of exposure; values were compared with those measured in samples from the general population of Quebec (Dewailly *et al.* 1991). Mean total levels of the two classes of compounds were 318 pg/g on a fat basis in the samples from the exposed women, compared with 243 pg/g for the control group. These values, and the contents of the major component (octachlorodibenzo-*p*-dioxin) and the hexachloro- and heptachloro-dibenzofurans, were significantly different ($p < 0.05$). Mean levels of TCDD were 2.59 and 2.33 pg/g lipid in the exposed and control samples, respectively. The authors point out that the mean level of polychlorinated compounds in human milk in Quebec translates to 13.3 ng/kg, when expressed in Toxic Equivalency Factors (TEFs; toxicity expressed relative to TCDD, see Barnes (1991)), which is much lower than those reported for other areas such as the U.K. (29.5 and 36.9) or Germany (26.9), but comparable with figures for the U.S.A. (Los Angeles, 16.6; Tennessee, 16.6). The report of Yu *et al.* (1991) on the Taiwanese children exposed *in utero* to PCB and PCDF contaminated oil, discussed in Section V B above, also draws attention to the role of breast milk as a source of accidentally-derived organochlorine compounds for infants. In that study, only the breast fed exposed infants had significant levels of PCBs (4.5 ppb versus 0.44 ppb in exposed bottle-fed infants).

Measures have been taken in a number of countries to restrict the use of organochlorine compounds so as to reduce environmental pollution. Noren and Lunden (1991) have followed the levels of PCDDs and PCDFs in human milk in the Stockholm region over the period 1972-1989, which marked the implementation of Swedish control measures. There was a continuous fall in PCB, PCDD and PCDF levels in milk samples from 4.5 to about 1.8 pg/g TCDD equivalents over the period 1972-1985, with PCBs as the major components, and TCDD as a very minor contributor. However, this decline now seems to have ceased, since values for 1989 were at or above the 1985 figures. It



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is possible that the 1989 values represent an anomaly due to factors such as a slightly higher age group, a smaller population of nursing mothers as a donor pool, and new restrictions applied to which women could serve as donors.

Sullivan *et al.* (1991) have modified an earlier pharmacokinetic model that describes the exposure of infants nursing from mothers who consume contaminated fish at the 25 ppt level of the FDA fish advisory. This model was validated by a study carried out in rhesus monkeys dosed with 0.13 mg/kg/day of dioxin for 16 months before parturition, and then throughout the period of lactation. The authors concluded that the intake of TCDD by the infant as a result of successive lipid partitioning was sufficient to approximately double the lifetime carcinogenic risk to the infant.

A number of studies have examined organochlorine compounds in the milk of different animal species. In a toxicokinetic study in 4 cows, the animals received $^{13}C$-labeled PCDDs and PCDFs dissolved in olive oil by the intraruminal route under light sedation. The fate of the labeled compounds was studied by gas chromatography-mass spectrometric assays of milk samples, adipose tissue biopsies, and tissues samples collected when the animals were slaughtered on day 93. Milk levels were maximal 1 day after dosing (about 200 pg/g for TCDD) falling to means around 2 pg/g by day 93. The initial rapid drop in milk fat levels occurred during the first 5 or 6 days, and was succeeded by a slow elimination phase that followed first order kinetics from days 27 to 93 for six of the eight congeners studied, including TCDD. The mean elimination half life of TCDD (dose received 3.7 ng/kg) was calculated as 40.3 ± 7.7 days, and its bioavailability as 29.5 ± 5.9 percent. The subcutaneous fat/milk fat ratio for TCDD was relatively stable at 1.0-1.5 between days 6 and 93 (Olling *et al.* 1991).

Several articles dealt with the transfer of organochlorine compounds both across the placenta and into the milk. Using pregnant marmoset monkeys (*Callithrix jacchus*), injected subcutaneously with a defined mixture of PCDDs and PCDFs 11 weeks before delivery, Hagenmaier *et al.* (1990) studied the transfer of these compounds via the placenta and through consumption of milk. Concentrations were measured in newborn (1 day) infants and after 33 days lactation. Fetal, infant, and maternal PCDD and PCDF tissue levels were measured and compared with those of other adults. Fetal liver levels,



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especially of PCDFs, were very low, but in suckling infants, hepatic levels of TCDD, the corresponding dibenzofuran, and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin were 2 to 4 times higher than maternal levels; in contrast, OCDD levels were only 10 % of those in the mothers. Adipose tissue and thymus levels of 2,3,7,8-substituted congeners were high. The data testified to the efficiency of transfer of TCDD in the milk as well as through the placenta. Although no assays of milk concentrations of TCDD were performed, two reports by Couture-Haws *et al.* (1991a; 1991b) demonstrated that the amounts of TCDD present in the milk from treated rats were sufficient to induce hydronephrosis in nursing pups, and were equally effective toxicologically to treatments received while the animals were *in utero*.

## D. Pharmacokinetic Studies in Animals

There have been several reported studies of the pharmacokinetics of TCDD in animals. For example, Banks and Birnbaum (1991) studied the percutaneous absorption of TCDD in 10-week-old male Fischer 344 rats. Absorption across the interscapular area was a first-order process with an absorption rate constant for tritiated TCDD of 0.005 per hour. Absorption reached 82 pmol (26 ng) in 120 hours, and the percentage of the dose that could be detected in the blood never exceeded 0.3%. In a second study from the same laboratory, Kedderis *et al.* (1991b) measured the distribution and excretion of the tetrabromo- analog (TBDD) of TCDD given intravenously at 0.001 or 0.1 μmol/kg to Fischer 344 rats. Both fecal (major route) and urinary excretion were nonlinear with respect to dose, although the terminal whole-body half-life calculated from fecal excretion in both dosage groups was 18 days. At 56 days, there was a disproportionate elevation in the ratio of the concentration in liver relative to adipose tissue at the high dose, 2.6 compared with 0.2 for the low dose. This may reflect to some extent the effects of binding to specific hepatic Ah receptors. Terminal excretion half-life from adipose tissue was about 60 days. The data were similar to earlier reports on TCDD. The same group of investigators in further reports (Kedderis *et al.* 1991a; 1991c) compared the distribution and excretion of tritiated TCDD and TBDD. Biliary excretion of TCDD (1 nmol/kg intravenously) over an 8-hour period was somewhat greater than that of TBDD, 10%



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versus 7% in 5 hours, all in the form of metabolites. Pretreatment of the rats with a single dose (100 nmol/kg) of unlabeled TCDD or TBDD 3 days before tracer did not alter biliary excretion, but did cause a doubling of hepatic radioactivity. It was apparent that autoinduction of the metabolism of TCDD and TBDD did not occur, despite demonstrable induction of CYPIA1 and CYPIA2. Furthermore, induction of the latter did not appear to account for all the dose-related increase in the ratio of liver to adipose tissue dioxin concentrations. This dose-dependence was evident on comparing TBDD at 1 and 100 nmol/kg, when at 56 days, liver/adipose tissue ratios were 0.2 and 2.6, respectively. Fecal excretion also showed some dose-dependence, reaching 50 and 70% of the administered dose, for the low and high doses, respectively, at 56 days. The terminal whole-body half-life was about 18 days at both dosage levels, but for excretion from the adipose tissue compartment it was about 60 days.

Some limited information on tissue levels of 2,4-D in dogs was published during 1991. Maximal serum concentrations measured in dogs given encapsulated oral formulations of 2,4-D were 1,075 ppm at 5 hours after 220 mg/kg, 718 ppm at 2 hours after 175 mg/kg and 121 ppm at 4 hours after 43.7 mg/kg in English Pointer dogs. Levels in the urine that were as high as 1,792 ppm, 2 hours after administration, were indicative of very rapid excretion (Arnold *et al.* 1991a). When the same breed of dogs were permitted to run on grass-plot enclosures sprayed with 2,4-D, serum concentrations of 2,4-D ranged from 0.02 to 26.4 ppm (Arnold *et al.* 1991b).



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## VI. BASIC STUDIES RELEVANT TO HEALTH EFFECTS

### A. Introduction

Recent volumes of the *Review* have documented a steady increase in the proportion of the literature on phenoxy herbicides and their dioxin contaminants that is devoted to basic research on mechanisms of action. This trend has continued throughout 1991. Indeed, during this year the basic research area has received particular attention as the major source of controversy regarding human health hazard assessments, and possible reevaluation of the Environmental Protection Agency's (EPA) regulations governing the dioxins, as can be seen for example in the article by Barnes (1991). This is due, at least in part, to differing opinions on what the wider implications of a mechanism of action that is based on interaction with receptors might be. Receptor-based mechanisms, which are common to most pharmaceutical agents for example, are usually associated with sigmoidal dose-response curves, and exhibit definitive threshold concentrations below which biological activity is negligible or nonexistent. In contrast, regulatory agencies such as the EPA and the Food and Drug Administration, use a more conservative model for hazard assessment of environmental dioxins that is based on extrapolating dose-response curves linearly down to zero, the linearized multistage model. This model assumes the worst case, that dioxins are complete carcinogens, for which it has generally not been possible to define threshold levels, since a single molecular interaction with DNA can in theory cause a mutational event that starts the process of carcinogenesis. A recent review discusses many of these environmental issues (Safe 1991). In view of their relevance both to interpreting the findings from toxicologic studies in experimental animals, and to making health hazard assessments in humans, it is only fitting that recent studies of the mechanism of action of dioxins and related compounds be considered in depth.

The major thrust of basic research over the past decade has established that most biological effects of TCDD and related compounds are exerted through a mechanism that involves interaction with an intracellular receptor. The steps involved have been concisely summarized in recent reviews by Denison (Denison 1991) and by Landers and Bunce



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(1991a). The receptor for TCDD occurs in the cytosol fraction of a wide range of tissues and organisms. It also appears to be involved in the action of a number of complex aromatic compounds. Because of the aromatic character of the ligands that interact with it, and the prototypical biochemical result of exposure to them, namely the induction of the hepatic enzyme aryl hydrocarbon hydroxylase (AHH), the receptor with which they interact was termed the aromatic hydrocarbon responsiveness (Ah) receptor. After TCDD binds to the Ah receptor, the complex undergoes a process of transformation, the details of which still remain to be completely elucidated, that enables it to translocate to the nucleus and interact with special sites on DNA, the dioxin-responsive elements (DRE). This interaction allows dioxins to modulate the activities of a battery of genes, most notably CYPIA1 and CYPIA2, which are the structural genes responsible for the synthesis of cytochromes P450IA1 and P450IA2. The increased levels of these cytochromes and other enzymes which result, bring about the metabolism of the ligands that initiated the process (and more especially of other compounds) to products which might include either detoxified materials that are excreted, or activated intermediates that can damage critical targets within the cell. Although most studies have concentrated on the CYPIA1 gene and its associated DRE, it is likely that there are analogous dioxin-responsive sites flanking other genes, and that altered expression of the latter may in part underlie the species and tissue variations in TCDD toxicity. These variations lead to interspecies $LD_{50}$ levels that range from 0.6-2.5 $\mu$g/kg in guinea pigs to 1,157-5,051 $\mu$g/kg in hamsters (World Health Organization 1989). Even two strains of a single species may show a difference in sensitivity of a similar order of magnitude. Han/Wistar rats, for example, can tolerate up to 3,000 $\mu$g/kg, while Long-Evans rats are killed by 20 $\mu$g/kg of TCDD (Tuomisto and Pohjanvirta 1991). At present there is insufficient information available to determine exactly where humans fit on the scale of species sensitivity.

In the sections that follow, we will consider recent work on the Ah receptor itself first, and then relate this to the various modulations in gene expression and other events that may stem from it.



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## B. The Ah Receptor

The Ah receptor is a member of the erb-A family which also includes the receptors for steroid and thyroid hormones and retinoic acid. It binds a variety of aromatic compounds, such as the polycyclic hydrocarbons, heterocyclic amines, and polychlorinated aromatics that include dioxins, dibenzofurans and biphenyls, and is able to mediate many of their biological actions. Some of these compounds, such as the polycyclic hydrocarbons, do not act exclusively through the Ah receptor but also interact with other receptors. No endogenous ligand for the Ah receptor has yet been identified, and indeed, it is possible that its function relates exclusively to exogenous agents that are continually entering living organisms, and must be eliminated in order to maintain the internal cellular milieu. Previous volumes of the *Review* have presented the literature in which the interaction of dioxins with the Ah receptor was initially demonstrated. Most current research is concerned with the nature and properties of the receptor, and the kinetics, mechanism and biological implications of this interaction.

Studies of the role of the Ah receptor in dioxin action continue, as in the past, to utilize for the most part, mammalian (usually rodent) liver or hepatoma tissue as the experimental system of choice. However, the receptor is widely distributed, and recent reports suggest that other systems may offer advantages in specific situations. One species that might be of relevance to questions that are of environmental concern, is the rainbow trout. The RTG-2 cell line which is derived from the embryonic gonad cells of this teleost fish, contains a 145 kDa Ah receptor protein, that is larger than the mammalian receptor, but shows an order of affinity for agonists that is similar to the latter for a range of ligands (Swanson and Perdew 1991). In another study, it was found that primary hepatocyte cell cultures from this fish are closely analogous to rodent liver, in terms of a dose-dependent increase in the activity of ethoxyresorufin O-deethylase (EROD) activity and levels of P450IA1 determined immunologically, on exposure to TCDD and $\beta$-naphthoflavone. This effect was especially long-lived for TCDD (Pesonen *et al.* 1991; Pesonen and Andersson 1992).

Closer to the purview of this *Review*, in an extension of earlier findings, the Ah receptor was characterized in human tonsillar tissue. The receptor, present at levels of



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100-300 fmol/ mg cytosol, could transform to a nuclear binding form sedimenting at 6 S (Lorenzen and Okey 1991). The human B lymphoblastoid cell line BCR-5 has also served as a source of a characterized human Ah receptor (Waithe *et al.* 1991). This receptor was present at levels of about 200 fmol/mg of protein as a 9 S peak that bound labeled TCDD, had an apparent binding affinity ($K_D$) of about 5nM, and was extracted from the nuclei as a complex with TCDD that sedimented at 5 S. These two systems offer the opportunity to study the mechanism of action of TCDD in a surgically-available human tissue and a standard cell line, respectively, which may be especially appropriate for approaching mechanistic questions regarding the potential human immunotoxicity of dioxins. Other potential sources of human material appear to be the Mz-Hep-1 human liver cell line described by Roberts *et al.* (1991), human placenta (Lucier 1991), and the human colon adenocarcinoma cell line LS 180 (Harper *et al.* 1991a). Levels of the receptor in the latter cells were as high as 500 fmol/mg protein, similar to those in mouse hepatoma cells. The cytosolic form corresponded to a multimer of molecular weight 285 Kda, compared to 175 Kda for the nuclear TCDD-bound form that sedimented at 6.2 S. The smallest ligand-binding subunit was a 110-Kda fragment. It is apparent from the reported characteristics of these human Ah receptor preparations that they are similar in their general properties to the rodent materials.

Nevertheless, there are sufficient interspecies variations in the properties of the various Ah receptors, especially in terms of ligand affinities, to justify the study of a range of systems. For example, tritiated TCDD and 7-($^{125}$I)iodo-2,3-dibenzo-*p*-dioxin as high-affinity ligands were used to photoaffinity label nuclear Ah receptor from rodent (H-4-II E and Hepa 1c1c7) and human (Hep G2) cells. Yields of photoaffinity-labeled nuclear Ah receptor were much lower (0.5-2.5%) from mouse cells compared to human (>15%), suggesting a difference in stability of the two complexes. In experiments using photolyzed or unphotolyzed complexes of the photoaffinity-labeled nuclear Ah receptor with synthetic DRE, gel mobilities of the rodent and human complexes were found to differ, and the binding of the human receptor complex underwent significant (27%) photolysis, in contrast to the rodent material (Wang *et al.* 1991). In the human colon carcinoma LS180, the affinity of the Ah receptor for TCDD ($K_d$ value about 5 Nm, also for 3-methylcholanthrene)



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and sensitivity of the cells to AHH induction were an order of magnitude lower than in the murine system (Harper *et al.* 1991a). Finally, a striking difference has been observed in the effect of sodium molybdate on human Ah receptor as contrasted with that from other species (Harper *et al.* 1991c). Molybdate at 20 Nm added before or during ligand binding by human receptor completely prevented formation of receptor-DNA complexes, whereas rodent preparations showed no such sensitivity. It appeared that molybdate stabilized the multimeric 9 S form of the receptor. This observation has practical consequences in studies of the Ah receptor, since molybdate has been used to help stabilize the receptor during manipulation, especially in the case of the human preparation, which appears to be more labile than that from rodents. Whether such differences underlie the extreme variations in species and strain sensitivity to dioxins that have been documented is at present unclear.

Mouse liver Ah receptor has been purified more than 150,000-fold from C57BL/6J mice to yield a 95 Kda protein with an N-terminal peptide sequence determined as: ala/asp-ser-Arg-Lys-arg-Lys-Pro-Val-Gln-Lys-Thr-Val-Lys-Pro-Ile-Pro-Ala-Glu-Gly-Ile-Lys-ser-Asn-Pro-ser-Lys-(the use of lowercase for certain residues indicates some uncertainty in their characterization)(Bradfield *et al.* 1991). However, it is known that more than one form of the receptor occurs, even within the same tissue, and modulation of these different forms may constitute a normal *in vivo* function. Using a combination of DNA-Sepharose chromatographic fractionation, SDS-polyacrylamide gel electrophoresis and photoaffinity labeling techniques with rat liver cytosols, it has been shown (Gasiewicz *et al.* 1991a) that the DNA-binding form of the Ah receptor is a multimer consisting of at least two components, of which the 100-kDa protein binds TCDD, whereas the 110-kDa peak does not. The 100-kDa monomer, bound to ligand, must interact with the 110-kDa protein to generate the 200-kDa form of the receptor that binds with high affinity to the dioxin-responsive elements (DRE), such as the DNA recognition motifs upstream of CYPRIA1 and other possible sites that are less well established, thus regulating gene expression. Landers *et al.* (1991b) have described an inducible Ah receptor-like protein in rat liver that was detectable after cotreatment with TCDD and 2,2',4,4',5,5'-hexa-chlorobiphenyl. This protein was essentially indistinguishable from the constitutive



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receptor in terms of chromatographic behavior and molecular weight (about 150 Kda), but was kinetically distinct, being more stable thermally, but with a first order rate constant for dissociation from TCDD of 0.55 versus $<0.0024$ $min^{-1}$ for the normal Ah receptor.

Like the steroid receptors, the Ah receptor is known to occur normally as an inactive complex with the heat shock protein hsp 90, sedimenting at 9-10 S. In Hepa 1c1c7 cells, for example, all the cytosolic Ah receptor is in the bound form, whereas in the nucleus there is also a 6 S form without hsp 90, which has a more basic pI and enhanced ability to specifically bind ATP (Perdew 1991). The cytosolic complex cannot bind to target DNA sequences until it is dissociated from this complex. It is of interest that apart from mild heating, which would be expected, given the nature of hsp 90, physiological levels of ATP also appear to stimulate the conversion of the complexed Ah receptor to its DNA-binding form (Cary and Dougherty 1991a; Cary *et al.* 1991b). However, this point is not entirely clear, since Perdew's data (Perdew 1991) would suggest that interaction with ATP occurs only after the Ah receptor has translocated to the nucleus. The availability of a cell-free system that exhibits dioxin-induced activation of latent Ah receptor to the form which binds DNA (Cuthill *et al.* 1991) may help elucidate the complete details of the transformation process. In this system, the presence of ligand alone was sufficient to activate the cytosolic receptor to a DNA-binding form. The order of ligand effectiveness in inducing activation in this system was closely correlated with relative affinity for the receptor and ability to lead to gene transcription *in vivo*. Prokipcak and Okey (1991) have studied the short-term fate of the Ah receptor in mouse hepatoma cells (Hepa-1) exposed to tritiated TCDD. During the first 2 hours, there was translocation of cytoplasmic Ah receptor with a rise in the nuclear form, but by 5 hours the latter had fallen to about 50% of maximal concentrations. This process was not accompanied by regeneration of the cytosolic form, or by recycling into that compartment of the nuclear receptor, so that by 6 hours the total cellular level of receptor was only 15-20% of the initial value. It could not be determined whether this short-term effect was due to reversible loss of ligand-binding capacity, resulting from some molecular modification, or to loss of receptor protein itself.



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The transformation of cytosolic receptor-TCDD complex to the active nuclear form may represent a possible site for differences in inherent sensitivity to dioxins. In a study of two classes of mutant strains of mouse hepatoma (Hepa 1c1c7) cells, class I was found to have low levels of both cytosolic and nuclear receptor, whereas in class II, levels of TCDD receptor in the cytosol were comparable to those in the wild strain, but the nuclear complex was significantly reduced. Since incubation of ligand-bound cytosol from class II cells with cytosol from class I cells transformed the ligand-bound receptor to active DNA-binding material, it was suggested that failure of class II cells to respond to TCDD was due, at least in part, to a defect in the factors responsible for transformation (Piskorska-Pliszczynska *et al.* 1991b).

There is increasing evidence for the existence of other factors which also may modulate the Ah receptor. By pretreating rat hepatic cytosol with activated charcoal before adding tritiated TCDD as the tracer ligand, transformation of receptor to the DNA binding form was inhibited. However, cytosol from either DBA/2J mice, which as was mentioned above shows negligible affinity for TCDD, or from rats where the Ah receptor had been prebound and thus saturated with unlabeled TCDD, stimulated the transformation (Henry and Gasiewicz 1991b). This implies the existence of a cytosolic transforming factor which is independent of ligand binding, that can be adsorbed or inactivated by charcoal. Gel retardation studies of the partially-purified untransformed receptor suggested that the factor is a heat-labile, trypsin-sensitive protein of molecular weight somewhat greater than 50 kDa, which associates with the monomeric TCDD-bound subunit to enable it to bind to the DRE that constitute the target DNA sequences. In the need for this additional factor(s) in order to interact with DNA, the Ah receptor differs from the steroid receptors, but resembles those for thyroid hormone and 1,25-dihydroxyvitamin $D_3$. Studies from Oliver Hankinson's group also have provided information about an additional factor required in the transformation process. The cDNA and part of the gene were cloned for a protein required in the translocation of the TCDD-bound subunit from the cytosol to the nucleus. This 87-kDa protein has certain features in its sequence that relate to the basic helix-loop-helix DNA binding-proteins, while others resemble two *Drosophila* proteins, Per and Sim (Hoffman *et al.* 1991).



