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(2)

IN THE CIRCUIT COURT
TWENTIETH JUDICIAL CIRCUIT OF ILLINOIS
ST. CLAIR COUNTY

FRANCES E. KEMNER, et al., Plaintiffs,	)	
vs.	)	NO. 80-L-970
MONSANTO COMPANY, et al., Defendants.	)	

Before the HON. RICHARD P. GOLDENHERSH, Judge

REPORT OF PROCEEDINGS

JURY TRIAL

April 12, 1984

APPEARANCES:

MR. REX CARR and MR. JERRY SEIGFREID, Attorneys at Law
Appeared on Behalf of the Plaintiffs

MR. KENNETH R. HEINEMAN and MS. JANE RUDOLPH,
Attorneys at Law
Appeared on Behalf of the Defendant Monsanto Company

MR. ALBERT SCHOENBECK and MR. STEPHEN M. SCHOENBECK,
Attorneys at Law
Appeared on Behalf of the Defendant Norfolk & Western

MARSHA SCHNIPPER
Official Court Reporter

BE IT REMEMBERED AND CERTIFIED that heretofore, on to-wit: Thursday, April 12, 1984, being one of the regular judicial days of this Court, the matter as hereinbefore set forth came on for hearing before the HON. RICHARD P. GOLDENHERSH, Circuit Judge in and for the Twentieth Judicial Circuit, State of Illinois, St. Clair County Building, Belleville, St. Clair County, Illinois, and the following was had of record, to-wit:

* * * * * * *

THE COURT: Good morning. We have a fine artist in the group. I'm sorry we're running a bit late. I had a criminal matter that had to be taken care of and that required that I do it and so I appreciate your patience. Mr. Carr, you may proceed.

MR. CARR: Your Honor, I can identify everyone on this drawing. I see that the jury is so much larger than the rest of us and I understand that with the exception of yourself. The lower right-hand corner, who is that?

JUROR: That's Marlene.

MR. CARR: All right, okay.

ELLEN KOVNER SILBERGELD,

resuming the witness stand, having been previously sworn, testified as follows:

DIRECT EXAMINATION (Continued)

BY MR. CARR:

Q Dr. Silbergeld, we were in the midst of examining you relative to the 75 publications that you authored, and I would just like to read excerpts from some of the titles to you as I go along just from time to time and ask you about a few additional of these. And don't hold me if I can't pronounce some of these words. I think we were at about the release of dopamine in substantia nigra. You've also written in monitoring for pharmacology research, the quantitative aspect of normal -- we've read that one already. Let me pass that. You've studied at length and published at length on the affect of ergot drugs. Ergot drugs, what is that, what does that encompass? What is an ergot drug?

A Ergot is a natural fungus which occurs on wheat and the fungus secretes a number of chemicals. One of them is LSD and others of them, which have recently been purified by the Sandos Pharmaceutical Company has a very great promise for treating certain neurologic and psychiatric diseases.

Q And you've studied the effect of those drugs, is that what this means?

A Yes.

Q And published. You've also published -- there's an Erythrosin B as it inhibits dopamine transport in the rat caudate synaptosomes. What does that mean? What is the sig-

nificance of that, Doctor?

A Erythrosin B is Red No. 3, a very widely used food, drug, and cosmetic dye and we were looking at a possible neuroactive effect in preparations from the rat brain.

Q And did you conclude that this food additive had harmful effects on beings, living beings?

A We concluded that in the test tube this compound was very active in affecting brain function.

Q And has that study been used in determining to what extent this food additive should be used in our everyday life?

A I believe it has been used, that and other publications of mine in instigating a review of the safety of Red No. 3, yes.

Q Doctor, you've also published in Environmental Research the effects of lead and other things upon seizure activity, and the effects of ergot drug on serotonergic function and the effects of kainic acid on behavorial and biochemical aspects of cholinergic function on dopaminergic and serotonergic interactions in the some kind of syndrome, the role of striatal cholinergic neurons and the effects of intrastriatal kainic acid, problems in studying lead poisoning, estrogen treatment enhancing a receptor sensitivity in the rat striatum, electron probe microanalysis of isolated brain capillaries that have been poisoned with lead. What's the

purpose of that study in Brain Research?

A That was a study to determine where lead actually goes in the brain, and we used a very sophisticated instrument which is able to detect molecules and atoms of a substance in very small spaces.

Q And a number of other publications here relating to cortical neurochemical changes after injection of certain drugs, the effect of ergot derivatives on post-decapitation convulsions, hypophysectomy preventing some kind of dopamine receptor supersensitivity produced by chronic haloperidol treatment. I'm not going to ask what that means. Neurochemical investigations further in lead exposure, and the role of the altered heme synthesis in lead neurotoxicity. Doctor -- and that was published in the Journal of Occupational Medicine. What role did you find this particular poison, that is, lead had in altering the synthesis for blood cells and heme synthesis?

A Lead is a very powerful inhibitor of heme synthesis.

Q Heme is another word for blood or heme is a part of the blood, the word hemoglobin, part of that is heme?

A Yes, heme is one of the molecules in our blood, but heme has a very major role to play in many other systems in the body, including the brain.

Q Other than just making blood?

A Absolutely.

Q What is the role of heme then in other parts of the body?

A Heme is a very important part of many enzymes in the liver which take care of normal things in the body such as sex steroids, cholesterol, and also handle a variety of compounds that are introduced to the body such as drugs and chemicals. Heme is also important in maintaining the insulation around the nerves of our body and has a variety of other functions of carrying oxygen within cells to maintain cell energy and activation, so that anything that interferes with heme synthesis has effects far beyond an effect on red blood cells, and indeed the purpose of these studies was to examine how an interference in heme synthesis might lead to very serious effects on the nervous system.

Q And did you conclude that the interference with the heme synthesis did indeed have as far reaching effects?

A Yes, we did.

Q And you published accordingly at least as far back as 1980?

A Yes.

Q And Doctor, have you also published for the FDA methods of detection of neurotoxicity using neurochemical methods in so detecting?

A Yes.

Q And you've also published Erythrosin B as a specific inhibitor of high affinity -- why don't you read that title for me. I'm messing it up.

A Erythrosin B is the food dye Red No. 3 specifically inhibits, prevents, the binding or the interactions of the chemical known as ouabain to the rat brain. Now ouabain is a drug used in treating heart disease. It's a very important drug and it's also a drug which has a very specific interaction with membranes, it has a receptor and you can use that interaction of ouabain with membranes as a way of studying the chemical state of a nervous system and other cells.

Q And you also published as to the efficacy of using animal models in studies of various diseases, more specifically in the study of parkinsonism?

A That's right.

Q Did you conclude that -- you and your associate there -- that animal models were effective in such studies?