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## C. Mechanism of Ah Receptor Interaction with TCDD

The mechanism whereby TCDD interacts with the Ah receptor and modulates gene expression is becoming better understood as an increasing variety of techniques is applied to the problem. Studies with inhibitors are frequently very fruitful in providing information about the underlying mechanism of action of imperfectly understood processes like the dioxin interaction. In the case of TCDD, such studies are providing information about other factors that may be involved in the basic interaction. Inhibitory effects of two different enzymes on TCDD-receptor function have been described. In one case, the specific DNA-binding ability of the TCDD-Ah receptor complex was reduced or abolished by incubating with acid phosphatase, an effect that was in its turn inhibited by sodium phosphate (Pongratz *et al.* 1991). These findings suggest that as in other transcriptional processes, the function of the dioxin receptor may be regulated by phosphorylation.

Acting at a somewhat earlier step in the process, ribonuclease A decreased the affinity of TCDD-Ah receptor complex for DNA, and inhibited transformation of the TCDD-bound receptor to the DNA-binding form, without altering the number of potential binding sites, or affecting the preformed TCDD-receptor complex (Henry *et al.* 1991a). This introduces the possibility that, as in the case of the steroid hormone receptors, RNA plays some as yet undefined role in Ah receptor transformation. A different mechanism is indicated for the inhibitory effect of α-naphthoflavone (Gasiewicz and Rucci 1991b). This compound apparently functions as an antagonist of TCDD, competing for binding to the Ah receptor, and blocking the ability of TCDD to transform the receptor to a form able to bind to DRE. In a similar fashion, 6-$^{125}$I-methyl-8-iodo-1,3-dichlorodibenzofuran, an antagonist of TCDD, was found to act by competition between the ligand-receptor complexes for nuclear binding (Piskorska-Pliszczynska *et al.* 1991a). Chlorinated *trans* stilbenes also compete with TCDD for receptor binding, and act as antagonists of monooxygenase induction by TCDD, while themselves functioning as weak agonists for enzyme induction (Bunce *et al.* 1990). Finally, administration of the tumor promoter 12-*O*-tetradecanoylphorbol-13 acetate to C57BL/6 mice at the same time as TCDD, abolished the accumulation of the nuclear dioxin receptor observed on treatment with TCDD alone,



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thereby inhibiting transcriptional activation of the CYPIA1 and CYPIA2 genes (Okino and Tukey 1991). It is possible that this also represents a competitive action.

With respect to the molecular details of the interaction with specific DNA sequences, a gel retardation study undertaken with rat hepatic cytosol (Denison and Yao 1991) indicated that there is a protein factor(s) which binds to DRE in a manner that is TCDD-inducible, and dependent on sequence, time and temperature. This factor has Ah receptor ligand specificity. The affinity of the complex for DRE was more than 3800 times stronger than for non-specific DNA sequences. The total concentration of transformed receptor was estimated as 56.1 fmole/mg protein, and a chelatable divalent cation appeared to play a role in the transformation. In rat liver, the two DRE sites located about 1 kb upstream of the cytochrome P 450IA1 gene (CYPIA1) exist prior to ligand induction, a process which does not affect their Dnase I-hypersensitivity. A constitutive, labile factor, which is distinct from the Ah receptor recognizes and binds to the DRE *in vitro*. However, there is another Dnase I-hypersenitive site that is responsive to xenobiotics located near the transcription initiation region. This differs from the DRE sites in that its DNase sensitivity markedly increases after induction by $\beta$-naphthoflavone (Hapgood *et al.* 1991).

Attention has been given to structure-activity relationships in Ah receptor interactions. While some studies have determined the actual amount of bound ligand, others have used some surrogate measure of receptor interaction, such as enzyme induction. The Computer-Automated Structure Evaluation Program, automatically selects descriptors for structure-activity relationships. It was applied to Ah receptor binding by 223 compounds, using data taken from the literature. These compounds included polycyclic aromatic hydrocarbons (PAH), substituted dibenzo-*p*-dioxins, dibenzofurans, biphenyls, nitro-PAH, halo-PAH and *N*-heterocyclics, from two databases, one comprising 136 compounds studied by sucrose density gradient techniques, and the other of 87 compounds that were subjected to electrofocussing assays (Rannug *et al.* 1991). Among the PAH and heterocyclic compounds, those fragments with the classical "bay" region, previously related to carcinogenesis, were the most strongly correlated with TCDD receptor binding. On the other hand, in the case of the dioxins and benzofurans,



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receptor binding affinity was associated with the presence of halogens in lateral positions; longitudinal substitutions decreased receptor affinity. The absence of common biophores between these two classes of compounds, both of which have high affinity for the Ah receptor, suggests that there may be two different recognition sites involved in receptor interaction.

Another study by Kobayashi *et al.* (1991) that examined structure-activity relationships, correlated biological activity with calculations of the energy difference between the homo and the lowest unoccupied molecular orbitals. The order of decreasing energy difference from molecular orbital considerations was TCDD, followed by the 1,2,3,7,8-penta-chloro-, 1,2,3,7,8,9-hexachloro-, 2,3,7-trichloro- and 2,8-dichloro-analogs; this was consistent with the biological toxicity and AHH-inducing capacity of the compounds.

In an assessment of the biological activities of mixtures of various polychlorinated dioxins, as measured by the induction of EROD activity in primary rat hepatocyte cultures and the hepatoma H4IIE cell line, activity was found to reflect the additive effects of the 2,3,7,8-substituted components (Schrenk *et al.* 1991b). A similar relationship was evident in a comparison of the efficacy for hepatic AHH induction in C57 and DBA mice of TCDD, 2,3,4,7,8-pentachlorodibenzofuran, and 3-methyl-sulfonyl-4,5,3',4'-tetrachlorobiphenyl, as compared with 7,8-benzoflavone and methylcholanthrene (Nagayama *et al.* 1991). Koga *et al.* (1991) found TCDD and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin to be similarly potent in enzyme induction in rat liver, but the pentachloro- derivative persisted in the animal for a longer period of time. Studies in which the inductive potency of TCDD has been compared with its tetrabromo-analog, TBDD, or mixed halogenated congeners, in terms of EROD activity, have shown them to be essentially equipotent (Kedderis *et al.* 1991; Schulz-Schalge *et al.* 1991).

It is possible that differences in the properties of Ah receptor with respect to its interaction with TCDD might affect an organism's inherent sensitivity to this agent. Thus, in a comparison of hepatic cytosols from C57BL/6J mice, which are responsive to TCDD, in terms of the induction of cytochrome P450 and aryl hydrocarbon hydroxylase (AHH) on exposure to this dioxin, and the nonresponsive strains DBA2J, AKR/J and SWR/J,



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Harper and coworkers had shown in 1989 that the amount of Ah receptor and its affinity for TCDD were both much lower in the latter strains. When the study was extended to embryonic cells, this distinction still existed, but was found to be less pronounced, with a two-fold rather than a ten-fold difference in affinity for TCDD (Harper *et al.* 1991b). At present there is no obvious explanation for the difference between adult and embryonic tissues. Strain differences in the distribution pattern of the $Ah^d$ and $Ah^{b-3}$ alleles of the mouse Ah receptor gene have been described recently by Poland and Glover (1991).

We will next turn to the biochemical implications of Ah receptor interactions, many of which can be understood best in terms of a battery of six Ah-related genes (Nebert *et al.* 1989a; 1989b). In the conventional terminology used for drug metabolism, there are two Phase I genes, CYPIA1 and CYPIA2, which encode for cytochrome P450 forms, and four Phase II genes encoding for: NAD(P)H:quinone oxidoreductase (NQO1, alternatively termed NMO1 for menadione as the natural quinone); aldehyde dehydrogenase (ALDH-3) associated with tumor; UDP-glucuronyl transferase (UGT-1); and glutathione transferase (GT-1). TCDD induces all members of this battery.

## D. Induction of Cytochrome P450

The recent reports of receptor interactions outlined above have continued to stress the resultant induction of one form of cytochrome P450, cytochrome P450IA1. Indeed, so characteristic is the induction of this cytochrome by polychlorinated dibenzo-*p*-dioxins and dibenzofurans, that Schrenk *et al.* (1991a) have suggested that the presence of the hepatic microsomal enzyme EROD, which is a functional parameter of P450IA1, is a useful bioindicator of exposure of feral animal populations to these agents. Anderson and her coworkers (1991) have demonstrated that P450IA1 and EROD activities, once induced, may persist at high levels for prolonged periods. In adult male Swiss mice, both parameters were still elevated in the liver one month after a single low dose (5 nmole/kg) of TCDD, while in the lung, EROD activity was even more pronounced, being elevated 10-fold at 12 weeks. These authors considered that such extreme persistence in the lung, which was even more pronounced in animals treated with Aroclor 1254, would be sufficient for tumor promotion, if P450IA1 induction was indeed a factor in tumorigenesis.



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Studies by Jones *et al.* (1991), in which transgenic mice were created by using a DNA fragment containing the CYPIA1 enhancer elements and promoter, coupled with the chloramphenicol acetyltransferase reporter (CAT) gene, have indicated that this region functions as a strongly-inducible promoter *in vivo*, and that there are gender-specific differences in response to induction. Even in a fish such as the rainbow trout, induction of P450IA1, together with MRNA for the responsible CYPIA1 gene, can readily be demonstrated (Pesonen and Andersson 1992). The central role played by the P450 family of cytochromes in the oxidation of drugs, toxins and various exogenous compounds is well known; a recent review has covered aspects most relevant to the metabolism of toxins and carcinogens (Guengerich and Shimada 1991).

The molecular regulation of gene expression for the P450IA family has received recent attention. Nemoto *et al.* (1991) have stressed that regulation of aryl hydrocarbon hydroxylase (AHH) induction in primary hepatocyte cultures from TCDD responsive (C57BL/6) and nonresponsive (DBA/2) mice is qualitatively similar but quantitatively different. Thomsen and her colleagues (1991) have continued studies in human breast carcinoma cell lines of differing responsiveness to TCCD, by employing an expression vector containing the functional 5'-regulatory region of human CYPIA1 fused to the reporter gene CAT for chloramphenicol acetyltransferase. Lines highly responsive to TCDD, in terms of the amount of CYPIA1 mRNA induced, were also highly responsive to TCDD in the chloramphenicol acetyltransferase assay. These responsive cell lines expressed a nuclear protein that binds the DRE. A similar correlation between induction of CYPIA1 mRNA and of acetyltransferase held for the poorly or nonresponsive lines, and the authors concluded that poor response reflected altered *trans*-acting factors. In the case of one of these poorly-responsive lines (CAMA-1), an Ah receptor constitutively bound to the Ah responsive element was postulated, leading to high basal activity coupled with low induction. Studies using pyridine as the inducer have demonstrated an interesting difference between cytochrome P450 subfamilies. Induction of both P450IA1 and P450IA2 is associated with increased mRNA levels through either transcription or stabilization, a known outcome of earlier work, reviewed by Lusska *et al.* (1991), whereas



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in contrast, induction of P450IIE1 which belongs to a different cytochrome P450 subfamily, appears to result from the increased efficiency with which it is translated (Kim *et al.* 1991).

Immunological techniques have been used with success to demonstrate the localization of P450 induction. In rats, low doses of both TCDD and Aroclor 1254 induced P450IA1 primarily in the acinar zone 3 of the liver, whereas after high doses there was no zonal pattern of induction, as determined by polyclonal antibodies raised against this cytochrome (Bars and Elcombe 1991). It is of interest that similar immunologic probes, in addition to EROD activity, have been used to establish the induction of p450IA1 and other cytochromes in a human colon cell line; this system may be relevant to colon carcinogenesis (White *et al.* 1991). An analogous immunohistochemical technique has been adapted to demonstrate the localization of P450IA1 induced in the liver and other tissues of the teleost fish (*Stenotomus chrysops*) by chlorinated benzofuran and biphenyl derivatives (Smolowitz *et al.* 1991; Stegeman *et al.* 1991).

Among other Ah-dependent enzymatic effects that have been observed is the bilirubin-degrading system induced in rat liver microsomes by TCDD, which, like the well-correlated induction of EROD activity, is inhibited by a monoclonal antibody raised against cytochrome P450IA1 (DeMatteis *et al.* 1991). Another interesting effect of this type is the superinduction of the Phase II enzyme aldehyde dehydrogenase in rat hepatoma cells, whereby cotreatment with the protein synthesis inhibitors puromycin or cycloheximide caused a 10-fold greater accumulation of the ALDH-3 mRNA than the induction produced by TCDD alone. Transcription rates for the ALDH-3 gene were increased 4- to 5-fold, consistent with the existence of a labile protein factor for gene transcription that modulates the action of TCDD (Takimoto *et al.* 1991).

While nearly all the literature on induction of P450 and the hepatic microsomal system associated with it has been concerned with TCDD and its congeners, a few reports have examined 2,4-D. Thus, in the channel catfish, *Ictalurus punctatus*, a 10-day exposure to a mixture of 2,4-D and picloram led to increased serum levels of EROD. However, this change was not seen on exposure to either compound alone (Gallagher and DiGiulio 1991). In mice treated with various combinations of pesticides that included 2,4-D (Chaturvedi *et al.* 1991), induction of the hepatic microsomal mixed-function



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oxygenase system was clearly associated only with combinations containing toxaphene. In chicken embryo liver, 2,4-D (1, 2 or 4 mg/egg) raised the levels of hepatic post-microsomal glutathione-S-transferase and EROD activities, but not of other hepatic mixed-function oxygenases (Santagostino *et al.* 1991). Thus, the overall conclusion is that 2,4-D alone does not appear to be an effective inducer of the mixed-function oxygenase system, but can contribute to such an effect when it is administered as a component of the appropriate combinations.

## E. Interaction of TCDD with Other Receptors and Effects on Expression of Other Genes

Apart from its primary interaction with the Ah receptor, TCDD also intervenes in other receptor-mediated processes, albeit in most cases through processes that are Ah-dependent; however, some immunologic studies have suggested an Ah-independent mechanism. This has been discussed at some length in earlier volumes of the *Review*. Two recent examples of such interactions come from research by Goldstein's group at the National Institute of Environmental Health Sciences. In the first study, a single oral dose of TCDD in an Ah-responsive ($Ah^{b/b}$) strain of C57BL/6J mice led to a 30% decrease in the binding capacities of both hepatic glucocorticoid and estrogen receptors, and a 50-fold induction of EROD activity which is specifically associated with the P450IA subfamily of cytochromes. Ah-nonresponsive ($Ah^{d/d}$) mice showed a 10-fold lower level of enzyme induction, and a statistically-significant difference in the sensitivity of the estrogen receptor. However, there was a similar degree of reduction in binding capacity of the glucocorticoid receptor, and of tyrosine aminotransferase activity which is mediated by this receptor, in both responsive and nonresponsive strains (Lin *et al.* 1991b). This suggests that while the Ah receptor may mediate the effects of TCDD on the estrogen receptor, this mechanism does not apply to the glucocorticoid receptor. In females of the same responsive and nonresponsive mouse strains, TCDD caused an 80-90% decrease in the maximum binding capacity of the epidermal growth factor (EGF) receptor, but the $ED_{50}$ for this effect was 10-fold higher in the $Ah^{d/d}$ compared with the $Ah^{b/b}$ strain. Since TCDD did not affect total hepatic contents of the mRNA transcripts of either the EGF

receptor (both the 10 and 6 kb transcripts) or transforming growth factor alpha (TGF-$\alpha$), while markedly increasing mRNA for cytochrome P450IA1 with the same 10-fold difference in $ED_{50}$ for the two strains, it is most probable that the effects of TCDD on the EGF receptor are mediated by the Ah receptor (Lin *et al.* 1991a).

There have been a number of reports describing effects of TCDD on the expression of genes other than CYPIA1. Aoki *et al.* (1991) examined rat liver after both *in vivo* and *in vitro* exposure to TCDD. They identified induced P450IA1 and P450IA2 with specific antibodies, but also noted increased amounts of five other proteins with molecular weights of 26 (2 proteins), 36 and 39 (2 proteins) kD after *in vivo* treatment, and reductions in three additional proteins (24, 25 and 29 kD) when liver parenchymal cells were exposed to TCDD. No identity or functional role was ascribed to any of these new proteins, but some induction effects noted in the literature could have significant biological repercussions.

When cultures of human keratinocytes (SCC-12F) were exposed to TCDD on a continuing basis, TGF-$\alpha$ was released into the medium at a rate of about 30 fmol/ml/day, accompanied by a 3- to 6-fold increase in the expression of mRNA for this factor. The process appeared to be mediated through the Ah receptor (Choi *et al.* 1991). This may be a tissue- or species-dependent effect, since as described above, Lin *et al.* (1991a) failed to show an effect on TGF-$\alpha$ mRNA in mouse liver. It is interesting that treatment of C57BL/6J($Ah^{b/b}$) mice with TCDD (10-500 $\mu$g/kg) produced up to a 48-fold increase in the release of another biologically-active polypeptide, tumor necrosis factor-$\alpha$, when the animals were challenged with endotoxin. A much smaller effect was seen in the ($Ah^{d/d}$) strain which is Ah-receptor deficient. Thus this effect is mediated through the Ah receptor system (Clark *et al.* 1991a). Whether it plays any role in the wasting syndrome characteristic of TCDD intoxication is unknown.

The SCC-12F keratinocyte line also has been the source of five TCDD-responsive complementary clones from which cDNA libraries were prepared (Sutter *et al.* 1991). Of these four clones, one was found to encode plasminogen activator inhibitor-2 (which modulates proteolysis of extracellular matrix thus influencing growth and differentiation), and another encoded interleukin-1 $\beta$, permitting TCDD to affect both differentiation and



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inflammation. NAD(P)H:quinone oxidoreductase (NQO1), which is identical to diaphorase 4, is a flavoprotein which catalyzes the reduction of various quinones, and which is believed to protect against their toxicity and carcinogenicity. This enzyme is induced by TCDD, with an accompanying 3-fold increase in transcription of the NQO1 gene in human hepatoblastoma (Hep-G2) cells. The human gene for NQO1 has been cloned and partially sequenced, and the cDNA transfected into COS-1 monkey cells in which the enzyme was expressed (Jaiswal 1991; Shaw *et al.* 1991). Among the findings from sequence analysis was a copy of GCGTG at position 740 that resembled the xenobiotic/dioxin response elements in CYPIA1. It is interesting that TCDD, which has a number of antiestrogenic actions, decreased constitutive levels of *c-fos* mRNA in the rat uterus, and markedly inhibited the stimulatory effect of 17 $\beta$-estradiol on this parameter when administered at the same time as the hormone (Astroff *et al.* 1991). We shall consider some of the interrelationships of TCDD with steroid hormones in the next Section. There was a report in 1988 (Burt and Thorgeirsson 1988) that TCDD increased rodent liver levels of mRNA transcribed from both multidrug resistance (MDR) and CYPIA2 genes. Recent attempts to repeat these observations, studying CYPIA1, NQO-1 and MDR1, -2, and -3 have been unsuccessful, however (Teeter *et al.* 1991).

In a study with potential relevance to immunotoxicity, it was found that TCDD increases the phosphorylation of membrane protein in B lymphocytes, an action at least in part attributable to stimulation of tyrosine-specific phosphorylation (Clark *et al.* 1991b). This effect was observed within minutes, exhibited a dose-response curve identical to that for inhibition of antibody synthesis, and appeared to be unrelated to protein kinase C. The protein synthesis inhibitors, puromycin and cycloheximide, and an inhibitor of transcription, actinomycin D, partially prevented the increase, suggesting that new protein synthesis is required. This study confirms and extends earlier work in B cells and thymocytes. Holsapple *et al.* (1991) have reviewed the evidence for phosphorylation as an action of TCDD that might be independent of mediation by the Ah receptor, although such independence would be hard to establish if Ah receptor action itself involves some type of phosphorylation as the evidence discussed above would suggest.



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Finally, with regard to the enzymes of Phase II drug metabolism, a recent review has discussed the possible role played by phenol UDP-glucuronyl transferase, an isozyme induced by TCDD, as a control for proximate carcinogens, and a contributor to the persistently altered enzyme pattern in premalignant stages of cancer development (Bock 1991).

## F. General Metabolic Effects of Dioxins

The polychlorinated dioxins and biphenyls are capable of a wide range of biological actions. In the case of the polychlorinated biphenyls (PCBs), a recent review has attempted to attribute their effects to an Ah-mediated production of PCB metabolites which intervene in endocrine and Vitamin A metabolism (Brouwer 1991). TCDD shares at least some of the characteristics of PCBs, including interaction with the Ah receptor and intervention in endocrine systems, for which reason it has been termed an "environmental hormone" (Schmidt 1992).

### 1. Effects on Endocrine Systems

A number of studies have examined the question of modulation of steroid hormone function by TCDD, which has been shown to exert both antiestrogenic and antiandrogenic actions. The antiestrogenic character of TCDD and related compounds has been reviewed recently by Safe *et al.* (1991). Actions falling into this category include inhibition of 17 $\beta$-estradiol-induced increases in uterine weight, estrogen and progestin receptor levels, EGF receptor binding, *c-fos*- and EGF mRNA levels, and peroxidase activity. The structure-activity relationships for TCDD and similar compounds as antiestrogens closely parallels their affinities for the Ah receptor, and the effects of TCDD are inhibited by both actinomycin D and cycloheximide. In wild-type Hepa 1c1c7 cells, TCDD produced as much as a 74% decrease in immunodetectable cytosolic and nuclear estrogen receptor protein, but only if the cells were pretreated with TCDD for 1 to 42 hours before addition of labeled estradiol (Zacharewski *et al.* 1991). Mutant lines with defects in Ah receptor levels or in formation of transcriptionally-active receptor complexes, showed minimal or no response to TCDD. Reduction of receptor protein must also form the basis for other

recently-observed effects, such as inhibition of the estradiol-induced stimulation of glucose to lactate conversion in MCF-7 human breast cancer cells (Narasimhan *et al.* 1991). This NMR study of 1-$^{13}$C-glucose metabolism, demonstrated an inhibitory effect within 1 hour, in contrast to induced monooxygenase activity, which was not seen before 3 hours.

The antiandrogenic effects of TCDD appear to arise by a quite different mechanism, one that involves luteinizing hormone (LH). TCDD has long been known to cause ultrastructural changes in the testis, with impaired spermatogenesis in the rat, associated with reduced plasma concentrations of testosterone and its 5 $\alpha$-dihydro-derivative. Lowered androgen levels were associated with decreased levels of testicular cytochrome $P450_{17\alpha}$, 17 $\alpha$-hydroxylase and $C_{17\text{-}20}$ lyase activities. Although earlier data had suggested that levels of LH were unaffected, it now appears that the plasma level of this hormone is indeed reduced by 40% within one day. Treatment of rats with human chorionic gonadotropin (hCG) prevented the inhibition of these androgenic parameters (Ruangwises *et al.* 1991). Additional information has been obtained in this area by Moore *et al.* (1991) whose results suggested that TCDD inhibits the LH-dependent mobilization of cholesterol to the cytochrome $P450_{scc}$ system responsible for pregnenolone synthesis, by acting at a step subsequent to the formation of cAMP.

Another endocrine system that has been reported to be sensitive to the action of TCDD is melatonin synthesis or secretion. In order to clarify this effect, Linden *et al.* (1991) studied the most TCDD-resistant strain of rats (Han/Wistar) from 6 hours to 28 days after exposure to the dioxin. A single intraperitoneal injection of TCDD (50 $\mu$g/kg) lowered serum melatonin by 50% within a day, and kept it at this level for the total observation period. However, even after a dose as high as 1,000 $\mu$g/kg, there was no light or electron microscopic evidence of histopathology in the pineal gland 3 days after injection of TCDD. There is as yet no information regarding the mechanism involved.

2. Effects on Vitamin A Homeostasis

The ability of TCDD to interfere with Vitamin A metabolism figured prominently in the 1990 literature reviewed in Volume XVII of the *Review*. The analogies between the Ah and the retinoid receptors, and the superficial similarities in many of the symptoms



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resulting from Vitamin A deficiency and exposure to TCDD, namely hypophagia, weight loss, cutaneous morphologic changes, elevated renal levels of retinoids and diminished hepatic Vitamin A levels, make it plausible to consider that the same underlying mechanism is at work. To date, however, no studies have approached this problem at the molecular level which should provide the most definitive data, although work further documenting the interrelationship of Vitamin A and TCDD in whole animals has appeared recently.

Two reports from the Karolinska Institute dealt with this topic. In a study that included male Hartley guinea pigs, Sprague-Dawley rats, C57BL/6 and DBA/2 mice, and Golden Syrian hamsters, the animals were given intraperitoneal injections of isotoxic doses of TCDD (in the range 0.5 to 400 $\mu$g/kg), and sacrificed after 1, 7, 14, 28, 56 and 112 days. The time-related increase in hepatic storage of Vitamin A was inhibited by TCDD, but only the guinea pig, which is especially sensitive to dioxin, failed to have increased levels of the vitamin at the end of the experiment. Only in the rat could there be seen a marked increase in renal, and a slight increase in serum, levels of the vitamin. Pulmonary Vitamin A fell in all except C57BL/6 mice (Hakansson *et al.* 1991a). The same group supplemented the diets of rats given single oral doses of TCDD with Vitamin A at 2,000, 5,000, 8,000 or 21,000 IU per kg, and obtained data which suggested that low levels of dietary Vitamin A were associated with impaired ability to tolerate the lethal action of TCDD. Loss of total body or testicular weight, or liver enlargement, were more severe at low levels of dietary Vitamin A, but loss in thymus weight was equally severe in all groups. Except for the kidney, where there was an increase, levels of Vitamin A fell in most tissues examined (Hakansson *et al.* 1991b).

In hairless (hr/hr) mice, Vitamin A deficiency caused the keratinization of dermal epithelial cysts (structures derived from the involution of hair follicles), and enhanced the hyperkeratinization induced by topical treatment with TCDD; body weight and thymus gland atrophy were unaffected by Vitamin A status. No cutaneous changes were seen in the congenic haired mice. TCDD treatment did not affect the cutaneous levels of Vitamin A, but significant reductions in those in the liver occurred in both hairless (48% after 0.6 $\mu$g over 2 weeks) and haired (70% after 6 $\mu$g over 2 weeks) mice. The authors

suggested that the data are not consistent with the concept that TCDD toxicity is mediated via an induced Vitamin A deficiency state (Puhvel *et al.* 1991). Infant male Sprague-Dawley rats exposed to TCDD derived from their mothers' milk exhibited induction of EROD activity, reduction in liver and lung Vitamin A content, and rises in the levels of this vitamin in the kidney and serum. These changes were seen at doses of TCDD that did not affect significantly the food consumption, growth or organ weights of the dams, although liver, kidney and serum, but not lung Vitamin A levels, and hepatic EROD activities, showed similar changes to those seen in the nurselings (Waern *et al.* 1991).

Modulation of TCDD- or phenobarbital-induced promotion of hepatocarcinogenesis by manipulation of dietary Vitamin A has been studied in Sprague-Dawley rats (Flodstrom *et al.* 1991). Carcinogenesis was initiated with 30 mg/kg of nitrosodiethylamine, followed by the promoters at 0.07 or 0,7 $\mu$g per week by subcutaneous injection for TCDD, or 500 ppm in the drinking water in the case of phenobarbital, for a total of 16 weeks. The incidence of $\gamma$-glutamyltranspeptidase-positive altered hepatic foci (AHF) was used as a surrogate marker of hepatocarcinogenesis. Both TCDD and phenobarbital stimulated the development of AHF. Vitamin A deficiency also led to an increase in AHF by itself, and furthermore, enhanced the induction of foci by TCDD but not by phenobarbital. Vitamin A deficiency also tended to increase other toxic effects of TCDD. Feeding the animals a cereal diet rather than a purified diet based on casein, led to greater formation of AHF in groups treated with TCDD. Finally, both TCDD and phenobarbital lowered hepatic levels of Vitamin A, but plasma retinol concentrations were only affected by TCDD in rats on the purified diet. These data do not support the concept that a TCDD-induced vitamin A deficiency is the primary mechanism for hepatic tumor promotion by TCDD, but are compatible with a modulating role for this deficiency in concert with some other mechanism.

3. Effects on Intermediary Metabolism

The acute toxicity of TCDD is characterized by wasting which is believed to be associated primarily with food refusal, although it is possible that there might also be a



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contribution from other effects, such as the release of tumor necrosis factor (TNF-α), or the changes in hypothalamic histamine and β-endorphin discussed earlier. Whatever the mechanism, the resultant hypoglycemia is a well established effect of TCDD in rats, which is accompanied by early alterations in the release of $CO_2$ from administered labeled glucose, and evidence of a reduced rate of gluconeogenesis. Two recent reports (Weber *et al.* 1991a; 1991b) have ascribed this reduction to significant dose-dependent decreases in the activities of phosphoenol-pyruvate carboxykinase (PEPCK) and pyruvate carboxylase, enzymes generally considered to be rate-limiting steps in gluconeogenesis, and a trend toward reduction in glucose-6-phosphatase. These losses in enzyme activities were significant within 2 days, and maximal at 50% or more, 8 days after dosing with TCDD at 5-125 μg/kg. It appeared that the primary effect was exerted on PEPCK, which was affected earlier and more strongly; the other enzyme changes followed. It is entirely plausible that the inhibition of PEPCK results in early accumulation of tryptophan, a gluconeogenic substrate, and a precursor of the appetite suppressant neurotransmitter serotonin. Thus an increased serotonin turnover may occur with resulting food refusal. Impairment of the D-glucose transport system and $Na^+/K^+$ ATPase in the plasma membranes of human skin fibroblasts has been reported to occur after exposure to 2,4-D (Cascorbi and Foret 1991). Using various xenobiotics, a correlation emerged between this action and lipophilicity of the compound. It is not known whether TCDD has a similar action, and if it does, whether this effect is related to the changes in glucose utilization noted above.

Several reports were devoted to the interaction of TCDD with lipid metabolism. A single dose of 20 μg/kg of TCDD produced in rats a marked mobilization of depot fat, giving within 3 days up to a 2.8-fold increase in plasma free fatty acids. Significant inhibition of hepatic oleate oxidation occurred, together with even more marked (85 and 69%, respectively) stimulation of ketogenesis from oleate and octanoate. Ketogenesis from glycerol, and its oxidation to $CO_2$, were both inhibited. The authors suggested that TCDD inhibited complete oxidation of lipids via the tricarboxylic acid cycle, and the formation of acetyl CoA from glycerol, while diverting acetyl CoA derived from fatty acids to ketogenesis (Lakshman *et al.* 1991). Even if there is reduced oxidation of lipids via the



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tricarboxylic acid cycle, however, there remains the possibility that peroxisomal oxidation is able to sustain adequate levels of lipid oxidation. Two reports relevant to this question, described the induction of peroxisomal fatty acid oxidation in rat liver by TCDD (Al-Bayati and Stohs 1991) and by a number of chlorinated phenoxyacetic and phenoxypropionic acid derivatives, including 2,4,5-T (Kozuka *et al.* 1991). The study with TCDD suggested that phospholipase-$A_2$, lipoxygenase and hydrogen peroxide were involved in the microsomal peroxidation induced by 40 $\mu$g/kg of TCDD. On the other hand, another report (Sanner *et al.* 1991) concluded that there was no induction of this system in Syrian hamster cells exposed to 2,4-D or 2,4,5-T. McKim *et al.* (1991) showed that the TCDD-induced accumulation of free fatty acids in rats produced, by allosteric interaction, a 65% inhibition of hepatic acetyl CoA carboxylase, a key enzyme in fatty acid synthesis. This mobilization of fat is consistent with observations of changes in respiratory quotients made in the chick embryo (Lentnek *et al.* 1991), which demonstrated that exposure to TCDD increased dependence on fats as a fuel source. In the same study, experiments in which fatty acid oxidation was inhibited by aminocarnitine, gave results consistent with the suggestion that the reliance upon fatty acids resulted from impaired production, but not utilization, of carbohydrate. For such studies of respiratory quotients, the chick embryo system presents advantages over the use of adults of this or any other species, because it obviates the problems of compensating for both the energy entailed in movements by the animals, and the effect of hypophagia resulting from any TCDD toxicity.

When Chinese hamster ovary (CHO) cells were exposed to 2,4-D the synthesis of protein and DNA was inhibited, and the cells were arrested at the G1/S interphase. These effects appear to be related to alterations in polyamine metabolism, specifically an inhibition of ornithine decarboxylase activity, and reduction in intracellular levels of spermine and spermidine, without significant effects on putrescine (Rivarola and Balegno 1991a; 1991b).



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## G. Summary and Conclusions

Recent studies have further documented the central role of the Ah receptor system in the mechanism of TCDD-induced toxicity, and have provided additional information on the molecular nature of the interaction between ligand and receptor. This primary interaction serves as the basis for effects on other systems, most notably xenobiotic metabolism, steroidogenesis and lipid metabolism. However, the possibility of other mechanisms has not been excluded, and indeed, some evidence has been published during 1991 which favors such additional sites of action. Although TCDD induces a vitamin A-deficient state, this does not appear to be a primary mechanism of TCDD toxicity. The increasing use of a broader range of study systems affords the opportunity to define more clearly the mechanistic basis for differences in tissue and species sensitivity to TCDD. This is particularly true for human tissues, since the position of humans in the wide spectrum of species sensitivity to dioxin remains uncertain. Such understanding is essential for definitive assessment of the human health hazard presented by dioxins and related compounds.



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Weber, L.W.D., B.U. Stahl, M. Lebofsky, R.H. Alper, L. Kerecsen and K. Rozman. (1991b) Inhibition of phosphoenolpyruvate carboxykinase activity appears to be the key biochemical lesion in the acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Chemosphere 23(11-12): 1957-1962.

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# REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

## Volume XX: Annotated Bibliography of Recent Literature on Health Effects Published in 1991

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Abbott, B. and L. Birnbaum (1991) TCDD exposure of human embryonic palatal shelve s in organ culture alters the differentiation of medial epithelial cells. Teratology 43(2): 119-132.

Key Terms: teratologic effects, acute toxicity, experimental exposure, dioxins, in vitro, journal article

See pages 41 and 42.

Abenhaim, L., S. Cordier, D.D. Le, D. Bard, D.C. Hoang, B. Larouze and M.F. Gonnord (1991) Consequences of Agent Orange on health - the INSERM study in Vietnam. Arch. Environ. Health 46(2): 119.

Key Terms: cancer, reproductive toxicity, chronic toxicity, environmental exposure, military exposure, dioxins, human, abstract

See page 24.

Adams, S.L., S.T. Horvat, A.E. Irwin, R.W. Junkin, N.M. Koreman and B.R. Blakley (1991) The effects of Tordon 202c exposure on urethan-induced lung adenoma formation in female CD-1 mice. Vet. Hum. Toxicol. 33(3): 209-211.

Key Terms: cancer, subchronic toxicity, oral, 2,4-D, picloram, mouse, journal article

See pages 33 and 74.

Al-Bayati, Z.A.F. and S.J. Stohs (1991) The possible role of phospholipase A2 in hepatic microsomal lipid peroxidation induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Arch. Environ. Contam. Toxicol. 20(3): 361-365.

Key Terms: hepatotoxicity, enzyme induction or inhibition, oral, dioxin, rat, journal article

See page 115.

Albanese, R.A. (1991) The chemical 2,3,7,8-tetrachlorodibenzo-p-dioxin and U.S. Army Vietnam-era veterans. Chemosphere 22(5-6): 597-604.

Key Terms: Tissue residues, military exposure, dioxins, human, model

See pages 27, 79 and 80.

Ames, B.N. (1991) Natural carcinogens and dioxin. Sci. Total Environ. 104(1-2): 159-166.

Key Terms: cancer, chronic toxicity, genetic toxicity, dioxins, unspecified route of exposure, human, other species, in vitro, commentary or opinion

The author states that studies of the toxicology of high doses of synthetic chemicals must be viewed in the context of the world of natural chemicals to which humans are exposed. When tested at near toxic doses, where cell killing occurs, about one half of all synthetic or natural compounds are carcinogens, one third are teratogens and one half are clastogens. At the very low doses of most human exposures, such synthetic chemicals do not kill cells and the health hazards are very low or zero; dioxin is used as an example.

Ames, B.N. and L.S. Gold (1991) Cancer prevention strategies greatly exaggerate risks. Chem. Eng. News Jan 7: 28-32.

Key Terms: cancer, chronic toxicity, genetic toxicity, teratologic effects, oral, dioxins, human, commentary or opinion

See page 44.

Anderson, L., L. Beebe, S. Fox, H. Issaq and R. Kovatch (1991) Promotion of mouse lung tumors by bioaccumulated polychlorinated aromatic hydrocarbons. Exp. Lung Res. 17(2): 455-471.

Key Terms: cancer, subchronic toxicity, enzyme induction or inhibition, gavage, dioxins, mouse, journal article

See page 104.

Andersson, L., E. Nikolaidis, B. Brunstrom, A. Bergman and L. Dencker (1991) Effects of polychlorinated biphenyls with Ah receptor affinity on lymphoid development in the thymus and the bursa of Fabricius of chick embryos in ovo and in mouse thymus anlagen in vitro. Toxicol. Appl. Pharmacol. 107(1): 183-188.

Key Terms: immunotoxicity, acute toxicity, other route of exposure, PCB, bird, journal article

See page 50.

Aoki, Y., E.K. Silbergeld, S.R. Max and B.A. Fowler (1991) Alterations in protein synthesis in rat liver cells by in vitro and in vivo exposure to 2,3,7,8-tetrachloro-dibenzo-p-dioxin. Biochem. Pharmacol. 42(6): 1195-1201.

Key Terms: hepatotoxicity, other toxic effects, mechanism of action, experimental, dioxins, in vitro, journal article



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See pages 68 and 108.

Arnold, E.K., V.R. Beasley, A.J. Parker and J.R. Stedelin (1991) 2,4-D toxicosis II: a pilot study of clinical pathologic and electroencephalographic effects and residues of 2,4-D in orally dosed dogs. Vet. Human Toxicol. 33(5): 446-449.

Key Terms: neurobehavioral effects, acute toxicity, oral, 2,4-D, dog, journal article

See pages 64, 65 and 89.

Arnold, E.K., R.A. Lovell, V.R. Beasley, A.J. Parker and J.R. Stedelin (1991) 2,4-D toxicosis III: an attempt to produce 2,4,-D toxicosis in dogs on treated grass plots. Vet. Human Toxicol. 33(5): 457-461.

Key Terms: neurobehavioral effects, other toxic effects, acute toxicity, environmental exposure, 2,4-D, dog, journal article

See pages 64, 65 and 89.

Ashby, J. and R.W. Tennant (1991) Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. Mutat. Res. 257(3): 229-306.

Key Terms: cancer, genetic toxicity, experimental, dioxins, picloram, rodent, in vitro, review

See pages 30 and 74.

Astroff, B., B. Eldridge and S. Safe (1991) Inhibition of the 17beta-estradiol-induced and constitutive expression of the cellular proto-oncogene c-fos by 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) in the female rat uterus. Toxicol. Appl. Pharmacol. 56(305-315.

Key Terms: alterations in sex hormones, other toxic effects, acute toxicity, mechanism of action, injection, dioxins, rat, journal article

See page 109.

Astroff, B. and S. Safe (1991) 6-Alkyl-1,3,8-trichlorodibenzofurans as antiestrogens in female Sprague-Dawley rats. Toxicology 69(2): 187-197.

Key Terms: alteration in sex hormones, acute toxicity, experimental, furans, rat, journal article



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Treatment of rats with 17 β-estradiol at 0.33 μmol/kg x 2 increased uterine wet weight, EGF, estrogen and progesterone receptor levels, and EGF receptor mRNA. 6-Methyl-1,3,8-trichlorodibenzofuran and its 6-t-butyl analog, which have moderate Ah receptor affinity, decreased the estradiol and constitutive response at a dose of 100 μmol/kg, whereas the low-affinity 6-cyclohexyl congener had no effect. These furans have low toxicity that may make them useful antiestrogens.

Bailar, J.C., 3d (1991) How dangerous is dioxin? [Editorial; comment]. N. Engl. J. Med. 324(4): 260-262.

Key Terms: cancer, chronic toxicity, occupational exposure, dioxin, human, commentary

This editorial accompanied the Fingerhut report on the NIOSH study of cancer in workers at 12 sites exposed to dioxin contamination. While admitting that the latter study did not disclose an overwhelming increase in overall cancer mortality, and that it involved few cancer deaths, he considered that it should be taken as a flag of a probable human risk. The estimated risk of soft tissue sarcoma of about 2 per 1,000 greatly exceeds acceptable public lifetime risks of 1 per 100,000 or 1 per million.

Banks, Y. and L. Birnbaum (1991) Absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after low dose dermal exposure. Toxicol. Appl. Pharmacol. 107(2): 302-310.

Key Terms: pharmacokinetics, tissue residues, dermal, dioxins, rat, journal article

See page 88.

Barnes, D.G. (1991) Toxicity equivalents and EPA's risk assessment of 2,3,7,8-TCDD. Sci. Total Environ. 104(1-2): 73-86.

Key Terms: miscellaneous study, dioxins, human, journal article

See pages 86 and 94.

Bars, R.G. and C.R. Elcombe (1991) Dose-dependent acinar induction of cytochromes P450 in rat liver. Evidence for a differential mechanism of induction of P450IA1 by β-naphthoflavone and dioxin. Biochem. J. 277(Pt 2): 577-580.

Key Terms: enzyme induction or inhibition, injection, dioxin, rat, journal article

See page 106.



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Beasley, V.R., E.K. Arnold and R.A. Lovell (1991) 2,4-D Toxicosis 1: a pilot study of 2,4-dichlorophenoxyacetic acid- and dicamba-induced myotonia in experimental dogs. Vet. Human Toxicol. 33(5): 435-440.

Key Terms: neurobehavioral effects, acute toxicity, oral, 2,4-D, dog, journal article

See pages 64 and 65.

Becker, M., T. Phillips and S. Safe (1991) Polychlorinated diphenyl ethers - a review. Toxicological and Environmental Chemistry 33(3-4): 189-200.

Key Terms: dioxins, fish, furans, rat, review, tissue residues

This is a review of the toxicity, measurement, metabolism, tissue retention, excretion and environmental/toxicologic implications of polychlorinated diphenyl ethers. Research data from rats and fish are examined.

Becker, M.C. (1991) Toxicity of polychlorinated diphenyl ethers in Hydra attenuata and in rat whole embryo culture (Thesis). 1-97.

Key Terms: teratologic effects, acute toxicity, experimental exposure, dioxins, rat, thesis

This thesis includes a review of the toxicity and environmental issues regarding these compounds, and the wide range of species and habitats in which they have been detected. New studies reported in the thesis include work that demonstrated in both the Coelenterate, Hydra, and in rat embryos, that these compounds, including TCDD, are neither embryotoxic nor teratogenic.

Beebe, L.E., S.D. Fox, H.J. Issaq and L.M. Anderson (1991) Biological and biochemical effects of retained polyhalogenated hydrocarbons. Environmental Toxicology and Chemistry 10(6): 757-763.

Key Terms: cancer, enzyme induction or inhibition, dioxins, furans, rat, mouse, review

In this review, both new data and the literature were used to examine the long term effects of persistent body burdens of these compounds, in terms of tumor formation and cytochrome P450-associated mixed function oxidase induction. Effects of specific congeners on lung tumor formation initiated by N-nitrosodimethylamine, their retention by tissues, and the induction of enzymes such as aminopyrine demethylase, are consistent with activation of the Ah receptor being integral to tumor promotion by these compounds.