A Yes, my associate, Dr. Calne, who was at the time the clinical director of the Neurology Institute at N.I.H. and I conclude that animal models, that's the use of rats and mice, have been very, very important in advancing our understanding and developing treatments for human parkinsonism.

Q And Doctor, did you also publish another study dealing

with the hypersensitivity of certain receptor activation in some experimental animals and the effects of certain drugs on various systems of theirs in Brain Research?

A Yes. That was the paper with Dr. Gadjusek, who won a Nobel Prize for his work in flow viruses.

Q Gadjusek, your associate, associated with you in that, won the Nobel Prize?

A Yes, he won the Nobel Prize, I think, in 1980.

Q And, Doctor, have you also published for the E.P.A. on an international symposium on heavy metal as to the effect of heavy metal neurotoxicity and porphyrinopathic mechanisms?

A Yes. This is -- was further research on the role of altering heme synthesis and porphyrin metabolism on the nervous system.

Q The jury has heard for the last several days considerable about porphyrins and did you in fact study and publish as to the effect of various substances, heavy metals in this instance, on the porphyrin system in our body?

A Yes, I did.

Q And that was in 1981?

A Starting in 1980 through the present time that's been an area of my research, yes.

Q Did you conclude that toxic substances can indeed affect the porphyrins?

A Yes.

Q Doctor, have you also published with relation to children as to excretion of homovanillic acid, on parkinson disease published as to another ergot derivative to the dopamine, have you published in neurochemical and kainic mechanisms of lead neurotoxicity; published with relation to prolactin increases of the density of striatal dopamine receptors in normal hypophysectomized male rats; and the effects of estrogen on the dopamine receptor in male and female rats; and in the effects of artificial food colors and childhood behavior disorders? Have you published in those areas?

A Yes.

Q Regarding that last publication did you and Dr. Anderson conclude that artificial food colors did play a role in childhood behavior and disorders in behavior?

A This paper reviewed both the clinical, that is, the studies in children, and the experimental studies on Red No. 3 primarily and childhood behavior problems and learning problems. We concluded that the animal studies were quite persuasive of neurotoxic effects of this dye, that the human studies suggested that there might be a small group of children who were predisposed to respond abnormally to high amounts of these colors.

Q The conclusion would be that for some children they are not misbehaving other than reacting to this particular food

additive?

A That is a very strong possibility.

Q And that's something that they would not have any control over, but it would depend on whether or not they are in that group of people that are sensitive to this kind of dye?

A That's right.

Q And, Doctor, did you also publish in Trends in Neuroscience, did you review the current status of the field of neurotoxicology, basic and applied?

A Yes.

Q What did you do in that publication? What was the role of that publication?

A The role of that paper, which was an invited paper by the editor of that journal, was to look at both clinical studies, studies in people which have been developed to try and detect neurotoxic symptoms in the work place or the general environment, to correlate these with the advances in basic research, studies with animals as to developing more sensitive and more reliable indicators of neurotoxic effects.

Q Now in the area of neurotoxic effects, would that include the effects of toxic substances such as 2,3,7,8 TCDD?

A Yes.

Q Now, Doctor, have you also published in the area of

interactions of these Erythrosin in the cortical membranes; neurotoxic aspects of porphyrinopathies, lead and succinylacetone?

A Yes.

Q Doctor, referring to the neurotoxic aspects of porphyrinopathies and the succinylacetone, that again is right in the area that we have just concluded these depositions dealing with the porphyrins. Did you find that there were additional neurotoxic effects that causes these alterations in the porphyrin pattern?

A Yes, what we were looking at were what can really be called acquired porphyrias.

Q What we've called intoxication or can be called intoxication porphyria?

A Yes. Lead can cause a type of acquired or intoxication porphyria and succinylacetone can also cause such a condition, and both of these agents, lead and succinylacetone, have very significant neurologic problems when exposure occurs in humans, and we were exploring the role of the alteration these chemicals indeed in heme synthesis, that is, the porphyrias that they produced, the role of that biochemical change in producing the neurologic syndrome and deficits. We concluded that that was quite significant.

Q Doctor, did you also publish relating to experimental

and environmental neurotoxins making an attempt to correlate behavior problems and biochemical effects of certain neurotoxins?

A Yes.

Q And did you -- did you succeed in making such a correlation?

A In part. We were looking at a range of -- I was looking at a range of compounds including some of the polycyclic halogenated hydrocarbons such as PCBs and kepone that we talked about yesterday, and I concluded then in some cases there are good correlations between the biochemical or molecular effects of these chemicals in physiologic symptoms and the kinds of symptoms you would observe in the whole animal or the person.

Q Doctor, did you also publish in the publication called Neurobehavior Toxicology work on your research as to the effects of altered porphyrin synthesis on brain neurochemistry?

A Yes.

Q And did you -- that again is related to the heme process?

A That's right.

Q And, Doctor, did you publish several other studies dealing with lead and various drugs and then in a journal

called Acta Psychiatric Scandinavia a work dealing with neurotoxins that don't act directly but act indirectly?

A Yes.

Q When was that, when did you publish there, Doctor?

A 1983.

Q And did you discover that there were neurotoxins that acted indirectly?

A Yes, this paper grew out of my research on both the chemicals that caused porphyria like lead, Dioxin, succinylacetone, and some of the sex hormones like estrogen and prolactin, and the paper discusses the role of these kinds of chemicals which are not thought to be primarily neurotoxins; that is, that their primary site of action is not thought to be the nervous system but the liver; for example, for a chemical which causes porphyria, for the gonads for a sex hormone, but indirectly alterations in those systems outside the brain may have very serious consequences for the brain.

Q And that was the conclusion that you reached, Doctor?

A Yes.

Q The journal Acta Psychiatric Scandinavia, where does that stand in the tier of authoritative publications?

A It is very highly regarded. I believe it's --

Q Internationally, is it not?

A I believe it's published by the Karolinska Institute

in Sweden, which is the institute that awards the Nobel Prizes in science.

Q And before this article dealing with these indirectly acting neurotoxins was accepted for publication by that professional publication was it so-called peer reviewed and examined for authenticity and the correctness of the conclusions?

A Yes.

Q And, Doctor, have you also just recently had published additional work as to the terato -- it's early, I can't -- my tongue isn't working right this morning -- behavioral teratology? That's not right, is it?

A Teratology.

Q Ma'am?

A Teratology.

Q Teratology, all right. Did you recently have a publication there?

A Yes.

Q And what did that deal with other than the fact that I can see that it deals with lead, but what's the rest of that mean?

A Behavioral teratology is a branch of the study of birth defects, which deals with those defects which are detectable primarily as an alteration in behavior or intelligence and may not show up as a gross malformation in the

physical makeup of the child or the animal.

Q In other words, you can't see the change physically by looking at the child, but you can see that there is a defect by the way the child behaves?

A That's right.

Q Is that what you're saying?

A There may well be a structural defect in the brain, but, of course, we can't see that.