Bertazzi, P. (1991) Long-term effects of chemical disasters. Lessons and results from Seveso. Sci. Total. Environ. 106(1-2): 5-20.

Key Terms: chloracne, neurobehavioral effects, cardiovascular toxicity, cancer, hepatotoxicity, chronic toxicity, other route of exposure, dioxins, human, journal article

See pages 28, 29, 59, 67 and 82.

Bestervelt, L.L., C.J. Nolan, Y. Cai, P. Maimansomsuk, C.A. Mousigian and W.N. Piper (1991) Tetrachlorodibenzo-p-dioxin alters rat hypothalamic endorphin and mu opioid receptors. Neurotoxicol. Teratol. 13(1-6): 495-497.

Key Terms: neurobehavioral effects, acute toxicity, oral, dioxins, rat, journal article

After acute oral dosage with TCDD (50$\mu$g/kg), hypophagia and weight loss occurred in rats, accompanied by initial increase in hypothalamic beta-endorphin to 166% of control on day 1. By days 2 and 3, levels of beta-endorphin had fallen to 39% and 49% control, respectively. Brain mu-opioid receptor number was increased 60% in TCDD-treated rats on day 3. These effects were not seen in food-restricted rats, implicating involvement of changes in these receptors in hypophagia.

Birnbaum, L.S., R.E. Morrissey and H. M.W. (1991) Teratogenic effects of 2,3,7,8-tetrabromodibenzo-p-dioxin and three polybrominated dibenzofurans in C57BL/6N mice. Toxicol. Appl. Pharmacol. 107(1): 141-152.

Key Terms: teratologic effects, acute toxicity, gavage, dioxins, mouse, journal article

See page 43.

Bishop, C., R. Brooks, J. Carey, P. Ng, R. Norstrom and D. Lean (1991) The case for a cause-effect linkage between environmental contamination and development in eggs of the common snapping turtle (Chelydra S.serpentina) from Ontario, Canada. J. Toxicol. Environ. Health 33(4): 521-547.

Key Terms: reproductive toxicity, chronic toxicity, environmental, dioxins, furans, turtle, journal article

See page 44.

Bjeldanes, L., J. Kim, K. Grose, J. Bartholomew and C. Bradfield (1991) Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol



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in vitro and in vivo: comparisons with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Proc. Natl. Acad. Sci. U.S.A. 88(21): 9543-9547.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

This study compared the binding by Ah receptor of the carbazole metabolite of the dietary carcinogenesis modulator, indole-3-carbinol, with that of TCDD. The role of this binding in different carcinogenic and anticarcinogenic actions of indole-3-carbinol was discussed.

Blevins, R. (1991) 2,3,7,8 Tetrachlorodibenzodioxin in fish from the Pigeon River of eastern Tennessee, USA: its toxicity and mutagenicity as revealed by the Ames Salmonella assay. Arch. Environ. Contam. Toxicol. 20(3): 366-370.

Key Terms: genetic toxicity, tissue residues, environmental, dioxins, fish, journal article

See page 38.

Bock, K. (1991) Roles of UDP-glucuronosyltransferases in chemical carcinogenesis. Crit. Rev. Biochem. Mol. Biol. 26(2): 129-150.

Key Terms: cancer, mechanism of action, experimental, dioxins, in vitro, review

See page 110.

Bock, K.W. (1991) Dioxin carcinogenicity. Dtsch. Med. Wochenschr. 116(24): 959.

Key Terms: cancer, dioxins, human, commentary or opinion, in German

Bradfield, C.A., E. Glover and A. Poland (1991) Purification and N-terminal amino acid sequence of the Ah receptor from the C57BL/6J mouse. Mol. Pharmacol. 39(1): 13-19.

Key Terms: mechanism of action, experimental, dioxins, mouse, journal article

See page 98.

Brouwer, A. (1991) The role of enzymes in regulating the toxicity of xenobiotics. Biochem Soc (London) 19(3): 731-737.



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Key Terms: enzyme induction or inhibition, mechanism of action, environmental exposure, other route of exposure, dioxins, PCBs, review

See page 110.

Buchta, M. and B. Dolezal (1991) Problems of polychlorinated dibenzo-p-dioxins and dibenzofurans. Chem. Listy 85(2): 158-170.

Key Terms: dioxins, furans, review

This is an analysis of the problems that are associated with the particular chemical and biological properties of the dioxins and furans.

Calvert, G.M., M.H. Sweeney, J.A. Morris, M.A. Fingerhut, R.W. Hornung and W.E. Halperin (1991) Evaluation of chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function among workers exposed to 2,3,7,8-tetrachloro-dibenzo-p-dioxin. Am. Rev. Respir. Dis. 144(6): 1302-1306.

Key Terms: other organic toxicity, chronic toxicity, occupational exposure, dioxins, human, journal article

See pages 70 and 81.

Campt, D.D., J.V. Roelofs and J. Richards (1991) Pesticide regulation is sound, protective, and steadily improving. Chem. Eng. News Jan 7: 44-47.

Key Terms: cancer, other toxic effects, chronic toxicity, oral, environmental, other route of exposure, pesticide, human, commentary or opinion

As participants in a C & EN News forum, the authors defend current regulatory practices, but stress that many chemicals registered years before lack the basis of scientific studies that is now required. This gap is being attended to. There is special need for knowledge of long-term, low-level exposure effects. The need for ensuring public trust is also stressed.

Carlo, G.L., K.G. Sund, R.W. Morgan, L. Hardell, M. Erikkson, O. Axelson, L.R. Goldman, D. Hayward, D.M. Siegel, R.D. Stephens et al. (1991) Dioxin and mortality from cancer [Letter]. N. Engl. J. Med. 324(25): 1809-1812.

Key Terms: cancer, chronic toxicity, occupational exposure, dioxins, human, commentary or opinion

See page 25.

Carpenter, W.D. (1991) Insignificant risks must be balanced against great benefits. Chem. Eng. News Jan 7: 37-39.

Key Terms: cancer, oral, pesticides, commentary or opinion

As a participant in a C & EN News forum, the author discusses the benefits provided by agricultural chemicals. He stresses that the Delaney clause is not compatible with today's highly sensitive assay technology, which can detect substances in the parts per billion or trillion range, at which levels there are no discernable risks.

Cary, A.J., P.A. Martin and J.J. Dougherty (1991) ATP promotes the appearance of two DNA-binding forms of the Ah receptor. Arch. Biochem. Biophys. 288(1): 287-292.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 99.

Cary, A.J. and J.J. Dougherty (1991) Nucleoside triphosphates promote the transformation of Ah receptor to its DNA form. Biochem. J. 274(Mar): 401-404.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 99.

Cascorbi, I. and M. Foret (1991) Interaction of xenobiotics on the glucose-transport system and the Na+/K(+)-ATPase of human skin fibroblasts. Ecotoxicol. Environ. Safety 21(1): 38-46.

Key Terms: enzyme induction or inhibition, mechanism of action, experimental exposure, 2,4-D, in vitro, journal article

See page 114.

Chahoud, I., R. Krowke, G. Bochert, B. Burkle and D. Neubert (1991) Reproductive toxicity and toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin. 2. Problem of paternally-mediated abnormalities in the progeny of rat. Arch. Toxicol. 65(1): 27-31.

Key Terms: reproductive toxicity, teratologic effects, dioxins, rats, journal article

See page 42.

Chaturvedi, A., D. Kuntz and N. Rao (1991) Metabolic aspects of the toxicology of mixtures of parathion, toxaphene and/or 2,4-D in mice. J. Appl. Toxicol. 11(4): 245-251.

Key Terms: mechanism of action, oral, 2,4-D, mouse, journal article

See pages 106 and 107.

Choi, E., D. Toscano, J. Ryan, N. Riedel and W.J. Toscano (1991) Dioxin induces transforming growth factor-alpha in human keratinocytes. J. Biol. Chem. 266(15): 9591-9597.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 108.

Cikryt, P. (1991) Ah-receptor, ARNT (Ah-receptor nuclear translocation) protein and toxicity of dioxins. Chemie in Unserer Zeit 25(4): 176.

Key Terms: mechanism of action, dioxins, experimental, journal article

Cikryt, P. (1991) Endangering mankind - dioxin and related compounds. Nachr. Chem., Tech. Lab. 39(6): 650-656.

Key Terms: chronic toxicity, environmental exposure, dioxins, human, review

Clapp, R.W., L.A. Cupples, T. Colton and D.M. Ozonoff (1991) Cancer surveillance of veterans in Massachusetts, USA, 1982-1988. Int. J. Epidemiol. 20(1): 7-12.

Key Terms: cancer, military exposure, phenoxy herbicides, human, journal article

See page 21.

Clark, G.C., J.A. Blank, D.R. Germolec and M.I. Luster (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin stimulation of tyrosine phosphorylation in B lymphocytes: potential role in immunosuppression. Mol. Pharmacol. 39(4): 495-501.

Key Terms: immunotoxicity, mechanism of action, experimental, dioxins, journal article

See pages 54, 55 and 109.

Clark, G.C., M.J. Taylor, A.M. Tritscher and G.W. Lucier (1991) Tumor-necrosis factor involvement in 2,3,7,8-tetrachlorodibenzo-para-dioxin-mediated endotoxin hyper-

sensitivity in C57BL/6J mice congenic at the Ah locus. Toxicol. Appl. Pharmacol. 111(3): 422-431.

Key Terms: toxicity, mechanism of action, dioxins, mouse, journal article

Clark, G., A. Tritscher, G. Lucier and M. Taylor (1991) Dose-dependent increase in tumor necrosis factor-alpha production in TCDD exposed mice is Ah dependent. Chemosphere 23(11-12): 1817-1823.

Key Terms: mechanism of action, unspecified route of exposure, dioxins, mouse, journal article

See page 108.

Coggon, D., B. Pannett and P. Winter (1991) Mortality and incidence of cancer at four factories making phenoxy herbicides. Br. J. Ind. Med. 48(3): 173-178.

Key Terms: cancer, chronic toxicity, occupational exposure, phenoxy herbicide formulations, human, journal article

See page 26.

Collins, J.J., J.F. Acquavella and B.R. Friedlander (1992) Reconciling old and new findings on dioxin. Epidemiology 3(1): 65-69.

Key Terms: cancer, chloracne, chronic toxicity, occupational exposure, dioxins, human, commentary or opinion

See page 29.

Cooper, K.R., H. Liu, P.-A. Bergqvist and C. Rappe (1991) Evaluation of Baltic herring and Icelandic cod liver oil for embryo toxicity, using the Japanese medaka (Oryzias latipes) embryo larval assay. Environ. Toxicol. Chem. 10(6): 707-714.

Key Terms: reproductive toxicity, chronic toxicity, environmental exposure, dioxins, furans, fish, journal article

See page 44.

Couture-Haws, L., M.W. Harris, A.C. Lockhart and L.S. Birnbaum (1991) Evaluation of the persistence of hydronephrosis induced in mice following in utero and/or lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 107(3): 402-412.

Key Terms: other toxic effects, acute toxicity, oral, dioxin, mouse, journal article

See pages 43 and 88.

Couture-Haws, L., M.W. Harris, M.M. McDonald, A.C. Lockhart and L.S. Birnbaum (1991) Hydronephrosis in mice exposed to TCDD-contaminated breast milk: identification of the peak period of sensitivity and assessment of potential recovery. Toxicol. Appl. Pharmacol. 107(3): 413-428.

Key Terms: other toxic effects, acute toxicity, oral, dioxin, mouse, journal article

See page 88.

Craig, T.O. and R.B. Grzonka (1991) A time-dependent 2,3,7,8-tetrachlorodibenzo-p-dioxin body-burden model. Arch. Environ. Contam. Toxicol. 21(3): 438-446.

Key Terms: pharmacokinetics, environmental exposure, dioxins, human, journal article

See pages 84 and 85.

Cuthill, S., A. Wilhelmsson and L. Poellinger (1991) Role of the ligand in intracellular receptor function: receptor affinity determines activation in vitro of the latent dioxin receptor to a DNA-binding form. Mol. Cell Biol. 11(1): 401-411.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 99.

Dalager, N.A., H.K. Kang, V.L. Burt and L. Weatherbee (1991) Non-Hodgkin's lymphoma among Vietnam veterans. J. Occup. Med. 33(7): 774-779.

Key Terms: cancer, chronic toxicity, military exposure, 2,4-D, 2,4,5-T, human, journal article

See page 22.

Daly, H. (1991) Reward reductions found more aversive by rats fed environmentally contaminated salmon. Neurotoxicol. Teratol. 13(4): 449-453.

Key Terms: neurobehavioral effects, acute toxicity, oral, fish, rat, environmental exposure, journal article



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See page 63.

Davis, D. and S. Safe (1991) Halogenated aryl hydrocarbon-induced suppression of the in vitro plaque-forming cell response to sheep red blood cells is not dependent on the Ah receptor. Immunopharmocology 21(3): 183-190.

Key Terms: immunotoxicity, acute toxicity, experimental, dioxins, mechanism of action, in vitro, journal article

See page 54.

Dearman, R.J. and I. Kimber (1991) Immunotoxicity and allergy - opportunities for in vitro analysis. Toxicology In Vitro 5(5-6): 519-524.

Key Terms: immunotoxicity, in vitro, journal article

DeFerrari, M., M. Artuso, S. Bonassi, S. Bonatti, Z. Cavalieri, D. Pescatore, E. Marchini, V. Pisano and A. Abbondandolo (1991) Cytogenetic biomonitoring of an Italian population exposed to pesticides: chromosome aberration and sister-chromatid exchange analysis in peripheral blood lymphocytes. Mutat. Res. 260(1): 105-113.

Key Terms: cancer, genetic toxicity, occupational exposure, 2,4-D, phenoxy herbicides, human, journal article

See page 38.

DeMatteis, F., S. Dawson, A. Boobis and A. Comoglio (1991) Inducible bilirubin-degrading system of rat liver microsomes: role of cytochrome P450IA1. Mol. Pharmacol. 40(5): 686-691.

Key Terms: hepatotoxicity, mechanism of action, enzyme induction or inhibition, injection, dioxins, rat, journal article

See page 106.

Denison, M.S. (1991) The molecular mechanism of action of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons. Chemosphere 23 (11-12): 1825-1830.

Key Terms: enzyme induction or inhibition, mechanism of action, unspecified route of exposure, dioxins, review

See pages 94 and 95.

Denison, M.S. and Y. E.F. (1991) Characterization of the interaction of transformed rat hepatic cytosolic Ah receptor with a dioxin responsive transcriptional enhancer. Arch. Biochem. Biophys. 284(1): 158-166.

Key Terms: mechanism of action, dioxins, experimental, in vitro, journal article

See page 102.

Dewailly, E., J.P. Weber, S. Gingras and C. Laliberte (1991) Coplanar PCB's in human milk in the province of Quebec, Canada - are they more toxic than dioxin for breast fed infants. Bull. Environ. Contam. Toxicol. 47(4): 491-498.

Key Terms: tissue residues, oral, dioxins, human, journal article

The levels of various coplanar PCB congeners were measured in human milk. Non-ortho coplanar congeners were found at ppt levels, and mono-ortho coplanar congeners were present at ppb levels. The authors conclude that in this study, PCBs represented a higher risk than PCDFs or PCDDs.

Dewailly, E., H. Tremblay-Rousseau, G. Carrier, S. Grouix, S. Gingras, K. Boffess, J. Stanley and J.P. Weber (1991) PCDDs, PCDFs and PCBs in human milk of women exposed to a PCB fire and of women from the general population of the province of Quebec - Canada. Chemosphere 23(11-12): 1831-1835.

Key Terms: tissue residues, other route of exposure, dioxins, furans, human, journal article

See page 86.

Dobkin, P., M. Dongier, D. Cooper and J.M. Hill (1991) Screening for alcoholism in a psychiatric-hospital. Can. J. Psychiatry 36(1): 39-45.

Key Terms: other toxic effects, military exposure, dioxins, human, journal article

This study investigated the correlation between alcoholism and various parameters, including military exposure to dioxins. No positive association with dioxin exposure was found.

Dragan, Y.P., T. Rizvi, Y.-H. Xu, J.R. Hully, N. Bawa, H.A. Campbell, R.R. Maronpot and H.C. Pitot (1991) An initiation-promotion assay in rat liver as a potential complement to the 2-year carcinogenesis bioassay. Fundam. Appl. Toxicol. 16: 525-547.



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Key Terms: cancer, enzyme induction or inhibition, experimental, dioxins, in vitro, journal article

See page 32.

Eisen, S.A., J. Goldberg, W.R. True and W.G. Henderson (1991) A co-twin control study of the effects of the Vietnam war on the self-reported physical health of veterans. Am J Epidemiol 134(1): 49-58.

Key Terms: cancer, other cutaneous effects, miscellaneous study, military exposure, phenoxy herbicide formulations, human, journal article

See page 17.

El Bahri, L. and S.B. Romdane (1991) Arsenic poisoning in livestock. Vet. Hum. Toxicol. 33(3): 259-264.

Key Terms: pharmacokinetics, oral, arsenic, cow, chicken, sheep, review

This article reviewed arsenic poisoning in cows, sheep and chickens by various arsenic-containing compounds, including cacodylic acid.

Elo, H.A., T. Luoma and P. Ylitalo (1991) Inhibition of human and rabbit platelet aggregation by chlorophenoxyacid herbicides. Arch. Toxicol. 65(2): 140-144.

Key Terms: hematologic effects, acute toxicity, injection, 2,4-D, 2,4,5-T, rabbit, journal article

See page 69.

Elsenhans, B., W. Forth and E. Richter (1991) Increased copper concentrations in rat tissues after acute intoxication with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Toxicol. 65(5): 429-432.

Key Terms: hepatotoxicity, acute toxicity, injection, dioxins, rat, journal article

When rats received 125 $\mu$g/kg of TCDD, and tissue metal contents determined by atomic emission spectrometry, there were increases in liver (>2-fold) and kidney (>4-fold) Cu relative to pair-fed controls. The effect was ascribed to impaired biliary excretion of Cu due to TCDD.

Eriksson, M. and L. Hardell (1991) New experiences strengthen the connection between dioxins, phenoxy acids and malignant tumors. Lakartidningen 88(24): 2210-2211.



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Key Terms: cancer, dioxins, phenoxy herbicides, human, journal article

This is a review in Swedish of the association of dioxins with non-Hodgkin's lymphoma and soft tissue sarcoma.

Fagan, J.B., F. Saatcioglu, D.J. Perry, M.E. Richardson and D.S. Pasco (1991) XF1 and XF2 act through xenobiotic response elements to modulate transcriptional activation of the cytochrome P450IA1 gene by the dioxin Ah receptor. J. Cell Biochem. Suppl. 15 Part B): 269.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, abstract

Two hepatic nuclear fractions, XF1 and XF2 were purified and characterized. These factors compete with the dioxin receptor for binding sites on the xenobiotic response elements, and may modulate the transcriptional regulatory function of the receptor.

Fahrig, R. (1991) Genetic effects of dioxin. Environ. Mol. Mutagen Suppl. 19): 24-25.

Key Terms: cancer, genetic toxicity, experimental exposure, dioxins, mouse, abstract

See page 38.

Fanelli, R. and S. Garattini (1991) Human exposure to dioxin. Prog. Clin. Biol. Res. 372: 167-177.

Key Terms: chronic toxicity, tissue residues, environmental exposure, occupational exposure, dioxins, human, review

This review covers the relative $LD_{50}$ values for TCDD compared with natural toxins, the sources of human exposure to dioxin, toxicology and dosimetry, and human serum levels in the NIOSH and Seveso studies.

Fingerhut, M.A., W.E. Halperin, D.A. Marlow, L.A. Piacitelli, P.A. Honchar, M.H. Sweeney, A.L. Greife, P.A. Dill, K. Steenland and A.J. Suruda (1991) Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. N. Engl. J. Med. 324(4): 212-218.

Key Terms: cancer, chronic toxicity, lethality, tissue residues, occupational exposure, dioxins, human, journal article

See pages 24 and 25.



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Fingerhut, M.A., K. Steenland, M.H. Sweeney, W.E. Halperin, L.A. Piacitelli and D.A. Marlow (1992) Old and new reflections on dioxin. Epidemiology 3(1): 69-72.

Key Terms: cancer, chronic toxicity, occupational exposure, dioxins, human, commentary

See page 29.

Flodstrom, S., L. Busk, T. Kronevi and U. Ahlborg (1991) Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin and phenobarbital-induced promotion of hepatocarcinogenesis in rats by the type of diet and vitamin A deficiency. Fundam. Appl. Toxicol. 16(2): 375-391.

Key Terms: cancer, subchronic toxicity, mechanism of action, oral, dioxins, rat journal article

See page 113.

Fokin, A.V., Y.A. Borisov, V.G. Enchev, N.I. Raevskii and N.P. Borob'eva (1991) Electron structure and geometry of the dioxin-type xenobiotics and their ecotoxicity. Dokl. Akad. Nauk. S.S.S.R. 316(5): 1165-1168.

Key Terms: toxicity, dioxins, mechanism of action, journal article

The toxicity of dioxins was analyzed in terms of their electronic structure and molecular configuration. The text is in Russian.

Forum (1991) Risk assessment of pesticides. Chem. Eng. News Jan. 7: 27-55.

Key Terms: cancer, chronic toxicity, unspecified route of exposure, dioxins, human, commentary or opinion

This is a compilation of several diverse views concerning pesticides and the risks which they pose to humans and the environment.

Gallagher, E. and R. DiGiulio (1991) Effects of 2,4-dichlorophenoxyacetic acid and picloram on biotransformation, peroxisomal and serum enzyme activities in channel catfish (Ictalurus punctatus). Toxicol. Lett. 57(1): 65-72.

Key Terms: other toxic effects, enzyme induction or inhibition, other route of exposure, 2,4-D, picloram, fish, journal article

See pages 75 and 106.