Q And Doctor, have you also recently published in the mechanisms of metal toxicity and the field of genetics of ovarian benzo pyrene, metabolism, oocyte destruction and impaired fertility?

A Yes.

Q What does that mean, genetics of ovarian benzo pyrene and metabolism?

A Benzo(a)pyrene is probably -- well, along with Dioxin one of the reference compounds for studying cancer and other adverse effects.

Q Now when you say reference compounds, you're already beyond me. What do you mean when you say it, along with Dioxin is a reference compound?

A It's a compound whose effects are so well known, so predictable and have been so often found that scientists aren't really interested in describing further what the effects of

these chemicals are, but more in using them as a tool to understand processes in the body.

Q And Dioxin is used in that way, Doctor?

A Yes, Dioxin, benzo(a)pyrene, there are several substances whose effects have been so well verified.

Q When Dioxin is used in the laboratory that way is there a special method for handling Dioxin -- and by Dioxin I'm using -- I mean to say 2,3,7,8 TCDD. Is there a method of handling that in the laboratory?

A Yes, there are very stringent rules for handling TCDD.

Q Would you describe how one in the laboratory goes about -- first of all, let me ask you this: Do all scientists and researchers in the areas where they are working with where one might want to discover the effects of toxic substances, do all scientists, have they all agreed to or are they all willing to work with Dioxin?

A No, many scientists of my acquaintance will not work with Dioxin because it's so toxic.

Q Are there stringent rules and regulations established for those researchers who indeed are willing to work with Dioxin?

A As far as I know there are. There certainly are at the National Institutes of Health.

Q And who sets the rules? Is it the National Institute of Health that sets the rules?

A I believe so.

Q And have you worked with Dioxin?

A Yes, I have.

Q What are the methods used or established for the use of Dioxin? Just exactly how do you go about using it?

A Basically the laboratory is supposed to be able to have all the safety facilities of a lab that would use bacterial viruses, that is, a laboratory that's cloning genes, and those are among the most stringent regulations for safety in handling and personnel that I know of. Special clothing has to be worn when Dioxin is being prepared. The Dioxin, first off, must be stored in a locked safe.

Q In a safe?

A In a safe. It is usually contained in a metal cylinder and several inner cylinders of glass and plastic before you come to the final small vial of the chemical itself.

Q What do you mean by that? You mean it's inside a vial that's inside a vial and then inside a vial and then inside of a metal case?

A That's right, and then inside a safe.

Q And then inside a safe. All right. You have to take a -- one bottle out of one container and then another

bottle out of that bottle and then another bottle out of that bottle. Why so many bottles in there?

A Well, it is considered a very, very toxic chemical for the scientists who are handling it. It must be kept in the safe which is kept in a special room which has been inspected for its safety by the Safety Committee. All preparations of Dioxin must be done in this room and final dilutions of the Dioxin powder made in that room and then only the very dilute material taken out of the room and administered to animals, to cell cultures and very careful collection of all the syringes, cloths, gloves, and other material which you use when you inject Dioxin into an animal or apply it to cell cultures. The animals must be collected at the end of the experiment and disposed of properly.

Q The vial that you take out of the last vial, what size is that vial that you get to that finally contains the Dioxin?

A Well, in our laboratory it's about this big. (Indicating)

Q All right. Indicating about an inch in height?

A And about a quarter of an inch in width.

Q After you take that vial out of the final container then what do you do with the Dioxin in that vial?

A You weigh out as small an amount as you can weigh

accurately while wearing gloves and a mask and a laboratory coat and then dissolve that amount in solvent or an oil. Then for the experiments we've conducted dilute that by approximately one to a hundred, take that very dilute solution and dilute it again and only that second step dilution is taken out of the chemical room and administered to animals.

Q And the pure Dioxin and the diluted Dioxin is required to remain within that room and within that locked safe?

A That's right.

Q And then you take the dilute, finally diluted substance out to inject into the animal?

A That's right.

Q How much of that do you inject in the animal or does it vary from experiment to experiment?

A It varies from experiment to experiment, but it certainly is a very, very small amount.

Q What happens to the animal?

A Well, the experiments we've been doing have been to look at the effects on reproduction and on the gonads and at very low doses --

Q When you say gonads, does that mean the male testicle?

A Well, the particular experiments we've most recently done have been female, so this is the ovary.

Q What does gonad mean --

A The sex organs.

Q Depending upon the sex, the ovaries for the female and the testicles for the male?

A That's right.

Q So when you use gonads it's interchangeable or all inclusive, male and female sex reproductive organs?

A That's right.

Q All right. Go ahead, Doctor.

A Well, after one administration, that's just one injection we've then examined them at various time points and treatment and found at the lowest doses we have given -- of course, we're not trying to establish the lowest possible dose. We're using Dioxin, as I mentioned, as a kind of tool for understanding how the ovary can be damaged and how ovulation can be suppressed and how a range of other effects might happen after Dioxin exposure, and we have certainly found that these do happen at very, very low doses.

Q What happens to the animal?

A The animal is infertile.

Q Now, Doctor, back, if you will, back to your publications. I think I'm close to through. You mentioned this article as to the genetics of ovarian metabolism. The word genetic there means the genes that we pass on from generation to generation?

A Yes. What's been shown is that for benzo(a)pyrene and probably for Dioxin as well in specially defined strains of rodents there are differences in response and so in this work we looked at the varying strains of mice and attempted to see whether all the effects of benzo(a)pyrene followed each other in terms of the genetic responsiveness of the animal.

Q Doctor, have you also published a review of all occupational health studies on PCBs? Have you published the effects of Dioxin, TCDD, on reproduction?

A These papers are in press. They have been accepted for publication.

Q They've been accepted for publication, they're being -- waiting a publication date now, is that correct?

A That's right.

Q And, Dr. Silbergeld, are you also working and do you have other books in preparation, a textbook on neurotoxicology?

A Yes.

Q And that's to be published by whom?

A Guilford Press.

Q And is this textbook -- well, describe what this textbook is, if you would?

A I was invited by Guilford Press to prepare a text-

book for the use of medical students and graduate students in the subject of neurotoxicology, which would cut across the disciplines of neuroscience, pharmacology, neurology, and psychiatry.

Q And that's what you've done then?

A That's what I'm working on.

Q Doctor, have you also either had published or in the process of publication a work dealing with the -- also on the effects of TCDD on -- that is the reproductive toxicity of TCDD?

A Yes.

Q And work place hazards on reproduction and managing risks in hazardous wastes and exposure to chemical carcinogens and effects on murine reproduction?

A Yes.

Q What does that mean, Doctor?

A Murine reproduction is reproduction in the mouse.

Q All right. And you're publishing or going to publish whether or not -- what cancers may be caused by exposure to certain chemical substances?

A No, our interest is the action of chemical carcinogens like Dioxin on the reproductive system, and our research indicates that at extremely low levels these chemicals are highly toxic to the reproductive system.

Q Now, Dr. Silbergeld, how long have you yourself actually been working with and researching on the subject of this lawsuit, that is, 2,3,7,8 TCDD?

A About a year and a half.

Q All right. And, Doctor, in addition to the 75 or so publications that you've made, have you been called upon by various -- a large number of scientific and authoritative publications to abstract and review various works dealing with all these toxic substances?

A Yes, I've published abstracts which in some cases are summaries of presentations at international and national meetings on these topics.

Q And you've done so on at least 44 separate occasions in addition to the 75 publications?

A Yes.

Q And have you done it most recently on the neurotoxic implications of altered heme synthesis on the effects of oocyte destruction by polycyclic aromatic hydrocarbons on reproductive toxicity of polycyclic aromatic hydrocarbons, on the genetics of ovarian benzo metabolism, on the effects of benzo pyrene on the fertility and ovulation of mice, and in occupational risks to reproduction?

A Yes.

Q Now, Doctor, could you -- I know we've hit upon it

in passing, but could you tell the jury just what a toxicologist is? What does the word toxicologist mean and what do you do other than these things that you have described or is that what a toxicologist is, just as you've described in these various articles?

A A toxicologist is someone who studies the adverse effects of chemicals and other substances on living systems, and my entire research career has been in that area.

Q Doctor, in order to become a toxicologist is it necessary for you to achieve a certain level, high level of learning and knowledge in areas dealing with chemistry, areas dealing with medicine, physiology, neurology, immunology, genetics, and in addition to those is it necessary for you to know how these various toxins and toxic substances can come into contact with human beings and how these various substances can be absorbed or taken into a human being after being and coming into contact with such humans?

A Yes, all those disciplines are necessary to toxicology.

Q Is there any other professional field that is equivalent to or encompasses the same broad range of learning and knowledge specifically with toxic substances and how those toxic substances affect human beings and how they may come into contact with human beings other than toxicologists?

A Probably not, though some biochemical epidemiologists may have a large part of that body of knowledge as part of their discipline.

Q What is a epidemiologist?

A An epidemiologist, which is also a field I was trained in as part of my training in toxicology, is a person who studies the incidence of the disease or other effects in populations.

Q Now, Doctor, I want to direct your attention to Dioxin. Could you tell the jury what Dioxin is, how it comes into being?

A Dioxin is a synthetic chemical that is --

Q By synthetic you mean it's made and not -- and not a natural substance?

A As far as we know it doesn't occur naturally.

Q So it's made by man or made by some process?

A That's correct.

Q When you say synthetic.

A That's right. There's some evidence that combustion of certain products can produce Dioxin, but as far as we presently know, as Dr. Rappe pointed out this week in St. Louis, one of those products that has to be burned has to be synthetic, so ultimately we don't know of any naturally occurring process in the absence of man made chemicals which produces Dioxin.

Now Dioxin is one of those polycyclic aromatic or halogenated hydrocarbons. That is, it has three ring structures which are joined in a flat molecule. TCDD has four chlorines as the name indicates, tetrachloro, and 2,3,7,8 TCDD has those four chlorines attached to that tricyclic ring at the four positions which chemists standardly label as the 2,3,7, and 8 positions.

Dioxin was probably produced as early as the 1890s when trichlorophenols were first synthesized by BASF in Germany, although their detection and reliable identification probably didn't occur until the 1960s. However, as early as the first decade of this century --

Q Now that would be from 1900 to 1910 or thereabouts?

A That's right. You can see in the occupational medicine literature, particularly in Germany, discussions of chloracne and liver disorders in workers in the trichlorophenol and chlorinated napthalene, a related chemical industry in Germany and some discussion that something was happening in the processes making these chemicals which caused these sorts of very serious reactions which no one had described before. As a matter of fact, chloracne was first called naptha disease, although we now know it has nothing to do with naptha.

Throughout the 1930s and '40s similar kinds of observations and case reports of workers in these industries

were published indicating a range of relatively serious disorders, but it wasn't until really the first major industrial accident that we know of, that is, the 1949 explosion or exothermic reaction at the Monsanto Plant in Nitro, West Virginia that attention clearly focused on the production of a contaminant in triclorophenol manufacture, a contaminant whose production was enhanced with high temperatures, that research really focused in on this chloracneagen, that is, a substance that produces chloracne, in the early '50s and '60s and in that period a definitive identification of Dioxin molecule was made and we began to reach the understanding we have today that 2,3,7,8 TCDD of all the Dioxins is the most powerful toxic agent in these and a variety of other effects.

Q Now, Doctor, you mentioned that effects were seen or were known as far back as 1910 or thereabouts in the German chemical industry where they were manufacturing this chemical that ultimately, I suppose, one concluded contained 2,3,7,8 TCDD, did you?

A Yes, sir.

MR. HEINEMAN: Your Honor, may counsel approach the bench?

THE COURT: Sure.

(The following proceedings were had at the bench out of the hearing of the jury.)

MR. HEINEMAN: Your Honor, Monsanto at this point would like to interpose an objection to this witness testifying on a couple of levels.

THE COURT: Couple of what?

MR. HEINEMAN: Couple of levels. Your Honor, first of all, I don't think this witness has been properly qualified for chemistry. Secondly, she's testifying about things that occurred twenty years before she was born, and if we're talking about things she might have read about or things she might have learned from somebody else, that's one thing, but I object to her testifying as though it were personal knowledge with respect to things that she was not even alive at the time.

The second thing is that I object to her giving testimony with respect to chemistry, because she's not qualified or has not been qualified by direct examination of Mr. Carr to give opinions with respect to chemistry. She's already testified in her deposition in this case that she doesn't know anything about the chemistry of the process involved here. Therefore, I strongly object to her being permitted to testify on those subjects. I think it's beyond her ability, and I don't think she's been properly qualified.

MR. CARR: Your Honor, that objection is so ridiculous I won't bother to respond to it, absolutely absurd, she's not qualified. She's fully qualified in every way.

THE COURT: Okay. Are you --

MR. STEPHEN SCHOENBECK: We'll join in the objection of Monsanto.

THE COURT: Okay. Objection is overruled. She has been qualified to have expertise, she has shown herself in that qualification to have familiarity with both the actual physical properties, existence and literature concerning the particular chemicals she's talking of Dioxin. Objection's overruled.

MR. HEINEMAN: Please understand me, your Honor, I do not object that this witness testify in toxicology.

THE COURT: I understand that.

MR. HEINEMAN: Just chemistry. I'm talking about chemistry.

THE COURT: It's rather obvious from her -- from her direct examination that she has to have a working chemical knowledge of the substances with which she works, with which she's working on a toxicological level, and I think that's been fully qualified on her expertise in that as well as her familiarity with the literature about matters occurring before her birth and any of ours for that matter. So I think she's fully qualified. Your objection's overruled. For purposes of the record just to move the testimony along I'll consider it a continuing objection by both of you.