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Gasiewicz, T.A. and G. Rucci (1991) α-Naphthoflavone Acts as an antagonist of 2,3,7,8-tetrachlorodibenzo-p-dioxin by forming an inactive complex with the Ah receptor. Mol. Pharmacol. 40(5): 607-612.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 101.

Gasiewicz, T., C. Elferink and E. Henry (1991) Characterization of multiple forms of the Ah receptor: recognition of a dioxin-responsive enhancer involves heteromer formation. Biochemistry 30(11): 2909-2916.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 98.

Gawkrodger, D.J. (1991) Chloracne: causation, diagnosis and treatment. J. Dermatol. Treat. 2(2): 73-76.

Key Terms: chloracne, occupational exposure, dioxins, human, review

The author review the causes and clinical features of chloracne, stressing the principle signs (comedones) and the relative resistance to conventional acne treatments. Topical, but not systemic tretinoin may be of benefit, as is light cautery of comedones.

Gaylor, D.W. (1991) Biologically-based empirical dose-response model for cleft palate utilizing fetal weight reduction. Teratology 43(5): 436.

Key Terms: acute toxicity, experimental exposure, 2,4,5-T, mouse, abstract

Gebhardt, D.O.E., A.J. Moolenaar and A. Mohammed (1991) Distribution of lipophilic xenobiotics among plasma lipoproteins. Arch. Toxicol. 65(5): 436.

Key Terms: pharmacokinetics, dioxins, human, rat, commentary or opinion

This comment on the possible effect of hypertriglyceridemia on dioxin distribution among plasma lipoproteins is accompanied by a reply from A. Mohammed.

Gilman, A. and R. Newhook (1991) An updated assessment of the exposure of Canadians to dioxins and furans. Chemosphere 23(8-10): 1161-1167.



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Key Terms: oral, environmental exposure, dioxins, furans, human, journal article

Goldman, L.R., D. Hayward, D.M. Siegel and R.D. Stephens (1991) Dioxin and mortality from cancer (Letter). N. Engl. J. Med. 324(25): 1811.

Key Terms: cancer, tissue residues, occupational exposure, dioxins, human, commentary or opinion

See page 25.

Gordon, G.B. (1991) Induction of NAD(P)H:quinone reductase in human peripheral blood lymphocytes. Carcinogenesis 12(12): 2393-2396.

Key Terms: enzyme induction or inhibition, experimental, dioxins, in vitro, journal article

The authors describe a simple microtiter plate assay for quinone reductase activity. TCDD is among the compounds that induce this enzyme.

Gottlicher, M. and F.J. Wiebel (1991) 2,3,7,8-Tetrachlorodibenzo-para-dioxin causes unbalanced growth in 5L hepatoma-cells. Toxicol. Appl. Pharmacol. 111(3): 496-503.

Key Terms: other toxic effects, acute toxicity, experimental, dioxins, in vitro, journal article

Gough, M. (1991) Agent Orange: exposure and policy [Editorial]. Am. J. Public Health 81(3): 289-90.

Key Terms: cancer, other toxic effects, chronic toxicity, military exposure, dioxins, human, commentary or opinion

See page 13.

Gough, M. (1991) Human health effects: what the data indicate. Sci. Total Environ. 104(1-2): 129-158.

Key Terms: cancer, chloracne, chronic toxicity, acute toxicity, occupational exposure, dioxins, human, review

See page 29.

Green, L.M. (1991) A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. Br. J. Ind. Med. 48(4): 234-238.



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Key Terms: chronic toxicity, occupational exposure, phenoxy herbicides, human, journal article

Guengerich, F.P. and T. Shimada (1991) Oxidation of toxic and carcinogenic chemicals by human cytochrome P-450 enzymes. Chem. Res. Tox. 4(4): 391-407.

Key Terms: cancer, enzyme induction or inhibition, polycyclic hydrocarbons, review

See page 105.

Hakansson, H., E. Manzoor and U. Ahlborg (1991) Interaction between dietary vitamin A and single oral doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the TCDD-induced toxicity and on the vitamin A status in the rat. J. Nutr. Sci. Vitaminol. (Tokyo) 37(3): 239-255.

Key Terms: other toxic effects, acute toxicity, oral, dioxins, rat, journal article

See page 112.

Hakansson, H., L. Johansson, E. Manzoor and U. Ahlborg (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the vitamin A status of Hartley guinea pigs, Sprague-Dawley rats, C57Bl/6 mice, DBA/2 mice, and Golden Syrian hamsters. J. Nutr. Sci. Vitaminol. (Tokyo) 37(2): 117-138.

Key Terms: other toxic effects, subchronic toxicity, injection, dioxins, guinea pig, rat, mouse, hamster, journal article

See page 112.

Hall, T.A. (1991) The basis for measuring human exposure to dioxins, PCBs and their congeners. J. Occup. Med. 33(4): 538.

Key Terms: dioxins, PCBs, human, method, journal article

Hankinson, O., B. Brooks, K. Weir-Brown, E. Hoffman, B. Johnson, J. Nanthur, H. Reyes and A.J. Watson (1991) Genetic and molecular analysis of the Ah receptor and of Cypla1 gene expression. Biochimie 73(1): 61-6.

Key Terms: dioxin, mechanism of action, experimental, journal article

Hanson, D. (1991) EPA to take another hard look at dioxin health risk. Chemical and Engineering News 69(17): 13-14.

Key Terms: cancer, environmental exposure, dioxins, human, news report

This news report provides a concise, simply-written, overall view of developments in the areas of mechanism of action of dioxin, historical background to current controversy, the Ranch Hand Study, measurements of TCDD levels in special groups and the general population, antiestrogenic actions, and environmental findings. It deals with the effect of these factors on regulatory standards of the EPA.

Hanson, D.J. (1991) Dioxin toxicity: new studies prompt debate, regulatory action. Chem. Eng. News 69(32): 7-14.

Key Terms: chronic toxicity, acute toxicity, mechanism of action, dioxins, human, news report

Hapgood, J., S. Cuthill, P. Söderkvist, A. Wilhelmsson, I. Pongratz, R. Tukey, E. Johnson, J. Gustafsson and L. Poellinger (1991) Liver cells contain constitutive DNase I-hypersensitive sites at the xenobiotic response elements 1 and 2 (XRE1 and -2) of the rat cytochrome P-450IA1 gene and a constitutive, nuclear XRE-binding factor that is distinct from the dioxin receptor. Mol. Cell Biol. 11(9): 4314-4323.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 102.

Hardell, L., M. Eriksson, O. Axelson and M. Fredriksson (1991) Increased risk of soft tissue sarcoma in persons exposed to dioxin. Lakartidningen 88(47): 4005-4006.

Key Terms: cancer, chronic toxicity, environmental exposure, occupational exposure, dioxins, human, journal article

See page 26.

Harper, P.A., C.L. Golas and A.B. Okey (1991) Ah receptor in mice genetically "nonresponsive" for cytochrome P4501A1 induction: cytosolic Ah receptor, transformation to the nuclear binding state, and induction of aryl hydrocarbon hydroxylase by halogenated and nonhalogenated aromatic hydrocarbons in embryonic tissues and cells. Mol. Pharmacol. 40(5): 818-826.

Key Terms: mechanism of action, enzyme induction or inhibition, experimental, dioxins, in vitro, journal article

See pages 103 and 104.



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Harper, P., R. Prokipcak, L. Bush, C. Golas and A. Okey (1991) Detection and characterization of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in the human colon adenocarcinoma cell line LS180. Arch. Biochem. Biophys. 290(1): 27-36.

Key Terms: cancer, mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 98.

Harper, P.A., A.B. Okey and M.S. Denison (1991) Transformation of human Ah receptor to a form binding to a dioxin responsive element inhibition by sodium molybdate. J. Cell Biochem. Suppl. 15(Part B): 244.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, abstract

See page 98.

Haugland, R., U. Sangodkar, P. Sferra and A. Chakrabarty (1991) Cloning and characterization of a chromosomal DNA region required for growth on 2,4,5-T by Pseudomonas cepacia AC1100. Gene 100: 65-73.

Key Terms: 2,4,5-T, in vitro, bacteria, mechanism of action, experimental, journal article

Hayes, H.M., R.E. Tarone, K.P. Cantor, C.R. Jessen, D.M. McCurnin and R.C. Richardson (1991) Case-control study of canine malignant lymphoma: positive association with dog owner's use of 2,4-dichlorophenoxyacetic acid herbicides. JNCI 83(17): 1226-1231.

Key Terms: cancer, chronic toxicity, environmental exposure, 2,4-D, dog, journal article

See pages 32 and 33.

Health, N.I.F.O.S.A. (1991) Occupational Safety and Health for Fiscal Year 1988 under Public Law 91-596. 1-43.

Key Terms: chronic toxicity, occupational exposure, dioxins, human, government report

Helferich, W.G. and M.S. Denison (1991) Ultraviolet photoproducts of tryptophan can act as dioxin antagonists. 40(5): 674-678.



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Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

This article suggests that UV-light induced tryptophan photoproducts may specifically bind to the Ah receptor, thereby inducing aryl hydrocarbon hydroxylase activity.

Henry, E.C. and T.A. Gasiewicz (1991) Inhibition and reconstitution of Ah receptor transformation in vitro: role and partial characterization of a cytosolic factor(s). Arch. Biochem. Biophys. 288(1): 149-156.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 100.

Henry, E., K. Hayden, P. Bauman and T. Gasiewicz (1991) Ribonuclease inhibits Ah receptor transformation in vitro. Biochem. J. 279(3): 689-294.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 101.

Hirakawa, H., T. Matsueda, T. Iida, K. Fukamachi, K. Takahashi, J. Nagayama and T. Nagata (1991) Coplanar PCBs, PCDFs and PCDDs in the subcutaneous adipose tissue of Yusho patients and normal controls. Fukuoka Igaku Zasshi 82(5): 274-279.

Key Terms: tissue residues, other route of exposure, furans, dioxins, human, journal exposure

See pages 82 and 83.

Hirano, S., C. Tohyama, F. Mitsumori, H. Ito and K. Suzuki (1991) Identification of metabolites of 2-chlorodibenzofuran in the rat. Arch. Environ. Contam. Toxicol. 20(1): 67-72.

Key Terms: miscellaneous study, furans, method, injection, rat, tissue residue journal article

Hirose, R., M. Hori, H. Toyoshima, T. Shukuwa, M. Udono and H. Yoshida (1991) A study of epidermal alterations induced by PCDF on experimental carcinogenesis. Fukuoka Igaku Zasshi 82(5): 240-245.

Key Terms: cancer, acute toxicity, dermal, furans, mouse, journal article



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Hoffman, E.C., H. Reyes, F.F. Chu, F. Sander, L.H. Conley, B.A. Brooks and O. Hankinson (1991) Cloning of a factor required for activity of the Ah (dioxin) receptor. Science 252(5008): 954-958.

Key Terms: mechanism of action, dioxins, in vitro, journal article

See page 100.

Holladay, S.D., P. Lindstrom, B.L. Blaylock, C.E. Comment, D.R. Germolec, J.J. Heindell and M.I. Luster (1991) Perinatal thymocyte antigen expression and postnatal immune development altered by gestational exposure to tetrachlorodibenzo-p-dioxin (TCDD). Teratology 44(4): 385-393.

Key Terms: immunotoxicity, acute toxicity, oral, dioxins, mouse, journal article

See page 50.

Holsapple, M., N. Snyder, S. Wood and D. Morris (1991) A review of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced changes in immunocompetence: 1991 update. Toxicology 69(3): 219-255.

Key Terms: immunotoxicity, dioxins, review

See pages 47 and 48.

Holsapple, M., D. Morris, S. Wood and N. Snyder (1991) 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced changes in immunocompetence: possible mechanisms. Annu. Rev. Pharmacol. Toxicol. 31: 73-100.

Key Terms: immunotoxicity, mechanism of action, dioxins, human, review

See pages 47 and 109.

Holsapple, M.P., N.K. Snyder, V. Gokani, R.E. Blair and D.L. Morris (1991) Role of Ah-receptor in suppression of in vivo antibody-response by 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) is dependent on exposure conditions (Abstract). FASEB J. 5(4): 508.

Key Terms: immunotoxicity, acute toxicity, subchronic toxicity, experimental exposure, dioxins, mouse, abstract

See page 54.



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Hong, R. (1991) Effects of environmental toxins on lymphocyte function: studies in rhesus and man. Ann. Allergy 66(6): 474-480.

Key Terms: immunotoxicity, chronic toxicity, oral, dioxins, monkey, journal article

See page 48.

Hori, M., M. Udono, H. Toyoshima, R. Hirose and H. Yoshida (1991) Influences of polychlorinated dibenzofuran on pUC18 plasmid DNA. Fukuoka Igaku Zasshi 82(5): 228-231.

Key Terms: genetic toxicity, experimental exposure, furans, plasmid, journal article

Huang, L., B. Eitzer, C. Moore, S. McGown and K. Tomer (1991) The application of hybrid mass spectrometry/mass spectrometry and high-resolution mass spectrometry to the analysis of fish samples for polychlorinated dibenzo-p-dioxins and dibenzofurans. Biol. Mass Spectrom. 20(4): 161-168.

Key Terms: analytical method, dioxins, journal article

Huang, S.W. and G.G. Gibson (1991) Differential induction of cytochromes-P450 and cytochrome-P450-dependent arachidonic-acid metabolism by 3,4,5,3',4'-pentachlorobiphenyl in the rat and the guinea-pig. Toxicol. Appl. Pharmacol. 108(1): 86-95.

Key Terms: enzyme induction or inhibition, rat, guinea pig, journal article

Huang, L.Q. (1991) The application of hybrid mass spectrometry/mass spectrometry and high resolution mass spectrometry to the analysis of fish samples for polychlorinated dibenzo-p-dioxins and dibenzofurans. Chemosphere 23(8-10): 1043-1053.

Key Terms: method, fish, dioxins, journal article

Huff, J.E. and J.K. Haseman (1991) Exposure to certain pesticides may pose real carcinogenic risk. Chem. Eng. News Jan 7: 33-37.

Key Terms: cancer, chronic toxicity, experimental, dioxins, 2,4-D, rodent, commentary or opinion

As invited participants in a C & EN News forum, the authors defend the value of current animal carcinogenesis studies, stressing that exposure at high levels is essential for thorough exploration of the risk that such compounds pose. It is the inherent insensitivity of a bioassay that prevents relatively small increases in tumor



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incidence from being apparent at lower doses. They stress that carcinogenicity is not always associated with toxicity.

Huff, J., A. Salmon, N. Hooper and L. Zeise (1991) Long-term carcinogenesis studies on 2,3,7,8-tetrachlorodibenzo-p-dioxin and hexachlorodibenzo-p-dioxins. Cell Biol. Toxicol. 7(1): 67-94.

Key Terms: cancer, chronic toxicity, dioxins, review

See page 30.

Huff, J., J. Cirvello, J. Haseman and J. Bucher (1991) Chemicals associated with site-specific neoplasia in 1394 long-term carcinogenesis experiments in laboratory rodents. Environ. Health Perspect. 93: 247-270.

Key Terms: cancer, chronic toxicity, experimental, dioxins, rodents, journal article

See pages 30 and 38.

Iida, T., H. Hirakawa, T. Matsueda, R. Nakagawa, S. Takenaka, K. Morita, Y. Narazaki, K. Fukamachi, H. Tokiwa, K. Takahashi et al. (1991) Therapeutic trial for promotion of fecal excretion of PCDFs and PCBs by the administration of cholestyramine in Yusho patients. Fukuoka Igaku Zasshi 82(5): 317-325.

Key Terms: chronic toxicity, pharmacokinetics, other route of exposure, furans, human, journal article

See page 213.

Iida, J., T. Takeda, T. Takasuga, J. Moncur, P. Ireland and B. Wright (1991) Approaches to dioxin analysis by HRGC-HRMS and hybrid HRGC-MS-MS. J. High Resolut. Chromatogr. 14(2): 103-109.

Key Terms: method, dioxins, journal article

Jacobi, H. and I. Witte (1991) Synergistic effects of U46 D fluid (dimethylammonium salt of 2,4-D) and $CuCl_2$ on cytotoxicity and DNA repair in human fibroblasts. Toxicol. Lett. 58(2): 159-167.

Key Terms: other toxic effects, acute toxicity, experimental, 2,4-D, in vitro, journal article

The cytotoxicity of U46 D fluid, as manifested by inhibition of cell growth and DNA synthesis in human fibroblast cultures, was enhanced by $CuCl_2$; $CuCl_2$ alone had



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no effect. Preincubation with $CuCl_2$, followed by exposure to U46 D fluid, induced DNA repair, as measured by unscheduled synthesis. Neither agent alone exhibited this effect.

Jaiswal, A.K. (1991) Human NAD(P)H:quinone oxidoreductase ($NQO_1$) gene structure and induction by dioxin. Biochemistry 30(44): 10647-10653.

Key Terms: mechanism of action, injection, dioxins, in vitro, journal article

See page 109.

Janz, D.M. and C.D. Metcalfe (1991) Nonadditive interactions of mixtures of 2,3,7,8-TCDD and 3,3',4,4'-tetrachlorobiphenyl on aryl-hydrocarbon hydroxylase induction in rainbow-trout (Oncorhynchus mykiss). Chemosphere 23(4): 467-472.

Key Terms: enzyme induction or inhibition, experimental exposure, dioxins, fish, journal article

Janz, D.M. and C.D. Metcalfe (1991) Relative induction of aryl-hydrocarbon hydroxylase by 2,3,7,8-TCDD and 2 coplanar PCBs in rainbow-trout (Oncorhynchus-mykiss). Environmental Toxicology and Chemistry 10(7): 917-923.

Key Terms: enzyme induction or inhibition, dioxins, fish, journal article

Jappinen, P. and E. Pukkala (1991) Cancer incidence among pulp and paper workers exposed to organic chlorinated compounds formed during chlorine pulp bleaching. Scand. J. Work Environ. Health 17(5): 356-359.

Key Terms: cancer, chronic exposure, occupational exposure, dioxins, human, journal article

Johnson, E. (1991) A partnership between the dioxin receptor and a basic helix-loop-helix protein. Science 252(5008): 924-925.

Key Terms: mechanism of action, dioxins, review

Jones, S.N., P.G. Jones, H. Ibarguen, C.T. Caskey and W.J. Craigen (1991) Induction of the CYP1A-1 dioxin-responsive enhancer in transgenic mice. Nucleic Acids Res. 19(23): 6547-6551.

Key Terms: enzyme induction or inhibition, injection, mouse, 3-methyl-cholanthrene, journal article

See page 105.



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Kamrin, M. and L. Fischer (1991) Workshop on human health impacts of halogenated biphenyls and related compounds. Environ. Health Perspect. 91: 157-164.

Key Terms: acute toxicity, chronic toxicity, dioxins, human, other species, meeting report

Kanetoshi, A., A.M. Ward and A.B. Rifkin (1991) Immunochemical separation of cytochrome P-450S metabolizing arachidonic acid AA in 2,3,7,8-tetrachlorodibenzo-p-dioxin TCDD and phenobarbital PB induced livers. FASEB 5(6): 1570.

Key Terms: enzyme induction or inhibition, experimental exposure, dioxins, in vitro, abstract

Kang, H.K., K.K. Watanabe, J. Breen, J. Remmers, M.G. Conomos, J. Stanley and M. Flicker (1991) Dioxins and dibenzofurans in adipose tissue of US Vietnam veterans and controls. Am. J. Public Health 81(3): 344-349.

Key Terms: tissue residues, military exposure, dioxins, human, journal article

See pages 78 and 79.

Karch, N.J. (1991) The toxicological basis for predicting the human health risk from exposures in dioxins, PCBs and their congeners. J. Occup. Med. 33(4): 538.

Key Terms: acute toxicity, chronic toxicity, dioxins, PCBs, human, abstract

Kedderis, L.B., J.J. Diliberto and L.S. Birnbaum (1991) Disposition and excretion of intravenous 2,3,7,8-tetrabromodibenzo-p-dioxin (TBDD) in rats. Toxicol. Appl. Pharmacol. 108(3): 397-406.

Key Terms: pharmacokinetics, injection, dioxins, rat, journal article

See page 88.

Kedderis, L.B., J.J. Diliberto, P. Linko, J.A. Goldstein and L.S. Birnbaum (1991) Disposition of 2,3,7,8-tetrabromodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat: biliary excretion and induction of cytochromes CYP1A2 and CYP1A2. Toxicol. Appl. Pharmacol. 111(1): 163-172.

Key Terms: pharmacokinetics, oral, dioxins, rat, journal article

See pages 88, 89 and 103.



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Kedderis, L.B., J.J. Diliberto and L.S. Birnbaum (1991) Disposition and excretion of intravenous 2,3,7,8-tetrabromodibenzo-p-dioxin (TBDD) in rats. Toxicol. Appl. Pharmacol. 108(3): 397-406.

Key Terms: pharmacokinetics, injection, dioxins, rat, journal article

See pages 88 and 89.

Keenan, R., D. Paustenbach, R. Wenning and A. Parsons (1991) Pathology reevaluation of the Kociba et al. (1978) bioassay of 2,3,7,8-TCDD: implications for risk assessment. J. Toxicol. Environ. Health 34(3): 279-296.

Key Terms: cancer, chronic toxicity, experimental, dioxins, rat, journal article

See page 31.

Kim, S.G., S.L. Reddy, J.C. States and R.F. Novak (1991) Pyridine effects on expression and molecular regulation of the cytochrome P450IA gene subfamily. Mol. Pharmacol. 40(1): 52-57.

Key Terms: enzyme induction or inhibition, in vitro, journal article

See page 106.

Kimbrough, R.D. (1991) Uncertainties in risk assessment. Appl. Occup. Environ. Hyg. 6(9): 759-763.

Key Terms: cancer, other toxic effects, chronic toxicity, unspecified route of exposure, dioxins, human, commentary or opinion

This is the text of the 1991 Herbert E. Stokinger Lecture, in which the author reviews the extrapolation of animal data to set standards for contaminants in the workplace and general environment. Predictions are made about potential adverse effects in humans based on the toxicity observed in animals if human data do not exist. If chemicals cause cancer in animals at doses at which pronounced damage occurs to the target organ, there would be a less than linear response, or no tumors at all, at lower doses where no tissue damage took place. The major chronic diseases are multifactorial in origin, and the contribution from trace amounts of environmental contaminants is likely to be minimal. Recent work on TCDD is cited which shows that the potential human health risks have been exaggerated.