MR. HEINEMAN: I would appreciate it if it would be a continuing objection throughout her testimony at any time that she's starting to offer opinions with respect to chemistry or with respect to incidents where there's been no foundation laid as to her knowledge with respect to those incidents.

THE COURT: As to these particular matters that have been pointed out this is a continuing objection by both of you.

(The following proceedings were had in the hearing and presence of the jury.)

Q Doctor, when you practice your profession of toxicology, is it absolutely necessary and essential that you learn everything that there is to know about the chemical structure of the toxic substances upon which you do research and work and attempt to discover the effects of?

MR. HEINEMAN: Your Honor, may I object to the form as leading and suggestive. I'd like to hear what the witness has to say on the subject, not Mr. Carr.

THE COURT: All -- the objection is overruled. I don't think it is leading and suggestive.

A My particular interest in toxicology, as you can see from my papers, is very much in the area of molecular toxicology, that is, how a chemical actually produces its toxic effect and therefore, I must know about chemical structure, structure

activity with relation to the impact of small changes in the chemical nature or the shape of the chemical.

Q And, Doctor, in the practice of your profession do you draw upon the body of knowladge in printed form and in some instances in oral form by conferences with others in order to gain the expertise that you need to have in order to function as a toxicologist?

A Of course.

MR. HEINEMAN: Same objection, your Honor.

THE COURT: Objection is overruled.

MR. HEINEMAN: Thank you.

Q Have you drawn upon in the course of your training in the academic world and thereafter, do you go to the great works in scientific literature dealing with the areas in which you have an interest and need to be trained therein?

A Yes.

Q And in working with 2,3,7,8 TCDD could you state please how far back in literature or what investigative research did you do as to the history of 2,3,7,8 TCDD and as to when it came into existence and its history thereafter -- not by existence, I mean when in fact it was known about.

A I've consulted the work of Wilhelm Huepper, who is probably the father of chemical carcinogenesis and himself lived through the great explosion of organic chemistry in

the 1880s and 1890s in Germany. With respect to Dioxin specifically the works by Dr. Renate Kimbrough, Dr. Frederick Coulston and Dr. Alistair Hay have provided a great deal of my knowledge and citations to other references on the history of Dioxin and chloracne illness industry.

Q Now you obviously --

MR. HEINEMAN: Excuse me, Mr. Carr. I didn't hear the second name, Doctor.

THE WITNESS: Dr. Renate Kimbrough, Dr. Frederick Coulston and Dr. Alistair Hay.

Q And Dr. Silbergeld, in your study of this Dioxin, of this chemical do you read as -- well, is there any way of learning about substances that -- where past research has taken place other than read what others have learned unless you must perform all that experimentation and all that original investigation yourself? How else do you learn other than reading what others have done actually, I suppose, is what I wanted to ask you.

A Well, I don't know. There are a variety of very comprehensive literature data bases as they're known which allow scientists to go into the world literature on a subject way back in the past and the present.

Q And is that --

A And find out everything that's been done on the topic.

Q Is that a standard method of learning about things that scientists such as yourself use and regularly rely upon?

A Yes, it is.

Q Is there any way of learning other than that unless you undertake to start research from the very foundation yourself?

A When it comes to looking at the history of events, unless one were to reconstruct that history, I can't imagine.

Q All right. Now, Doctor, relating back to the history of this Dioxin in ascertaining the toxic effects of Dioxin upon human beings was it essential that you investigate the history of Dioxin?

A Yes.

Q And we were talking about the effects in 1910 or the first decade of this century. Was the state of knowledge at that time with relation to Dioxin is that something must be in these chemicals that these German workers are handling that causes a particular disease, effect, or problem, but that scientists didn't have enough knowledge then to know what it was in that chemical that was causing these problems?

A Yes, I think that's an accurate description.

Q Now the chemicals that were being made in Germany at that time as far back as 1910 did the American chemical industry manufacture these products or products akin to those

products in West Virginia in 1949 in a town called Nitro?

MR. HEINEMAN: Let me object to the form, your Honor, only that I don't know which date he's talking about. Is it 1910 or 1949? I'm confused by the question.

THE COURT: I think the question was clear. Could you restate it?

Q Dr. Silbergeld, the chemicals that the German chemical industry was engaged in manufacturing in the first part of the century that caused these diseases and toxic effects that you have described, did the American chemical industry manufacture related or akin chemicals in Nitro, West Virginia in 1949?

MR. HEINEMAN: Your Honor, may I please object to the form of the question as to the nonspecificity of the words related or akin, pretty broad categories when you're talking about chemistry, and object to its being too general.

THE COURT: Overruled. I think it's a proper question. I don't think it is too general or nonspecific to be answered by this witness.

MR. HEINEMAN: I respectfully disagree, your Honor.

A Yes. The trichlorophenol and phenols and benzine compounds which were the industries cited by the early German occupational physicians were indeed being made in Nitro, West Virginia by Monsanto.

Q Now, Dr. Silbergeld, is that a rare or esoteric or secretive kind of fact or is that fact well known and well published and known by everybody that that is in the chemical and toxicology business that it was trichlorophenol and the benzines and the phenols that the Germans were working with in 1910 that were the same, in the same halogenated hydrocarbon family that Monsanto was working with in 1949?

A I think for anyone who's thought about it it's obviously the same.

Q And this is not something, some unique knowledge that you have. Anybody that picks up a book that wants to read the history of it would know that, would they not, Dr. Silbergeld?

A Well, the easiest way to find it out is to take the Merck Index, which is the chemical industry's own record of the history of chemical production, if you will, in a kind of skeleton form, and in the Merck Index you can see the first date at which a chemical was synthesized and registered, for instance, trichlorophenol, the company that did it or the laboratory and then the initial dates at which the chemical was synthesized and produced by other companies around the world.

Q Dr. Silbergeld, these effects that you have described as having been known as far back as 1910 or in that first

decade, were these effects published, that is, in magazines such as you have described by doctors who were dealing with these German workers at that time?

A They were published in the German medical literature.

Q And are these literatures and are these publications, are they available and have they been available in the United States?

A Yes.

Q Now, directing your attention to the occurrence that took place in Nitro, West Virginia at the Monsanto Plant was that plant indeed manufacturing trichlorophenols?

A Yes, it was.

Q All right. Was -- could you please describe what occurred there and more specifically what occurred to the workers that were exposed to these trichlorophenols?

MR. HEINEMAN: Your Honor, if the Court please, I don't think there's any doubt here as to what occurred at Nitro, West Virginia, and all I'm objecting to is from this witness' standpoint it's clearly hearsay, and I would object to it on that basis.

MR. CARR: Your Honor, everything that we know, that we have learned in school up to date is -- falls in the realm of hearsay. There is no dispute about these facts. Counsel well admits that. If he's saying that Dr. Silbergald

as a scientist may not rely upon what she has read on uncontested, undisputed facts because it's written as hearsay, I have to learn some other rules of evidence.

MR. HEINEMAN: Your Honor, as I said, I'm not disputing the facts of what happened at Nitro, West Virginia, but I'm just saying that for this witness to testify about what happened at Nitro, West Virginia, but I'm just saying for this witness to testify about what happened at Nitro, West Virginia has got to be hearsay because the witness wasn't there.

THE COURT: Overruled. I think it's properly a subject of testimony by this witness on the basis of her shown expertise and familiarity with the existent contemporary background literature on Dioxin and other related subjects. Overruled.

Q Could you please now, Doctor, state what occurred at Nitro based upon the research that you conducted in order to gain your expert knowledge in the area of toxicology insofar as it relates trichlorophenols, chlorophenols, and 2,3,7,8 TCDD Dioxin?

A I'd first say that the Nitro explosion is indeed a very well known event in the field of toxicology, and it's one that's been described and discussed extensively in the scientific literature, including literature published by

consultants or scientists employed by the Monsanto Company, notably Dr. Suskind and Dr. Gafney -- Gaffey and Dr. Zack. In addition it has been described in a number of chapters --

Q Let me interrupt you. My question is please describe what occurred in 1949 at Nitro, West Virginia.

A In 1949 in the Monsanto Plant in Nitro there was an uncontrolled chemical reaction in the trichlorophenol phenoxia acetic acid area of the plant such that a great deal of heat was generated in the process area and an explosion or rapid release of chemical occurred from the batch mixing area and batch drying area. As a consequence a number of workers in that building and nearby were directly exposed to trichlorophenols and TCDD and other compounds which escaped during that explosion. However, in addition, the literature makes clear that industrial hygiene in that plant for some time up to 1949 and thereafter was such that workers at Monsanto in Nitro were clearly being exposed to Dioxin independent of this single event of an exothermic or explosive reaction.

Q About how many workers were exposed in the explosion itself and by the explosion itself to these trichlorophenols that were being manufactured?

A That's a matter of some discussion depending on whether or not one uses a set of health effects to indicate

exposure. Clearly somewhere between 100 and 600 persons were exposed.

Q All right. Now, Dr. Silbergeld, does the literature show and reveal that Monsanto had physicians to examine those people at that time?

A Yes, it did.

Q And did they hire outside people to come in to examine those people at that time?

A They did.

Q Does the literature reveal that Monsanto has followed those workers and the health effects of those workers from that time indeed up to the very present time?

A To a certain extent Monsanto has, yes.

Q Now, Dr. Silbergeld, at that time in 1949 had 2,3,7,8 TCDD, that Dioxin, had it been then identified as the substance in this chemical that was causing certain health effects?

A No, it had not.

Q Was it known, however, at that time that there was something in that chemical causing health effects similar to the health effects that had been earlier identified as having had occurred in Germany in the first decade of this century?

A It was --

MR. HEINEMAN: Excuse me, your Honor. May my objec-

tion be a continuing one to this entire line?

THE COURT: So noted as continuing objection.

A It was known that there was something in the process of trichlorophenol and 2,4,5-T, that's the trichlorophenoxia acetic acid herbicide, there was something in those manufacturing processes which appeared to be very toxic and that was known in 1949.

Q All right. Is it necessary that one identify with specificity the exact makeup of the chemical that's causing the adverse health effect for one to be able to have knowledge as to those health effects? That's poorly stated, I'm sure. Maybe I should phrase it a different way. Do you have to know what's specifically the chemical description and structure of something that's in a poison to know that it's poisoning you?

A No, and the best example is cigarette smoke. It's very recent and it's still not entirely certain that the major ingredient in cigarette smoke, which is responsible for lung cancer and other types of cancer is probably benzo(a)pyrene, but certainly enough was known long before the identification of benzo(a)pyrene to know that cigarette smoke was dangerous to human health.

Q Now, Dr. Silbergeld, leave cigarette smoke alone. That's another problem. We're interested in TCDD, if you would.

My question is did Monsanto have to know that it was something called 2,3,7,8 TCDD that was causing these health effects in order for Monsanto to conclude that what it was producing was indeed a toxic substance?

MR. HEINEMAN: Your Honor, I'm going to object to that. It's surely calling for speculation on the part of this witness, and I think it's a question for the jury as well. It invades the province of the jury.

MR. CARR: Your Honor, I don't think it's any such thing. It's an open and obvious question, your Honor.

MR. HEINEMAN: Well, if it's open and obvious, it doesn't need to be testified to.

MR. CARR: It sure isn't speculation if it's open and obvious, Mr. Heineman.

THE COURT: Overruled. You may proceed.

THE WITNESS: Could you read back the question?

(At this time the court reporter read back the last question.)

A No.

Q All right. Now, Dr. Silbergeld, in the years that followed the Monsanto Nitro explosion was there another event that occured in Germany following that again dealing with these chlorinated carbons?

A Yes.

Q And what was that, Doctor?

A A similar type of accident at the BASF Plant in Germany.

Q What is the BASF Plant?

A Bayerische Anilin und Soda Fabrik, I think is what it stands for, it's a major chemical company in Germany.

Q Go ahead, Doctor.

A And it was indeed the synthesizor of trichlorophenol. They had a similar uncontrolled chemical reaction in their plant and cleared out most of the workers fairly rapidly and then attempted to do some on the spot toxicologic investigation after the explosion, which I think were rather imaginative. They took some cages of rabbits and put the cages in the room where the explosion had occurred. This was several weeks after the explosion. Within a week all the rabbits were dead.

Q Now at this time, Dr. Silbergeld, the explosion had taken place, the atmosphere presumably had cleared of the initial explosive effect. The room was closed, nothing going on in the room, you could go into that room and couldn't see a thing and they put rabbits in that room?

A They put rabbits in the room in cages. Within a week the rabbits were dead. They then brought in some new cages with new rabbits. Within, I think, ten days all those rabbits were dead. They then took the cages out of the room

and put some rabbits in the cages back in the laboratory and those rabbits, which never went into the room where the explosion occurred also died. On the basis of that BASF's toxicology staff determined they were dealing with something very, very toxic and indeed began to characterize it as the most toxic substance they had encountered.

Q And this was in 1953?

A Between 1953 and '57, I think, was the development of this knowledge by BASF.

Q And again was this knowledge, was it known, was it published, was it disseminated on the basis so that American industry would know of that having taken place?

A Scientists from BASF did make contact with the American chemical industry and reported these findings. I don't know whether the findings were reported to the scientific world at large, but there are recorded communications from BASF to Dow Chemical and to Monsanto.