Kamrin, M. and L. Fischr biphenyls and re sition and excretion of rats. Toxicol. Appl.

Key Terms: ar report rticle

Kanetoshi, A., A chrome r p-dioxir reevaluation

Key ns for risk vitr

Kang, H ticle

(1991) In vitro effects of L-ascorbic-acid oxylase-activity in hepatic microsomes of

dioxins, mouse, journal article

lorophenoxyacetic acid-exposed Occup. Environ. Health 63(5):

ietics, occupational exposure, 2,4-D,

., A. Tanaka and S. Tobinaga (1991) Relationship between y of polychlorinated dibenzo-para-dioxins and their electronic narm. Bull. 39(8): 2100-2105.

is: mechanism of action, dioxins, model

ee page 103.

oga, N., J. Kuroki, H. Nakashima, Y. Hokama-Kuroki, H. Yoshimura, H. Kuroki and Y. Masuda (1991) Acute toxicity, inductive effects of liver enzymes and distribution in the liver of 1,2,3,7,8-pentachlorodibenzo-p-dioxin in rats. Fukuoka Igaku Zasshi 82(5): 197-206.

Key Terms: hepatotoxicity, enzyme induction or inhibition, acute toxicity, chronic toxicity, unspecified route of exposure, dioxins, rat, journal article

See pages 68 and 103.

Kononen, D.W. and R.C. Schwing (1991) Comments on "background exposure to chemicals: What is the risk?". Risk Anal. 11(3): 375.

Key Terms: cancer, environmental exposure, dioxins, human, commentary or opinion

Koppe, J.G., H.J. Pluim, K. Olie and J. van Wijnen (1991) Breast milk, dioxins and the possible effects on the health of newborn infants. Sci. Total Environ. 106(1-2): 33-41.



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Key Terms: hematologic effects, enzyme induction or inhibition, oral, dioxins, human, journal article

See pages 69 and 70.

Koppe, J., H. Pluim, K. Olie and J. van Wijnen (1991) Breast feeding, PCBs and dioxins. Tijdschr. Kindergeneeskd 59(1): 9-15.

Key Terms: hematologic effects, tissue residues, oral, dioxins, furans, journal article

See pages 85 and 86.

Korte, M., R. Stahlmann, M. Kubickamuranyi, E. Gleichmann and D. Neubert (1991) Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune-system. 3. No immunosuppressive effect of 2,3,7,8-TCDD in the popliteal lymph-node assay (PLNA) in rats. Arch. Toxicol. 65(8): 656-660.

Key Terms: immunotoxicity, acute toxicity, injection, dioxins, furans, rat, journal article

See page 52.

Korte, M., R. Stalhlmann, R. Thiel, T. Nagao, I. Chahoud, H. Van Loveren, J.G. Vos and D. Neubert (1991) Resistance to Trichinella spiralis infection, induction of hepatic monooxygenases, and concentrations in thymus and liver in rats after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere 23(11-12): 1845-1854.

Key Terms: immunotoxicity, enzyme induction or inhibition, tissue residues, injection, dioxins, rat, journal article

See page 50.

Kozuka, H., J. Yamada, S. Horie, T. Watanabe, T. Suga and T. Ikeda (1991) Characteristics of induction of peroxisomal fatty acid oxidation-related enzymes in rat liver by drugs. Relationships between structure and inducing activity. Biochem. Pharmacol. 41(4): 617-623.

Key Terms: enzyme induction or inhibition, oral, 2,4-D, 2,4,5-T, rat, journal article

See page 115.



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Kruger, N., H. Helge and D. Neubert (1991) Significance of PCDD/PCDF (dioxins) in pediatrics. Monatsschr. Kinderheilkd. 139(8): 434-441.

Key Terms: enzyme induction or inhibition, oral, dioxins, human, journal article

The authors suggested that a breath test to determine induction of monooxygenase activity by TCDD should be administered to human breast-fed newborns and infants. This would facilitate the study of possible biologic effects of TCDD in breast-fed children.

Kuroda, K., A. Okamoto, G. Endo, S. Horiguchi and Y.S. Yoo (1991) Colchicine-like effects of cacodylic acid. Mutat. Res. 252(1): 95.

Key Terms: cacodylic acid, genetic toxicity, experimental exposure, hamster, journal article

See page 75.

Lakshman, M.R., P. Ghosh and S.J. Chirtel (1991) Mechanism of action of 2,3,7,8-tetrachlorodibenzo-p-dioxin on intermediary metabolism in the rat. J. Pharmacol. Exp. Ther. 258(1): 317-319.

Key Terms: hepatotoxicity, mechanism of action, dioxins, rat, journal article

See page 114.

Lamm, S.H. (1991) The epidemiological basis for assessing human risk from exposures in dioxin. 33(4): 538.

Key Terms: cancer, chronic toxicity, occupational exposure, military exposure, dioxins, human, abstract

Landers, J. and N. Bunce (1991) The Ah receptor and the mechanism of dioxin toxicity. Biochem. J. 276(2): 273-287.

Key Terms: mechanism of action, enzyme induction or inhibition, dioxins, human, rodents, review

See pages 94 and 95.

Landers, J., M. Winhall, T. McCready, D. Sanders, D. Rasper, J. Nakai and N. Bunce (1991) Characterization of an inducible aryl hydrocarbon receptor-like protein in rat liver. J. Biol. Chem. 266(15): 9471-9480.



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Key Terms: hepatotoxicity, mechanism of action, dioxins, rat, journal article

See pages 98 and 99.

LeBel, G.L., D.T. Williams, F.M. Benoit and M. Goddard (1991) Polychlorinated dibenzo-dioxins and dibenzofurans in human adipose tissue samples from five Ontario municipalities. Chemosphere 21(12): 1465-1475.

Key Terms: tissue residues, environmental exposure, dioxins, human, journal article

Lentnek, M., O.W. Griffith and A.B. Rifkind (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin increases reliance on fats as a fuel source independently of diet: evidence that diminished carbohydrate supply contributes to dioxin lethality. Biochem. Biophys. Res. Commun. 174(3): 1267-1271.

Key Terms: other toxic effects, mechanism of action, dioxins, bird, journal article

See page 115.

Lerda, D. and R. Rizzi (1991) Study of reproductive function in persons occupationally exposed to 2,4-dichlorophenoxyacetic acid (2,4-D). Mutat. Res. 262(1): 47-50.

Key Terms: reproductive toxicity, chronic toxicity, occupational exposure, 2,4-D, human, journal article

See page 41.

Lin, F.H., S.J. Stohs, L.S. Birnbaum, G. Clark, G.W. Lucier and J.A. Goldstein (1991) The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the hepatic estrogen and glucocorticoid receptors in congenic strains of Ah responsive and Ah nonresponsive C57BL/6J mice. Toxicol. Appl. Pharmacol. 108(1): 129-139.

Key Terms: alteration in sex hormones, mechanism of action, oral, dioxins, mouse, journal article

See page 107.

Lin, F.H., G. Clark, L.S. Birnbaum, G.W. Lucier and G. J.A. (1991) Influence of the Ah locus on the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the hepatic epidermal growth factor receptor. Mol. Pharmacol. 39(3): 307-313.

Key Terms: other toxic effects, mechanism of action, experimental, dioxins, mouse, journal article



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See pages 107 and 108.

Linden, J., R. Pohjanvirta, T. Rahko and J. Tuomisto (1991) TCDD decreases rapidly and persistently serum melatonin concentration without morphologically affecting the pineal gland in TCDD-resistant Han/Wistar rats. Pharmacol. Toxicol. 69(6): 427-432.

Key Terms: other toxic effects, acute toxicity, injection, dioxins, rat, journal article

See page 111.

Lloyd, O.L., M.M. Lloyd, F.L.R. Williams, A. McKenzie and A. Hay (1991) Toxicity from ragwort and fat cow syndrome, or from industrial chemicals - the value of epidemiologic analysis for interpreting clinicopathological findings. Sci. Total Environ. 106(1-2): 83-96.

Key Terms: other toxic effects, chronic toxicity, environmental exposure, dioxins, cow, journal article

Lorenzen, A. and A.B. Okey (1991) Detection and characterization of Ah receptor in tissue and cells from human tonsils. Toxicol. Appl. Pharmacol. 107(2): 203-214.

Key Terms: immunotoxicity, mechanism of action, experimental, dioxin, human, journal article

See pages 48, 96 and 97.

Lucier, G.W. (1991) Humans are a sensitive species to some of the biochemical effects of structural analogs of dioxin. Environmental Toxicology and Chemistry 10(6): 727-735.

Key Terms: cancer, enzyme induction or inhibition, tissue residues, experimental, dioxins, human, rat, journal article

See pages 83 and 97.

Lucier, G.W., A. Tritscher, T. Goldsworthy, J. Foley, G. Clark, J. Goldstein and R. Maronpot (1991) Ovarian hormones enhance 2,3,7,8-tetrachlorodibenzo-p-dioxin-mediated increases in cell proliferation and preneoplastic foci in a two-stage model for rat hepatocarcinogenesis. Cancer Res. 51(5): 1391-1397.

Key Terms: cancer, steroid hormones, mechanism of action, oral, dioxins, rat, model, journal article



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See page 32.

Lundberg, K., K.O. Gronvik and L. Dencker (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induced suppression of the local immune response. Int. J. Immunopharmacol. 13(4): 357-368.

Key Terms: immunotoxicity, acute toxicity, injection, dioxins, mouse, journal article

See page 52.

Lundberg, K. (1991) Dexamethasone and 2,3,7,8-tetrachlorodibenzo-p-dioxin can induce thymic atrophy by different mechanisms in mice. Biochem. Biophys. Res. Commun. 178(1): 16-23.

Key Terms: immunotoxicity, acute toxicity, dioxins, mouse, journal article

See page 50.

Lundgren, K., C. Rappe and H.-R. Buser (1991) Detection of alkylated polychlorodibenzofurans and alkylated polychlorodibenzo-p-dioxins by tandem mass spectrometry for the analysis of crustacean samples. Chemosphere 23(8-10): 1591-1604.

Key Terms: method, dioxins, journal article

Luotamo, M. (1991) Congener specific assessment of human exposure to polychlorinated biphenyls. Chemosphere 23(11-12): 1685-1698.

Key Terms: tissue residues, occupational exposure, environmental exposure, other route of exposure, PCBs, human, journal article

Lusska, A., K. Jones, C. Elferink, L. Wu, E. Shen, L. Wen and J.J. Whitlock (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin induces cytochrome P450IA1 enzyme activity by activating transcription of the corresponding gene. Adv. Enzyme Regul. 31: 307-317.

Key Terms: mechanism of action, enzyme induction or inhibition, experimental exposure, dioxins, in vitro, journal article

See page 105.

Manz, A., J. Berger, J.H. Dwyer, D. Flesch-Janys, S. Nagel and H. Waltsgott (1991) Cancer mortality among workers in chemical plant contaminated with dioxin. Lancet 338(8773): 959-964.



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Key Terms: cancer, chronic toxicity, occupational exposure, dioxins, human, journal article

See pages 26 and 27

Massa, T., A. Esmaeili, B. Schlatterer, H. Hagenmaier and P. Chandra (1991) Carcinogenic and co-carcinogenic potential of 2,3,7,8-tetrachlorodibenzo-p-dioxin in a host-mediated in vivo/in vitro assay. Chemosphere 23(11-12): 1855-1868.

Key Terms: cancer. other toxic effects, acute toxicity, injection, dioxins, mouse, in vitro, journal article

See pages 31 and 32.

Masuda, Y., H. Kuroki, K. Haraguchi, J. Ryan and S. Shu (1991) Elimination of PCDF and PCB congeners in the blood of patients with PCB poisoning in Taiwan. Fukuoka Igaku Zasshi 82(5): 262-268.

Key Terms: tissue residues, chronic toxicity, other route of exposure, furans, human, journal article

See page 83.

Masuda, Y. (1991) Toxic evaluation of chlorinated aromatic-hydrocarbons in human environments. Daiichi Coll. Pharmaceut. Sci. 7(5-6): 137-141.

Key Terms: chronic toxicity, environmental exposure, chlorinated hydrocarbons, human, journal article

Matsuoka, K., S. Nonaka, T. Ohgami, H. Yoshida and F. Murayama (1991) In vitro analysis of polychlorinated biphenyls (PCBs) and 2,3,4,7,8-pentachlorodibenzofuran (PCDF) cellular toxicity in PLC/PRF/5 cell proliferation - the effect of ursodeoxycholic acid, inchin-gorei-san and shou-saiko-to on cell toxicity. Fukuoka Igaku Zasshi 82(5): 232-239.

Key Terms: other toxic effects, furans, in vitro, journal article

Mattina, M.J.I. (1991) Determination of chlorophenoxy acids using high-performance liquic chromatography-particle beam mass spectrometry. J. Chromatogr. 542(385-395.

Key Terms: miscellaneous study, method, 2,4-D, 2,4,5-T, journal article

Using an isocratic mobile phase of methanol containing phenoxyacetic acid-dilute acetic acid (70:30), the author achieved good HPLC separation of phenoxy



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D.729

herbicides. The eluate was introduced into a mass spectrometer using methane-enhanced electron-capture negative ionization conditions through the particle beam interface. Detection limits were in the low μg/liter range.

McConnell, E.E., J.E. Huff, M. Hejtmancik, A.C. Peters and R. Persing (1991) Toxicology and carcinogenesis studies of 2 grades of pentachlorophenol in B6C3F1-mice. Fundam. Appl. Toxicol. 17(3): 519-532.

Key Terms: cancer, dioxins, mouse, journal article

McGregor, D.B., A.G. Brown, S. Howgate, D. McBride, C. Riach and W.J. Caspary (1991) Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. Environmental and Molecular Mutagenesis 17(3): 196-219.

Key Terms: genetic toxicity, experimental exposure, dioxins, in vitro, journal article

See page 38.

McKim, J.J., K. Marien, H. Schaup and D. Selivonchick (1991) Alterations of hepatic acetyl-CoA carboxylase by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Lipids 26(7): 521-525.

Key Terms: enzyme induction or inhibition, injection, dioxins, rat, journal article

See pages 68 and 115.

Mehta, S., T. Mazzonati and R. Kurl (1991) Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on human T cell proliferation. Proc. Am. Assoc. Cancer Res. Annu. Meet. 32: 273.

Key Terms: immunotoxicity, dioxins, human, abstract

Michalek, J.E., R.C. Tripathi, S.P. Caudill and J.L. Pirkle (1992) Investigation of TCDD half-life heterogeneity in veterans of Operation Ranch Hand. J. Toxicol. Environ. Health 35: 29-38.

Key Terms: tissue residues, military exposure, dioxins, human, journal article

See page 80.

Mirvish, S.S., J. Nickols, D.D. Weisenburger, D. Johnson, S.S. Joshi, P. Kaplan, M. Gross and H.Y. Tong (1991) Effects of 2,4,5-trichlorophenoxyacetic acid, pentachlorophenol, methylprednisolone, and Freund adjuvant on 2-hydroxyethylnitrosourea carcinogenesis in MRC-Wistar rats. J. Toxicol. Environ. Health 32(1): 59-74.



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D-730

Key Terms: cancer, subchronic toxicity, injection, dioxins, 2,4,5-T, rat, journal article

See page 33.

Mocarelli, P., L.L. Needham, A. Marocchi, D.G. Patterson Jr, P. Brambilla, P.M. Gerthoux, L. Meazza and V. Carreri (1991) Serum concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin and test results from selected residents of Seveso, Italy. J. Toxicol. Environ. Health 32(4): 357-366.

Key Terms: chloracne, tissue residues, other route of exposure, dioxins, human, journal article

See pages 67 and 82.

Moody, D.E., B.A. Narloch, L.R. Shull and B.D. Hammock (1991) The effect of structurally divergent herbicides on mouse-liver xenobiotic-metabolizing enzymes (P-450-dependent mono-oxygenases, epoxide hydrolases and glutathione S-transferases) and carnitine acetyltransferase. Toxicol. Lett. 59(1-3): 175-185.

Key Terms: cancer, enzyme induction or inhibition, experimental, 2,4-DP, mouse, journal article

Moore, R., C. Jefcoate and R. Peterson (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin inhibits steroidogenesis in the rat testis by inhibiting the mobilization of cholesterol to cytochrome P450scc. Toxicol. Appl. Pharmacol. 109(1): 85-97.

Key Terms: alteration in sex hormones, mechanism of action, dioxin, rat, journal article

See page 111.

Morgan, R.W. (1991) Dioxin and mortality from cancer (Letter). Environ. Health Strategies 324(25): 1810.

Key Terms: cancer, chronic toxicity, occupational exposure, dioxins, human, commentary or opinion

Morita, M. (1991) Dioxins, their chemistry and toxic effects. Kami Pa Gikyoshi 45(8): 887-901.

Key Terms: toxicity, dioxins, review



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D-731

Morris, D.L., S.D. Jordan and M.P. Holsapple (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on humoral immunity: I. Similarities to Staphylococcus aureus Cowan strain I (SAC) in the in vitro T-dependent antibody response. Immunopharmacology 21(3): 159-169.

Key Terms: immunotoxicity, acute toxicity, experimental, dioxins, in vitro, journal article

See page 53.

Morris, D.L. and M.P. Holsapple (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on humoral immunity: II. B cell activation. Immunopharmacology 21(3): 171-181.

Key Terms: immunotoxicity, acute toxicity, experimental, dioxins, in vitro, journal article

See page 53.

Morris, D.L. and M.P. Holsapple (1991) Gamma interferon (G-IFN) potentiates the activation and proliferation of dense resting B cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin TCDD. FASEB 5(5): 1206.

Key Terms: immunotoxicity, acute toxicity, experimental exposure, dioxins, in vitro, mouse, abstract

See page 53.

Morris, D.L., N.K. Snyder, V. Gokani, R.E. Blair and M.P. Holsapple (1991) Enhanced suppression of humoral immunity in DBA/2 mice following subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Appl. Pharmacol. 112(1): 128-132.

Key Terms: immunotoxicity, subchronic toxicity, gavage, dioxins, mouse, journal article

See pages 51 and 54.

Mueller, H.E. (1991) Rational and irrational danger of dioxins. Dtsch. Med. Wochenschr. 116(20): 786-793.

Key Terms: chloracne, environmental exposure, dioxins, human, review



703
D.732

Mussalorauhamaa, H. (1991) Partitioning and levels of neutral organochlorine compounds in human serum, blood-cells, and adipose and liver-tissue. Sci. Total Environ. 103(2-3): 159-175.

Key Terms: tissue residues, environmental exposure, furans, human, journal article

Muto, H., M. Shinada, T. Abe and Y. Takizawa (1991) The tissue distribution of 2,3,7,8-chlorine substituted dibenzo-p-dioxins in humans who died of cancer. Life Sci. 48(17): 1645-1657.

Key Terms: cancer, tissue residues, environmental, dioxins, human, journal article

See page 84.

Myers, J.P. and T. Colborn (1991) Blundering questions, weak answers lead to poor pesticide policies. Chem. Eng. News Jan 7: 40-43.

Key Terms: cancer, teratologic effects, other toxic effects, oral, environmental, other route of exposure, pesticides, bird, dog, human, commentary or opinion

See page 44.

Nagayama, J., K. Wada, K. Haraguchi, Y. Masuda and S. Handa (1991) Effects of 3-methylsulphonyl-4,5,3',4'-tetrachlorobiphenyl and 7,8-benzoflavone on aryl hydrocarbon hydroxylase activity in Ah responsive and Ah nonresponsive strains of mice. Fukuoka Igaku Zasshi 82(5): 207-214.

Key Terms: enzyme induction or inhibition, experimental exposure, furans, dioxins, mouse, journal article

See page 103.

Nagayama, J., M. Nagayama, K. Wada, T. Iida, H. Hirakawa, T. Matsueda and Y. Masuda (1991) The effect of organochlorine compounds on the induction of sister chromatid exchanges in cultured human lymphocytes. Fukuoka Igaku Zasshi 82(5): 221-227.

Key Terms: genetic toxicity, immunotoxicity, experimental, furans, in vitro, journal article

Nakagawa, R. and K. Takahashi (1991) Studies on the application of residual PCBs, PCQs and PCDFs concentrations to Yusho diagnosis. Fukuoka Igaku Zasshi 82(5): 280-294.



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D.733

Key Terms: other toxic effects, tissue residues, other route of exposure, furans, human, journal article

See page 83.

Nam, K.S., S. Kapila, A.F. Yanders and R.K. Puri (1991) A multiple sample extraction and on-line system for the analysis of chlorinated compounds. Chemosphere 23(8-10): 1109-1116.

Key Terms: method, dioxins, journal article

Narasimhan, T.R., S. Safe, H.J. Williams and A.I. Scott (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on 17$\beta$-estradiol-induced glucose metabolism in MCF-7 human breast cancer cells: 13C nuclear magnetic resonance spectroscopy studies. Mol. Pharmacol. 40: 1029-1035.

Key Terms: alteration in sex hormones, other toxic effects, mechanism of action, acute toxicity, experimental exposure, dioxins, human, journal article

See pages 110 and 111.

Nemoto, N., J. Sakurai, A. Tazawa and T. Ishikawa (1991) Regulation of mouse P(1)450 gene expression in monolayer-cultured hepatocytes from responsive and non-responsive strains. Carcinogenesis 12(4): 623-629.

Key Terms: enzyme induction or inhibition, mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 105.

Nemoto, N. and J. Sakurai (1991) Proline is required for transcriptional control of the aromatic hydrocarbon-inducible $P_1$450 gene in C57Bl/6 mouse monolayer-cultured hepatocytes. Jpn. J. Cancer Res. 82(8): 901-908.