Q And does the reports indicate that Monsanto was advised because of its prior experience or was it connected with its prior experience in 1949?

A I believe so.

MR. HEINEMAN: Your Honor, may I object to this as blatant hearsay unless we find out what the source of this information is.

MR. CARR: Let me ask.

Q Where is this information that you're relating here? Where is it reported?

A Some of it is reported in Dr. Hay's book on the history of Dioxin and others in materials from Monsanto in the Nitro case.

MR. HEINEMAN: Your Honor, I do object to her testifying about that. It's hearsay.

THE COURT: Overruled.

Q Is Dr. Alistair Hay an internationally known researcher into the toxicity of 2,3,7,8 TCDD?

A Yes.

Q And has he published, is it a book that one can go into a scientific book store and buy a book on that?

A Yes.

Q And are these facts that you're relating about this history of Dioxin, are these facts laid out in that book by Dr. Hay?

A Many of them are, yes.

THE COURT: Ladies and gentlemen, we'll take a break in proceedings now, and I would admonish you now on this break and this admonishment holds true for all breaks in the proceedings today that you're not to discuss this matter among yourselves or discuss it with anyone outside the jury panel or

as yet form any conclusions or opinions about the matters on trial. Court will be in a short recess.

(At this time a short recess was taken.)

Q Dr. Silbergeld, in addition to the effect upon the rats in the BASF accident --

MR. HEINEMAN: Rabbits.

MR. CARR: Rabbits.

Q In addition to the effect upon the rabbits were there workers exposed in that explosion as well?

A Yes, there were.

Q And were there certain health effects that were recorded and to some extent followed thereafter?

A Yes.

Q Were these health effects published and made known in the literature and publications and health related publications and chemical related publications in the scientific world thereafter?

A Yes, they were.

Q Now, Doctor, was there other industrial accidents subsequenc to the 1953 BASF accident involving trichlorophenol?

A Yes, there have been.

Q And was there one in England?

A Yes, there was the Coalite accident as it's known.

Q And about when did that occur, Dr. Silbergeld?

A I think the late '50s. I'm not sure.

Q And again were workers exposed to trichlorophenol at that time?

A Yes.

Q And were the health effects upon these workers, was that followed in literature and published, was it known through the '70s at least?

A Yes.

Q And were there other accidents involving the manufacturing of TCP that involved portions of the public, more specifically in Italy, associated with an industrial accident?

A Yes.

Q Now, the jury's heard about that. Both counsel have advised and mentioned about the Seveso, and other witnesses have mentioned it. Could you please tell the jury in 1976 in Seveso, Italy?

A In 1976, in July, I believe, in Seveso a chemical plant belonging to ICMESA, which was related to Hoffman LaRoche had a similar uncontrolled chemical reaction occur in their trichlorophenol process which led to the rupture of a pipe and a release of a fairly significant amount of trichlorophenol heavily contaminated with 2,3,7,8 TCDD into the general environment outside the plant. This chemical cloud was carried over the town of Seveso and then over the course

of the next couple of days there was rainfall and precipitation of the particles so that the chemicals emitted from the plant would indeed come into direct contact with people and animals and vegetation and surface water in that community.

Q What happened to the animals?

A Many of the animals died acutely.

Q When you say acutely, what do you mean?

A They died within several days after the accident.

Q And what happened to the -- did the Italian authorities take measures to evacuate the people from the contaminated areas?

A Yes. Within approximately two weeks after the explosion the town was evacuated and sealed off.

Q And is a -- that occurred in '76?

A That's right.

Q Is a portion of that town yet sealed off to the public to this very day?

A I believe the area which was considered to be most contaminated is still sealed off.

Q All right. And Dr. Silbergeld, has the health effects upon the -- to some extent at least upon the part of the Italian populus that had been exposed to this industrial accident, had those health effects been followed?

A Yes, they have, by an international commission.

Q Have they been -- again those health effects, were they published and have they been published, is it known by persons involved in toxicology and the health industry and in the chemical industry as to these health effects following this explosion?

A Yes.

Q Now, Dr. Silbergeld, by this time has the toxicologist, have they now and the chemists, have they now identified this toxic substance in trichlorophenol?

A By the present time? Yes.

Q By '76, by '77, by the time of the Seveso accident.

A Yes.

Q And do they know then that it is 2,3,7,8 TCDD that's in the trichlorophenol that causes the health effects?

A They know that 2,3,7,8 -- they knew 2,3,7,8 TCDD was in trichlorophenol and that along with trichlorophenol themselves they were responsible for the health effects.

Q Now when you say along with the trichlorophenols themselves, is there an -- is there an acknowledged and known health effect or toxic reaction to the substance called trichlorophenol independently of its 2,3,7,8 TCDD contaminant?

MR. HEINEMAN: Your Honor, excuse me. May I object to the general form of the word trichlorophenol without identification of an isomer.

THE COURT: Overruled.

Q And how long has it been known that trichlorophenols have health effects, adverse health effects?

A That knowledge --

Q Independently now, independent of the 2,3,7,8 TCDD contaminant.

A That knowledge goes back a long way. Certainly their properties as irritants and as agents which damage the liver has been known for decades.

Q Now, Dr. Silbergeld, has there been -- strike that. Is the substance known as Agent Orange that was used in Viet-Nam in the '60s and I guess the '70s as well, early '70s, has that substance in Agent Orange been identified, that is, the substance that's responsible for the health effects of those exposed to Agent Orange? Has that been identified?

A Yes.

Q What is that substance in Agent Orange that is known to be toxic to those exposed to it?

A 2,3,7,8 TCDD.

Q All right. Now is that the same 2,3,7,8 TCDD that we have been discussing with relation to these other accidents, Seveso and up to the -- well, that's the basis of this case. Is that the same 2,3,7,8 TCDD?

A It is the same. The name means it's exactly the same

molecule.

Q And is this a fair statement, that when 2,3,7,8 TCDD is present in any substance or any chemical, it is the same molecule or some constructive molecule regardless of what it might be in at a particular time?

A Yes.

Q It can be in a herbicide, it can be in a pesticide, it could be in a paint, it could be in water, it could be in any substance, and when you say 2,3,7,8 TCDD, you're talking about the same thing, is that correct?

A That's right.

Q All right. Now has the -- there been in the '60s and '70s up to January of 1979, has there been extensive investigation and publication as to the results of that investigation as to the effects of Agent Orange and its contaminant, 2,3,7,8 TCDD, upon human beings?

A There have been published reports on the effects of Agent Orange and also on the effects of one of its constituents, which is 2,4,5-T, which is where the 2,3,7,8 TCDD comes from. Agent Orange is just a blend of 2,4,5-T and 2,4-D.

Q 2,4-D is 2,4 dichlorophenol?

A 2,4, diphenoxia acetic acid.

Q Well, let's just call it 2,4-D then, all right?