Key Terms: enzyme induction or inhibition, mechanism of action, mouse, aryl hydrocarbon hydroxylase, journal article

Induction of AHH by polycyclic aromatic hydrocarbons is dependent on a proline-related metabolism which influences transcription of the $P_1$450 gene.

Neuberger, M., W. Landvoigt and F. Derntl (1991) Blood levels of 2,3,7,8-tetrachloro-dibenzo-p-dioxin in chemical workers after chloracne and in comparison groups. Int. Arch. Occup. Environ. Health 63(5): 325-327.



705
D.734

Key Terms: chloracne, tissue residues, occupational exposure, dioxins, human, journal article

See pages 67 and 81.

Neubert, R., U. Jacob-Müller, H. Helge, R. Stahlmann and D. Neubert (1991) Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune system. 2. In vitro effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on lymphocytes of venous blood from man and a non-human primate (Callithrix jacchus). Arch. Toxicol. 65(3): 213-219.

Key Terms: immunotoxicity, acute toxicity, experimental, dioxins, furans, in vitro, journal article

See page 47 and 48.

Neubert, R., H. Helge, R. Stahlmann and D. Neubert (1991) Some effects of 2,3,7,8-tetrachlorodibenzo-para-dioxin (T4CDD) and of 2,3,4,7,8-pentachlorodibenzofuran (P5CDF) on peripheral lymphocytes of primates in vivo and in vitro. Allergologie 14(9): 360-371.

Key Terms: immunotoxicity, injection, experimental exposure, dioxins, furans, primate, in vitro, journal article

See page 48.

Neubert, D. and H. Helge (1991) Problems with xenobiotics - especially 'dioxins' - in human milk. Arch. Gynecol. Obstet. 250(1-4): 853-858.

Key Terms: tissue residues, oral, dioxins, furans, human, journal article

Neubert, D. (1991) Peculiarities of the toxicity of polyhalogenated dibenzo-p-dioxins and dibenzofurans in animals and man. Chemosphere 23(11-12): 1869-1893.

Key Terms: cancer, immunotoxicity, mechanism of action, pharmacokinetics, dioxins, furans, rat, in vitro, human, review

See page 77.

Nishizumi, M. (1991) Carcinogenicity of 2,3,4,7,8-pentachlorodibenzofuran and 1,2,3,4,7,8-hexachlorodibenzofuran when given by gavage to rats. Fukuoka Igaku Zasshi 82(5): 246-250.

Key Terms: cancer, acute toxicity, oral, furans, mouse, journal article



706
D.735

Noren, K. and A. Lunden (1991) Trend studies of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans in human milk. Chemosphere 23(11-12): 1895-1901.

Key Terms: pharmacokinetics, tissue residues, environmental, dioxins, furans, human, journal article

See pages 86 and 87.

O'Brien, T.R., P. Decoufle, 2nd and C.A. Boyle (1991) Non-Hodgkin's lymphoma in a cohort of Vietnam veterans. Am. J. Public Health 81(6): 758-760.

Key Terms: cancer, chronic toxicity, military exposure, dioxins, human, journal article

See pages 21 and 22.

Okino, S.T. and R.H. Tukey (1991) Phorbol ester treatment to mice inhibits DNA binding of the TCDD inducible nuclear dioxin receptor to CYPIA1 enhancer elements. FASEB J. 5(5): 1162.

Key Terms: enzyme induction or inhibition, mechanism of action, experimental exposure, dioxins, mouse, abstract

See pages 101 and 102.

Olling, M., H.J.G.M. Derks, P.L.M. Berende, A.K.D. Liem and A.P.J.M. De Jong (1991) Toxicokinetics of eight $^{13}C$-labelled polychlorinated dibenzo-p-dioxins and -furans in lactating cows. Chemosphere 23(8-10): 1377-1385.

Key Terms: pharmacokinetics, oral, dioxins, cows, journal article

See page 87.

Overby, L.H., G.T. Carver and R.M. Philpot (1991) Localization of messenger RNA for cytochrome P-450IA1 in lungs of rabbits treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin TCDD. Am. Rev. Respir. Dis. 143(4 Part 2): 135.

Key Terms: enzyme induction or inhibition, injection, dioxins, rabbit, abstract

Paulino, C.A. and J. Palermoneto (1991) Effects of acute 2,4-dichlorophenoxyacetic acid intoxication on some rat serum components and enzyme-activities. Braz. J. Med. Biol. Res. 24(2): 195-198.



707
D.736

Key Terms: acute toxicity, enzyme induction or inhibition, 2,4-D, rat, journal article

Paustenbach, D.J., M.W. Layard, R.J. Wenning and R.E. Keenan (1991) Risk assessment of 2,3,7,8-TCDD using a biologically based cancer model: a reevaluation of the Kociba et al. bioassay using a 1978 and 1990 histopathology criteria. J. Toxicol. Environ. Health 34(1): 11-26.

Key Terms: cancer, chronic toxicity, dioxins, rat, model

See page 31.

Pavlica, M., D. Papes and B. Nagy (1991) 2,4-Dichlorophenoxyacetic acid causes chromatin and chromosome abnormalities in plant cells and mutation in cultured mammalian cells. Mutat. Res. 263(2): 77-81.

Key Terms: genetic toxicity, acute toxicity, experimental, 2,4-D, in vitro, journal article

See pages 38 and 39.

Perdew, G. (1991) Comparison of the nuclear and cytosolic forms of the Ah receptor from Hepa 1c1c7 cells: charge heterogeneity and ATP binding properties. Arch. Biochem. Biophys. 291(2): 284-290.

Key Terms: mechanism of action, experimental, dioxin, in vitro, journal article

See page 99.

Pesonen, M. and T. Andersson (1991) Characterization and induction of xenobiotic metabolizing enzyme activities in a primary culture of rainbow trout hepatocytes. Xenobiotica 21(4): 461-471.

Key Terms: enzyme induction or inhibition, experimental exposure, dioxin, fish, journal article

See page 96.

Pesonen, M., A. Gokoyr and T. Andersson (1992) Expression of P450IA1 in a primary culture of rainbow trout hepatocytes exposed to $\beta$-naphthoflavone or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Biochem. Biophys. 292(1): 228-233.

Key Terms: mechanism of action, enzyme induction or inhibition, experimental, dioxins, in vitro, journal article



708
D.737

See pages 96 and 105.

Peto, R. (1991) Occupational exposure to chlorophenoxy herbicides and chlorophenols [Letter]. Lancet 338(8779): 1392.

Key Terms: cancer, chronic toxicity, military exposure, dioxins, phenoxyherbicides, human, commentary or opinion

See pages 25 and 26.

Pettit, K., R.S. Brown and P.W. Jones (1991) The DB5 capillary column: the search for sensitivity. Chemosphere 23(8-10): 1117-1123.

Key Terms: method, dioxins, journal article

Phillips, L. and G. Birchard (1991) Regional variations in human toxics exposure in the USA: an analysis based on the National Human Adipose Tissue Survey. Arch. Environ. Contam. Toxicol. 21(2): 159-168.

Key Terms: tissue residues, environmental exposure, dioxins, human, journal article

See pages 83 and 84.

Piskorska-Pliszczynska, J., B. Astroff, T. Zacharewski, M. Harris, R. Rosengren, V. Morrison, L. Safe and S. Safe (1991) Mechanism of action of 2,3,7,8-tetrachloro-dibenzo-p-dioxin antagonists: characterization of 6-[125I]methyl-8-iodo-1,3-dichlorodibenzofuran-Ah receptor complexes. Arch. Biochem. Biophys. 284(1): 193-200.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 101.

Piskorska-Pliszczynska, J., V. Morrison, T. Zacharewski and S. Safe (1991) DNA binding properties of the Ah receptor in wild-type and variant mouse hepatoma cells. Arch. Biochem. Biophys. 290(2): 362-368.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 100.



709
D.738

Pohjanvirta, R., M. Unkila and J. Tuomisto (1991) Characterization of the enhanced responsiveness to postingestive satiety signals in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated Han/Wistar rats. Pharmacol. Toxicol. 69(6): 433-441.

Key Terms: neurobehavioral effects, subchronic toxicity, injection, dioxins, rat, journal article

See pages 62 and 63.

Pokrovsky, A.G., A.I. Cherykh, O.N. Yastrebova and I.B. Tsyrlov (1991) 2,3,7,8-tetrachlorodibenzo-p-dioxin as a possible activator of HIV infection. Biochem. Biophys. Res. Commun. 179(1): 46-51.

Key Terms: immunotoxicity, other toxic effects, acute toxicity, experimental, dioxins, in vitro, journal article

See page 49.

Poland, A. and E. Glover (1991) Characterization and strain distribution pattern of the murine Ah receptor specified by the $Ah^{d}$ and $Ah^{b-3}$ alleles. Mol. Pharmacol. 38: 306-312.

Key Terms: mechanism of action, murine, journal article

See page 104.

Poland, A., E. Glover and C.A. Bradfield (1991) Characterization of polyclonal antibodies to the Ah receptor prepared by immunization with a synthetic peptide hapten [published erratum appears in Mol Pharmacol 1991 Apr. 39(4):435]. Mol. Pharmacol. 39(1): 20-26.

Key Terms: mechanism of action, dioxins, journal article

The authors describe the use of a synthetic peptide based on the N-terminal sequence of the Ah receptor from C57BL/6J mice, coupled with a keyhole limpet hemocyanin, to produce polyclonal antiserum to Ah receptor in rabbits. Sensitivity for Ah detection on a blot is 60-120 pg/200 mg protein/gel lane.

Politzer, P. and J.S. Murray (1991) Electrostatic potential analysis of dibenzo-p-dioxins and structurally similar systems in relation to their biological activities. Theor. Biochem. Mol. Biophys. 2: 165-191.

Key Terms: other toxic effects, mechanism of action, dioxins, journal article



D.1379

Pongratz, I., P.-E. Stromstedt, G.G.F. Mason and L. Poellinger (1991) Inhibition of the specific DNA binding activity of the dioxin receptor by phosphatase treatment. J. Biol. Chem. 266(25): 16813-16817.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article

See page 101.

Precht, C. (1991) Dioxins (Letter). Dtsch. Med. Wochenschr. 116(35): 1332-1333.

Key Terms: environmental exposure, dioxins, human, journal article

This letter in German mentions dioxins, furans, and the anticarcinogens in broccoli as they relate to the Ah receptor.

Prokipcak, R.D. and A.B. Okey (1991) Down-regulation of the Ah receptor in mouse hepatoma-cells treated in culture with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Can. J. Physiol. Pharmacol. 69(8): 1204-1210.

Key Terms: enzyme induction or inhibition, mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 99.

Puhvel, S.M., M.J. Connor and M. Sakamoto (1991) Vitamin A deficiency and the induction of cutaneous toxicity in murine skin by TCDD. Toxicol. Appl. Pharmacol. 107(1): 106-116.

Key Terms: other cutaneous effects, acute toxicity, dermal, dioxins, mouse, journal article

See pages 67 and 113.

Purchase, R. (1991) Meeting report - Dioxins revisited. Food Chem. Toxicol. 29(12): 863-864.

Key Terms: tissue levels, environmental, dioxins, furans, human, meeting report

Raha, A., V. Reddy, L. Xu, W. Houser and E. Bresnick (1991) Presence of the 4 S polycyclic hydrocarbon-binding protein in H4-II-E cells. Toxicology 66(2): 175-186.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article



711
D.740

Rannug, U., M. Sjogren, A. Rannug, M. Gillner, R. Toftgard, J.-A. Gustafsson, H. Rosenkranz and G. Klopman (1991) Use of artificial intelligence in structure-affinity correlations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor ligands. Carcinogenesis 12(11): 2007-2015.

Key Terms: mechanism of action, dioxins, model

See page 102.

Ray, P.K., K.P. Singh, Raiduddin and A.K. Prasad (1991) Immunological responses to aflatoxins and other chemical carcinogens. J. Toxicol. - Toxin Reviews 10(1): 63-85.

Key Terms: immunotoxicity, dioxins, human, review

Rivarola, V.A. and H.F. Balegno (1991) Effects of 2,4-dichlorophenoxyacetic acid on polyamine synthesis in Chinese hamster ovary cells. Toxicol. Lett. 56(1-2): 151-157.

Key Terms: enzyme induction or inhibition, mechanism of action, experimental, 2,4-D, in vitro, journal article

See page 115.

Rivarola, V. and H. Balegno (1991) 2,4-Dichlorophenoxyacetic acid effects on polyamine biosynthesis. Toxicology 68(2): 109-119.

Key Terms: mechanism of action, experimental, 2,4-D, in vitro, journal article

See page 115.

Roberts, E.A., K.C. Johnson and W.G. Dippold (1991) Ah receptor mediating induction of cytochrome P450IA1 in a novel continuous human liver cell line (Mz-Hep-1). Detection by binding with [3H]2,3,7,8-tetrachlorodibenzo-p-dioxin and relationship to the activity of aryl hydrocarbon hydroxylase. Biochem. Pharmacol. 42(3): 521-528.

Key Terms: hepatotoxicity, mechanism of action, experimental, dioxins, in vitro, journal article

See page 97.

Roberts, L. (1991) Dioxin risks revisited [News]. Science 251(4994): 624-626.



D.741

Key Terms: mechanism of action, dioxins, human, news report

This news report discusses the controversial suggestion that the risk assessment of dioxin should reflect its molecular mechanism of action. It discusses the merits of the linear multistage model versus the receptor/threshold model relative to setting acceptable exposure limits for dioxin.

Rodriguez, E. and R. Lombardo (1991) Acute toxicity of parathion and 2,4 D to estuarine adult crabs. Bull. Environ. Contam. Toxicol. 46(4): 576-582.

Key Terms: acute toxicity, environmental exposure, 2,4-D, crab, journal article

The time- and concentration-dependence curves for the toxicity of 2,4-D and parathion were determined in two species of crabs. Parathion was 2,500- and 6,000-fold more toxic than 2,4-D in these two species.

Rodriguez-Pichardo, A., F. Camacho, C. Rappe, M. Hansson, A.G. Smith and I.B. Greig (1991) Chloracne caused by ingestion of olive oil contaminated with PVDDs and PCDFs. Human and Experimental Toxicology 10(5): 311-322.

Key Terms: chloracne, oral, dioxins, furans, human, journal article

Roegner, R.H., W.D. Grubbs, M.B. Lustik, A.S. Brockman and S.C. Henderson (1991) An epidemiologic investigation of health effects in air force personnel following exposure to herbicides. Air Force Health Study 1-9(Mar)

Key Terms: cancer, other toxic effects, pharmacokinetics, chronic toxicity, tissue residues, military exposure, dioxins, human, government report

See page 21.

Roegner, R.H., W.D. Grubbs, M.B. Lustik, A.S. Brockman and S.C. Henderson (1991) An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Introduction, background and conclusions. Air Force Health Study Chapters 1-5, 18, 19(1-133).

Key Terms: chronic toxicity, military exposure, phenoxy herbicides, dioxins, human, government report

See pages 14, 15, 16, 47, 59, 67, 68 and 78.

Rozman, K., B. Pfeifer, L. Kerecsen and R.H. Alper (1991) Is a serotoninergic mechanism involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced appetite suppression in the Sprague-Dawley rat. Arch. Toxicol. 65(2): 124-128.



D.7713

Key Terms: neurobehavioral effects, acute toxicity, injection, other route of exposure, dioxins, rat, journal article

This study investigated the role of serotonin in TCDD-induced appetite suppression. Transfusion experiments demonstrated that TCDD-treated rats were not satiated, but that their hunger was inhibited. Tryptophan in plasma and hypothalamus, and 5-HT and 5-HIAA in the hypothalamus, increased progressively in TCDD-treated rats. This indicates that a serotoninergic mechanism may be involved in TCDD-induced appetite suppression.

Rozman, K. (1991) ED50 for EROD induction and ED50 for PFCs/spleen [letter; comment]. Toxicol. Appl. Pharmacol. 108(3): 568-569.

Key Terms: enzyme induction or inhibition, mechanism of action, dioxins, commentary or opinion

This letter discussing the findings of Howie et al. in Toxicol. Appl. Pharmacol. 105: 254-263 (1990), points out that the two potent isomers of hexaCDE have about the same chance of being in a TCDD-like configuration, whereas the medium potency isomer has only half this chance and the low potency isomer does not enter a TCDD-like configuration. This is accompanied by a letter from S.H. Safe in reply.

Ruangwises, S., L. Bestervelt, D. Piper, C. Nolan and W. Piper (1991) Human chorionic gonadotropin treatment prevents depressed 17 alpha-hydroxylase/C17-20 lyase activities and serum testosterone concentrations in 2,3,7,8-tetrachlorodibenzo-p-dioxin-treated rats. Biol. Reprod. 45(1): 143-150.

Key Terms: alteration in sex hormones, enzyme induction or inhibition, oral, dioxins, rat, journal article

See page 111.

Rune, G., P. deSouza, R. Krowke, H. Merker and D. Neubert (1991) Morphological and histochemical effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on marmoset (Callithrix jacchus) testes. Arch. Androl. 26(3): 143-154.

Key Terms: reproductive toxicity, acute toxicity, experimental exposure, dioxins, marmoset, journal article

Rune, G.M., P. De Souza, R. Krowke, H.J. Merker and D. Neubert (1991) Morphological and histochemical pattern of response in rat testes after administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Histol. Histopathol. 6(4): 459-467.



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Key Terms: reproductive toxicity, alteration in sex hormones, injection, dioxins, rat, journal article

See page 42.

Safe, S., B. Astroff, M. Haris, T. Zacharewski, R. Dickerson, M. Romkes and L. Biegel (1991) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds as antioestrogens: characterization and mechanism of action. Pharmacol. Toxicol. 69(6): 400-409.

Key Terms: alteration in sex hormones, acute toxicity, experimental exposure, dioxins, in vitro, review

See page 110.

Safe, S. (1991) Polychlorinated dibenzo-p-dioxins and related compounds: sources, environmental distribution and risk assessment. Environ. Carcino. Ecotox. Revs. C9(2): 261-302.

Key Terms: cancer, other toxic effects, mechanism of action, occupational, environmental, other route of exposure, dioxins, human, review

See page 94.

Sanders, V.M., B.A. Fuchs, S.B. Pruett, N.I. Kerkvliet and N.E. Kaminski (1991) Symposium on indirect mechanisms of immune modulation. Fundam. Appl. Toxicol. 17(4): 641-650.

Key Terms: immunotoxicity, mechanism of action, experimental, dioxins, mouse, journal article

Sanner, T., S. Mikalsen and E. Rivedal (1991) Hepatic peroxisome proliferators induce morphologic transformation of Syrian hamster embryo cells, but not peroxisomal beta oxidation. Prog. Clin. Biol. Res. 369: 77-89.

Key Terms: cell transformation, experimental exposure, 2,4-D, 2,4,5-T, in vitro, journal article

See page 115.

Santagostino, A., M. Leone, R. Maci, A. Casale and L. Marabini (1991) Effects of phenoxyacetic acid herbicides on chicken embryo liver drug metabolizing enzymes. Pharmacol. Toxicol. 68(2): 110-114.



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D.744

Key Terms: hepatotoxicity, enzyme induction or inhibition, injection, 2,4-D, bird, journal article

See page 68 and 107.

Saracci, R., M. Kogevinas, P.-A. Bertazzi, B.H. Bueno de Mesquita, D. Coggon, L.M. Green, T. Kauppinen et al. (1991) Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338(8774): 1027-1032.

Key Terms: cancer, chronic toxicity, occupational exposure, phenoxy herbicide formulations, dioxins, human, journal article

See page 25.

Schecter, A.J., R. Malkin, O. Päpke, M. Ball and P.W. Brandt-Rauf (1991) Dioxin levels in blood of municipal incinerator workers. Med. Sci. Res. 19(11): 331-332.

Key Terms: tissue residues, occupational exposure, dioxins, human, journal article

Schecter, A.J., B.J. Poiesz, P.W. Brandt-Rauf, O. Päpke and M. Ball (1991) Dioxin levels in blood of AIDS patients and controls. Med. Sci. Res. 19(9): 273-275.

Key Terms: immunotoxicity, environmental exposure, dioxins, furans, human, journal article

See pages 48 and 49.

Schecter, A., P. Furst, C. Furst, O. Päpke, M. Ball, L.C. Dai, H.T. Quynh, N.T.N. Phoung, A. Beim, B. Vlasov, V. Chongchet, J.D. Constable and K. Charles (1991) Dioxins, dibenzofurans and selected chlorinated organic compounds in human milk and blood from Cambodia, Germany, Thailand, the U.S.A., the U.S.S.R., and Vietnam. Chemosphere 23(11-12): 1903-1912.

Key Terms: tissue residues, environmental exposure, occupational exposure, military exposure, dioxins, furans, human, journal article

See page 85.

Schecter, A., O. Päpke, M. Ball and J.J. Ryan (1991) Partitioning of dioxins and dibenzofurans: whole blood, blood plasma and adipose tissue. Chemosphere 23(11-12): 1913-1919.

Key Terms: pharmacokinetics, tissue levels, environmental exposure, dioxins, furans, human, journal article



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D.745

See page 77.

Schecter, A. and J.J. Ryan (1991) Brominated and chlorinated dioxin blood levels in a chemist 34 years after exposure to 2,3,7,8-tetrachlorodibenzodioxin and 2,3,7,8-tetrabromodibenzodioxin. Chemosphere 23(11-12): 1921-1924.

Key Terms: tissue residues, other route of exposure, dioxins, human, journal article

See pages 77 and 81.

Schmidt, K.F. (1992) Dioxin's other face. Science News 141: 24.

Key Terms: cancer, other toxic effects, chronic toxicity, dioxins, news report

See page 110.

Schrenk, D., H.-P. Lipp, T. Wiesmuller, H. Hagenmaier and K.W. Bock (1991) Assessment of biological activities of mixtures of polychlorinated dibenzo-p-dioxins: comparison between defined mixtures and their constituents. Arch. Toxicol. 65(2): 114-118.

Key Terms: enzyme induction or inhibition, experimental, dioxins, in vitro, journal article

See page 103.

Schrenk, D., H.-P. Lipp, H. Brunner, T. Wiesmuller, H. Hagenmaier and K.W. Bock (1991) Induction of hepatic P450-dependent monooxygenase in feral mice from a PCDD/PCDF-contaminated area. Chemosphere 22(11): 1011-1018.

Key Terms: hepatotoxicity, enzyme induction or inhibition, environmental, dioxins, mouse, journal article

See page 104.

Schroder, C., E. Kruger and J. Abel (1991) Acute poisoning caused by the herbicide dichlorprop (preparation SYS 67 PROP). Kinderarztl Prax. 59(3): 81-84.

Key Terms: hematologic effects, other toxic effects, environmental exposure, 2,4-D, human, journal article

This case report discussed the acute poisoning of a 5-year-old boy by dichlorprop. Toxic effects were observed in almost all organs, but the predominant effect was hemolytic anemia. Pathology was reversed by symptomatic treatment.



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Schulz-Schalge, T., E. Koch, G. Golor, T. Wiesmuller, H. Hagenmaier and D. Neubert (1991) Comparison of the induction of cytochrome P450 and ethoxyresorufin O-deethylase by a single subcutaneous administration of TCDD in liver microsomes of marmoset monkeys (Callithrix jacchus) and rats. Chemosphere 23(11-12): 1933-1939.

Key Terms: enzyme induction or inhibition, injection, dioxins, monkey, rat, journal article

Schulz-Schalge, T., E. Koch, K.-H. Schwind, O. Hutzinger and D. Neubert (1991) Inductive potency of TCDD and three 2,3,7,8-mixed-halogenated dioxins in liver microsomes of male rats, enzyme kinetic considerations. Chemosphere 23(11-12): 1925-1931.

Key Terms: enzyme induction or inhibition, acute toxicity, injection, dioxins, rat, journal article

See page 103.

Seegal, R.F., B. Bush and W. Shain (1991) Neurotoxicology of ortho-substituted polychlorinated biphenyls. Chemosphere 23(11-12): 1941-1949.

Key Terms: neurobehavioral effects, mechanism of action, experimental, PCBs, dioxins, in vitro, journal article

Shaub, W.M., Editor (1991) Dioxins. Chemistry and Health Effects. Sci. Total Environ. 104(1-2): 1-166.

Key Terms: toxicity, dioxins, book

Shaw, P., A. Reiss, M. Adesnik, D. Nebert, J. Schembri and A. Jaiswal (1991) The human dioxin-inducible NAD(P)H: quinone oxidoreductase cDNA-encoded protein expressed in COS-1 cells is identical to diaphorase 4. Eur. J. Biochem. 195(1): 171-176.

Key Terms: mechanism of action, enzyme induction or inhibition, in vitro, journal article

See page 109.

Shen, E.S., S.I. Gutman and J.R. Olson (1991) Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin-mediated hepatotoxicity in C57BL/6J and DBA/2J mice. J. Toxicol. Environ. Health 32(4): 367-381.



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Key Terms: hepatotoxicity, acute toxicity, mechanism of action, injection, dioxins, mouse, journal article

See page 68.

Silbergeld, E.K. (1991) Carcinogenicity of dioxins [Editorial]. JNCI 83(17): 1198-1199.

Key Terms: cancer, chronic toxicity, dioxins, commentary or opinion

See page 32.

Smith, E.A. and F.W. Oehme (1991) A review of selected herbicides and their toxicities. Vet. Hum. Toxicol. 33(6): 596-608.

Key Terms: acute toxicity, unspecified route of exposure, arsenic, 2,4-D, 2,4,5-T, human, review

Smith, A.H., D.G. Patterson, M.L. Warner, R. MacKenzie and L.L. Needham (1992) Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels of New Zealand pesticide applicators and their implication for cancer hypotheses. J. Natl. Cancer Inst. 84(2): 104-108.

Key Terms: cancer, tissue residues, occupational exposure, 2,4,5-T, dioxins, human, journal article

Smolowitz, R., M. Hahn and J. Stegeman (1991) Immunohistochemical localization of cytochrome P-450IA1 induced by 3,3',4,4'-tetrachlorobiphenyl and by 2,3,7,8-tetrachlorodibenzofuran in liver and extrahepatic tissues of the teleost Stenotomus chrysops (Scup). Drug Metab. Dispos. 19(1): 113-123.

Key Terms: mechanism of action, injection, furans, fish, journal article

See page 106.

Spitsbergen, J.M., M.K. Walker, J.R. Olson and R.E. Peterson (1991) Pathological alterations in early life stages of lake trout, Salvelinus namaycush, exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin as fertilized-eggs. Aquatic Toxicology 19(1) 41-71.

Key Terms: acute toxicity, lethality, experimental exposure, dioxins, fish, journal article

Stahl, B.U., R.H. Alper and K. Rozman (1991) Depletion of brain serotonin does not alter 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced starvation syndrome in the rat. Toxicol. Lett. 59(1-3): 65-72.



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Key Terms: neurobehavioral effects, acute toxicity, dioxins, rat, journal article
See page 63.

Stanley, J.S., P.H. Cramer, K.R. Thornburg, J.C. Remmers, J.J. Breen and S. J. (1991) Mass spectral confirmation of chlorinated and brominated diphenylethers in human adipose tissues. Chemosphere 23(8-10): 1185-1195.

Key Terms: tissue residues, method, dioxins, human, journal article

Stegeman, J., R. Smolowitz and M. Hahn (1991) Immunohistochemical localization of environmentally induced cytochrome P450IA1 in multiple organs of the marine teleost Stenotomus chrysops (Scup). Toxicol. Appl. Pharmacol. 110(3): 486-504.

Key Terms: miscellaneous study, method, environmental exposure, furans, fish, journal article

See page 106.

Stohs, S., N. Alsharif, M. Shara, Z. al-Bayati and Z. Wahba (1991) Evidence for the induction of an oxidative stress in rat hepatic mitochondria by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Adv. Exp. Med. Biol. 283: 827-831.

Key Terms: other toxic effects, mechanism of action, dioxins, rat, journal article

Strubel, V., H.J. Knackmuss and K.H. Engesser (1991) Metabolism of dibenzofuran and dibenzodioxin as model for 2,3,7,8-tetrachlorodibenzodioxin degradation. Biochem. Eng. Proc. Int. Symp.(2): 421-424.

Key Terms: dioxins, furans, model, journal article

Sullivan, M.J., S.R. Custance and C.J. Miller (1991) Infant exposure to dioxin in mother's milk resulting from maternal ingestion of contaminated fish. Chemosphere 23(8-10): 1387-1396.

Key Terms: pharmacokinetics, oral, dioxins, human, model, journal article

See page 87.

Sutter, T.R., K. Guzman, K.M. Dold and W.F. Greenlee (1991) Targets for dioxin: genes for plasminogen activator inhibitor-2 and interleukin-1$\beta$. Science 254(5030): 415-418.

Key Terms: other toxic effects, mechanism of action, experimental, dioxins, in vitro, journal article



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See pages 108 and 109.

Svensson, B.G., A. Nilsson, M. Hansson, C. Rappe, B. Akesson and S. Skerfving (1991) Exposure to dioxins and dibenzofurans through the consumption of fish. N. Engl. J. Med. 324(1): 8-12.

Key Terms: tissue residues, oral, dioxins, human, journal article

See page 84.

Swain, W.R. (1991) Effects of organochlorine chemicals on the reproductive outcome of humans who consumed contaminated Great-Lakes fish - an epidemiologic consideration. J. Toxicol. Environ. Health 33(4): 587-639.

Key Terms: reproductive toxicity, oral, PCB, human, journal article

Swanson, H. and G. Perdew (1991) Detection of the Ah receptor in rainbow trout: use of 2-azido-3-[125I]iodo-7,8-dibromodibenzo-p-dioxin in cell culture. Toxicol. Lett. 58(1): 85-95.

Key Terms: mechanism of action, experimental exposure, dioxins, in vitro, journal article

See page 96.

Takayama, K., H. Miyata, O. Aozasa, M. Miumra and T. Kashimoto (1991) Dietary-intake of dioxin-related compounds through food in Japan. Journal of the Food Hygienic Society of Japan 32(6): 525-532.

Key Terms: oral, dioxins, human, journal article

Takayama, K., H. Miyata, M. Mimura, S. Ohta and T. Kashimoto (1991) Evaluation of biological effects of polychlorinated compounds found in contaminated cooking oil responsible for the disease Yusho. Chemosphere 22(5-6): 537-546.

Key Terms: enzyme induction or inhibition, oral, dioxins, furans, human, journal article

Takemori, H., K. Koga and Y. Masuda (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds on the somatic recombination and repair systems of Drosophila-melanogaster. Mutat. Res. 252(1): 111-112.

Key Terms: genetic toxicity, experimental exposure, dioxins, Drosophila melanogaster, journal article



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Takimoto, K., R. Lindahl and H. Pitot (1991) Superinduction of 2,3,7,8-tetrachlorodibenzo-p-dioxin-inducible expression of aldehyde dehydrogenase by the inhibition of protein synthesis. Biochem. Biophys. Res. Commun. 180(2): 953-959.

Key Terms: mechanism of action, enzyme induction or inhibition, experimental exposure, dioxins, in vitro, journal article

See page 106.

Tarone, R.E., H.M. Hayes, R.N. Hoover, J.F. Rosenthal, L.M. Brown, L.M. Pottern, N. Javadpour, K.J. O'Connell and R.E. Stutzman (1991) Service in Vietnam and risk of testicular cancer (brief communication). JNCI 83(20): 1497-1499.

Key Terms: cancer, chronic toxicity, military exposure (possible), human, journal article

See page 123.

Teeter, L.D., D.D. Petersen, D.W. Nebert and M.T. Kuo (1991) Murine mdr-1, mdr-2, and mdr-3 gene expression: no coinduction with the Cypla-1 and Nmo-1 genes in liver by 2,3,7,8-tetrachlorodibenzo-p-dioxin. DNA Cell Biol. 10(6): 433-441.

Key Terms: other toxic effects, mechanism of action, dioxins, rat, mouse, journal article

See page 109.

Theelen, R., A. Knaap and B. Sangster (1991) Dioxin; standards recommended by the World Health Organization. Ned. Tijdschr. Geneeskd. 135(20): 875-877.

Key Terms: dioxins, journal article

This article discusses variations in the standards based on the no-effect-observed level established by different countries. Text is in Dutch.

Theobald, H.M., G.B. Ingall, T.A. Mably and R.E. Peterson (1991) Response of the antral mucosa of the rat stomach to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 108(1): 167-179.

Key Terms: other toxic effects, acute toxicity, miscellaneous study, dioxins, rat, journal article

See pages 70 and 71.



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D.751

Thomas, T.L., H.K. Kang and N.A. Dalager (1991) Mortality among women Vietnam veterans, 1973-1987. Am. J. Epidemiol. 134(9): 973-980.

Key Terms: cancer, cardiovascular toxicity, chronic toxicity, military exposure (possible), human, journal article

See pages 13 and 21.

Thompson, T., T. Kolic and K. MacPherson (1991) Dual-column high-performance liquid chromatographic cleanup procedure for the determination of polychlorinated dibenzo-p-dioxins and dibenzofurans in fish tissue. J. Chromatogr. 543(1): 49-58.

Key Terms: analytical method, dioxins, journal article

Thomsen, J., L. Nissen, S. Stacey, R. Hines and H. Autrup (1991) Differences in 2,3,7,8-tetrachlorodibenzo-p-dioxin-inducible CYPIA1 expression in human breast carcinoma cell lines involve altered trans-acting factors. Eur. J. Biochem. 197(3): 577-582.

Key Terms: mechanism of action, enzyme induction or inhibition, experimental exposure, dioxin, in vitro, journal article

See page 105.

Tillitt, D., G. Ankley, D. Verbrugge, J. Giesy, J. Ludwig and T. Kubiak (1991) H4IIE rat hepatoma cell bioassay-derived 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents in colonial fish-eating waterbird eggs from the Great Lakes. Arch. Environ. Contam. Toxicol. 21(1): 91-101.

Key Terms: enzyme induction or inhibition, environmental exposure, dioxins, bird, journal article

Tillitt, D.E., J.P. Giesy and G.T. Ankley (1991) Characterization of the H4IIE rat hepatoma-cell bioassay as a tool for assessing toxic potency of planar halogenated hydrocarbons in environmental-samples. Environmental Science and Technology 25(1): 87-92.

Key Terms: enzyme induction or inhibition, experimental exposure, dioxins, furans, in vitro, journal article

bioassay method

Tollefson, L. (1991) Use of epidemiology data to assess the cancer risk of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Regul. Toxicol. Pharmacol. 13(2): 150-169.



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D·752

Key Terms: cancer, chronic toxicity, dioxins, human, review

See page 29.

Tomar, R.S. and N.I. Kerkvliet (1991) Reduced T-helper cell function in mice exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Lett. 57(1): 55-64.

Key Terms: immunotoxicity, acute toxicity, experimental, dioxins, mouse, in vitro, journal article

See page 52.

Trakayama, K., H. Miyata, M. Mimura, S. Ohta and T. Kashimoto (1991) Evaluation of biological effects of polychlorinated compounds found in contaminated cooking oil responsible for the disease Yusho. Chemosphere 22(5-6): 537-546.

Key Terms: acute toxicity, chronic toxicity, oral, dioxins, furans, PCBs, human, journal article

Travis, C.C. and H.A. Hattemer-Frey (1991) Human exposure to dioxin. Sci. Total Environ. 104(1-2): 97-127.

Key Terms: miscellaneous study, environmental exposure, occupational exposure, dioxins, human, review

The authors evaluated critical issues regarding the extent of background contamination by TCDD, the potential for human exposure via the food chain, the magnitude of various emissions of TCDD in the U.S., and the relationship of these factors to setting appropriate standards.

Triebig, G. (1991) Is dioxin carcinogenic? Lancet 338(8752): 1592.

Key Terms: cancer, chronic toxicity, occupational exposure, dioxins, human, commentary or opinion

See page 27.

Tsukazaki, N., S. Nonaka, T. Ohgami, H. Irifune, K. Tanaka, M. Yano and H. Yoshida (1991) The synergistic effect of chlorinated chemicals (trichlorosalicylanilid, 4-chloro-m-cresol, trichlorophenoxyacetic acid, trichloroethanol, trichloromethiazide, trichlorofon and trichloroacetaldehyde) and low concentrations of griseofulvin on porphyrin metabolism. Fukuoka Igaku Zasshi 82(5): 215-220.



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D.753

Key Terms: hepatotoxicity, mechanism of action, oral, 2,4,5-T, phenoxyacetic acid, mouse, journal article

Tuomisto, J. and R. Pohjanvirta (1991) Do new hypotheses on the mechanism of action of dioxins help in risk evaluation? Sci. Total Environ. 106(1-2): 21-31.

Key Terms: lethality, neurobehavioral effects, other toxic effects, dioxins, rat, journal article

See pages 62 and 95.

Tuomisto, J.T., M. Unkila, R. Pohjanvirta, M. Koulu and L. Tuomisto (1991) Effect of a single dose of TCDD on the level of histamine in discrete nuclei in rat brain. Agents Actions 33(1-2): 154-156.

Key Terms: neurobehavioral effects, acute toxicity, injection, dioxins, rat, journal article

See pages 63 and 64.

Van den Berg, K.J., J.A.G.M. Van Raaij, P.C. Bragt and W.R.F. Notten (1991) Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo. Arch. Toxicol. 65(1): 15-19.

Key Terms: thyroid effects, chronic toxicity, occupational exposure, phenoxy herbicides, human, journal article

Van der Heijden, C. (1991) How toxic are dioxins for man? Ned. Tijdschr. Geneeskd 135(40): 1860-1865.

Key Terms: chronic toxicity, other route of exposure, dioxins, human, journal article

This article deals with the way in which dioxins become contaminants in chemicals, incidents of environmental contamination, and the toxic sequelae and mechanism of action of dioxin. Text is in Dutch.

Van Loveren, H.K., H.-J. Schuurman, J. Kampinga and J.G. Vos (1991) Reversibility of thymic atrophy induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and bis(tri-n-butyltin)oxide (TBTO). Int. J. Immunopharmac. 13(4): 369-377.

Key Terms: immunotoxicity, acute toxicity, oral, dioxins, rat, journal article



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See pages 50 and 51.

Vineis, P., F. Faggiano, M. Tedeschi and G. Ciccone (1991) Incidence rates of lymphomas and soft-tissue sarcomas and environmental measurements of phenoxy herbicides. J. Natl. Cancer Inst. 83(5): 362-363.

Key Terms: cancer, chronic toxicity, environmental exposure, phenoxy herbicide formulations, 2,4-D, 2,4,5-T, human, journal article

See pages 27 and 28.

Waern, F., S. Flodstrom, L. Busk, T. Kronevi, I. Nordgren and U.G. Ahlborg (1991) Relative liver tumor promoting activity and toxicity of some polychlorinated dibenzo-p-dioxin- and dibenzofuran-congeners in female Sprague-Dawley rats. Pharmacol. Toxicol. 69(6): 450-458.

Key Terms: cancer, acute toxicity, injection, furans, dioxins, rat, journal article

See page 32.

Waern, F., E. Manzoor, U.G. Ahlborg and H. Hakansson (1991) Effects of 2,3,7,8-tetra-chlorodibenzo-p-dioxin (TCDD) in the lactating rat on maternal and neonatal vitamin A status and hepatic enzyme induction: a dose-response study. Chemosphere 23(11-12): 1951-1956.

Key Terms: other toxic effects, enzyme induction or inhibition, oral, dioxins, rat, journal article

See page 113.

Waithe, W., M. Michaud, P. Harper, A. Okey and A. Anderson (1991) The Ah receptor, cytochrome P450IA1 mRNA induction, and aryl hydrocarbon hydroxylase in a human lymphoblastoid cell line. Biochem. Pharmacol. 41(1): 85-92.

Key Terms: immunotoxicity, mechanism of action, enzyme induction or inhibition, dioxins, in vitro, journal article

See pages 48 and 97.

Wang, W., T.R. Narasimhan, V. Morrison and S. Safe (1991) In situ and in vitro photoaffinity labeling of the nuclear aryl hydrocarbon receptor from transformed rodent and human cell lines. Arch. Biochem. Biophys. 287(1): 186-194.

Key Terms: mechanism of action, experimental, dioxins, in vitro, journal article



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D.75

See page 97.

Watanabe, K.K., H.K. Kang and T.L. Thomas (1991) Mortality among Vietnam veterans: with methodological considerations. J. Occup. Med. 33(7): 780-785.

Key Terms: cancer, other toxic effects, military exposure, phenoxy herbicide formulations, human, journal article

See pages 13 and 21.

Weber, L.W.D., M. Lebofsky, H. Greim and K. Rozman (1991) Key enzymes of gluconeogenesis are dose-dependently reduced in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)- treated rats. Arch. Toxicol. 65(2): 119-123.

Key Terms: enzyme induction or inhibition, injection, dioxins, rat, journal article

See page 114.

Weber, L.W.D., M. Lebofsky, B.U. Stahl, J.R. Gorski, G. Muzi and K. Rozman (1991) Reduced activities of key enzymes of gluconeogenesis as possible cause of acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicology 66(2): 133-144.

Key Terms: lethality, neurobehavioral effects, enzyme induction or inhibition, injection, dioxins, rat, journal article

Weber, L., A. Zesch and K. Rozman (1991) Penetration, distribution and kinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in human skin in vitro. Arch. Toxicol. 65(5): 421-428.

Key Terms: pharmacokinetics, dermal, dioxins, human, journal article

Weber, L.W.D., B.U. Stahl, M. Lebofsky, R.H. Alper, L. Kerecsen and K. Rozman (1991) Inhibition of phosphoenolpyruvate carboxykinase activity appears to be the key biochemical lesion in the acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Chemosphere 23(11-12): 1957-1962.

Key Terms: neurobehavioral effects, enzyme induction or inhibition, acute toxicity, injection, dioxins, rat, journal article

See page 114.



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Webster, T. and P. Connett (1991) Estimating bioconcentration factors and half-lives in humans using physiologically based pharmacokinetic modelling: 2,3,7,8-TCDD. Chemosphere 23(11-12): 1763-1768.

Key Terms: pharmacokinetic, unspecified route of exposure, dioxins, human, model

See page 80.

Weinstein, I.B. (1991) Mitogenesis is only one factor in carcinogenesis. Science 251(4992): 387-388.

Key Terms: cancer, dioxins, human, commentary or opinion

This article discusses various aspects of carcinogenesis, in addition to mitogenesis, which should be considered when assessing the risk associated with a potential carcinogen.

White, T.B., D.K. Hammond, H. Vasquez and H.W. Strobel (1991) Expression of two cytochromes P450 involved in carcinogen activation in a human colon cell line. Mol. Cell. Biochem. 102(1): 61-69.

Key Terms: cancer, enzyme induction or inhibition, in vitro, journal article

See page 106.

Wiebel, F.J., U. Klose and F. Kiefer (1991) Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in vitro: H4IIEC3-derived 5L hepatoma cells as a model system. Toxicol. Lett. 55(2): 161-169.

Key Terms: other toxic effects, mechanism of action, experimental exposure, dioxins, in vitro, model, journal article

See page 68.

Williams, F.L.R. (1991) Is dioxin carcinogenic? Lancet 338(8752): 1592.

Key Terms: immunotoxicity, cancer, mechanism of action, unspecified route of exposure, dioxins, commentary or opinion

Wren, C. (1991) Cause-effect linkages between chemicals and populations of mink (Mustela vison) and otter (Lutra canadensis) in the Great Lakes basin. J. Toxicol. Environ. Health 33(4): 549-585.



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D·757

Key Terms: reproductive toxicity, chronic toxicity, environmental exposure, dioxins, mink, otter, journal article

See page 43.

Yasuda, M., T.J. Sato and H. Sumida (1991) Exencephalic mouse fetuses are resistant to cleft palate induction with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Teratology 43(5): 445.

Key Terms: neurobehavioral effects, other toxic effects, injection, dioxins, mouse, abstract

See page 43.

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