A That's all right.

Q Now -- and was Monsanto one of the manufacturers of the substance called Agent Orange?

A Yes, it was.

Q And do you know from your own research and documentation that Dow Chemical exchange information, gave information to Monsanto as to the contaminant that was in Agent Orange, that is, the 2,3,7,8 TCDD, that was responsible for certain adverse health effects?

MR. HEINEMAN: Your Honor, may I make the same objection with respect to hearsay.

THE COURT: Same objection, objection is overruled, same basis.

A Yes, Dow Chemical did communicate a number of times with Monsanto.

Q And is that fact a matter of public record?

A Yes, it is.

Q Now with regard to Dioxin, I've got some charts. I think -- I believe I used them already in the opening statement.

MR. CARR: Can you all see that all right?

Q Dr. Silbergeld, when we have used the phrase Dioxin in this case we have most of the time referred to the 2,3,7,8 TCDD as Dioxin. Are there other isomers of Dioxin that are

created in the chemical process, in the manufacturing process in addition to 2,3,7,8 Dioxin?

A Yes. Depending on the process and the precursors, yes.

Q Now these other Dioxins, they have for instance on this chart --

MR. CARR: Let's mark -- this hasn't been marked. Please put a label on this one. Counsel, you -- where did you go?

MR. HEINEMAN: I'm just sitting over here, Mr. Carr.

MR. CARR: You've previously seen this, have you not?

MR. HEINEMAN: Yes.

MR. STEPHEN SCHOENBECK: What's its current identification?

MR. CARR: It's now Plaintiffs' Exhibit 230.

Q Dr. Silbergeld, does Plaintiffs' Exhibit 230 represent a chart as to the relative toxicities of certain isomers chlorodibenzo-para-dioxin?

A Yes.

Q And is the drawing on this chart, at the very bottom of this chart, does it represent a drawing of the molecular structure of 2,3,7,8 TCDD?

A It does.

Q Where there's the little Cl at four different places on this drawing what do those letters Cl mean?

A They indicate an atom of chlorine, and the places that they are marked indicate where on the ring structure they are attached.

Q Now the Cl that I'm pointing to now is at what place on the ring structure?

A 2.

Q And the next Cl?

A 3.

Q And the next one?

A 7.

Q And the next one?

A 8.

Q And thereby the name 2,3,7,8 TCDD, is that correct?

A That's right.

Q All right. Now what's these little Os in between?

A Those are oxygen atoms.

Q And the big O in the middle, what does that mean of each of these two whatever they are -- those are not trapezoids -- well, whatever they are.

A Hexagons.

Q What are they?

A Hexagons.

Q Thank you, Doctor. What are --

A That means that those are saturated rings. That means that every position which is free on that ring is occupied in this case by either a hydrogen, a chlorine, or an oxygen atom.

Q All right. And what does the hexagon itself, what does it represent?

A It's a benzine ring.

Q All right. Now, Doctor, the use of the word isomer, what does isomer mean?

A Isomer is a name chemists give to molecules which are basically similar and differ only slightly in additions to the basic structure. The basic structure here is the dibenzo-para-dioxin, and isomers that are shown are several different dibenzo-para-dioxins which differ only by the number and placement of attached chlorine atoms.

Q All right. And approximately how many isomers are there that are called Dioxins?

A There are approximately -- somewhere around 250 chlorinated dibenzo-para-dioxins. It's also possible for Dioxins to have bromine, which is another halogen at the same places where you have chlorine, so you can add another 250 or so; somewhere in the neighborhood of 500 to 600.

Q All right. Now we're dealing with one of these

Dioxins called 2,3,7,8 tetrachloro-dioxin, all right.

A Yes.

Q All right. Now, Dr. Silbergeld, on this -- this is a scale that represents what as far as these various Dioxins are concerned?

A It represents the relative toxicity, that's the relative hazard of these molecules to -- I think this is from rat lethality tests, the dose required to kill a rat acutely, within a short time after treatment.

Q All right. Now do all of these Dioxins, going from the one that's called 2,3 Dioxin and 1,6 and 2,3,7 and 2,3,7,9 Dioxin do they all have some degree of toxicity?

A I'm not sure of that. The ones -- very lower chlorinated substances probably have no more particular toxicity than chlorinated phenols but they do have some biological properties, yes, they are active molecules.

Q And by the lower you mean as far as this chart is concernad, Exhibit 230, you mean those that are at the top part and not at the low end of the chart?

A That's right.

Q All right. So the ones at the top of the chart have a lesser toxicity than the one at the bottom of the chart?

A That's right.

Q All right. Now the one -- one of the top is in-

dicated for a standard as has a toxicity of 1.0. What does the next one have a toxicity of, Doctor?

A 5.0, five times as toxic as the first one.

Q Now you mentioned that toxicity in the -- did you say phenols in which this isomer occurs?

A Yes.

Q Is there -- are phenols themselves toxic, do they have toxic qualities?

A Yes, they do.

Q And are these -- we'll get to those perhaps later, but are these toxic qualities of phenol has that been researched and published and are the toxic qualities of phenols known in the scientific world and in the chemical industry?

A Very widely.

Q All right. But on a relative scale are -- do the phenols stand in the same relative scale of toxicity as Dioxin?

A No, and you must keep in mind this is a specific toxic effect, that is, lethality, the ability to kill.

Q And by that you're suggesting, I take it, that there are a lot of toxic effects other than or in addition to the ability to kill?

A That's right.

Q We'll get into a lot of those later today or tomorrow, Doctor. But now on this scale you mentioned that the isomer

known as 1,6 Dioxin, chlorobenzo-para-dioxin is five times more toxic than 2,3. What about the 2,3,7, how does it compare to the 2,3?

A It's 30,000,000 times as toxic as the 2,3, because now you've entered that molecular structure where you're occupying what toxicologists consider to be the critical sites of the Dioxin molecule.

Q And those sites are what?

A 2,3,7 as can be seen here.

Q In other words, the one that's 30,000,000 times more toxic than 2,3 has these three points occupied by a chlorine atom?

A That's right.

Q And have you toxicologists determined that it is the occupation of these points in the ring that makes this substance so highly toxic?

A That's right.

Q Now, Doctor, the next drawing is known as the 2,3,7,9 Dioxin, and the 2 position, the 3 position, the 7 position are occupied, and we know, and what is this position that's occupied at the top?

A That's the 9 position on the ring.

Q All right. The 8 position was skipped in the process that this molecule was formed and instead of occupying

the position No. 8 it occupied the position No. 9? How much more toxic is that than the one -- than the 2,3 Dioxin?

A 34,000,000 times as toxic. Again it's got those three critical positions occupied by a chlorine.

Q Now, Doctor, the one at the bottom, the one that we are talking about, the 2,3,7,8 Dioxin, how many more times toxic, that is, for a lethal effect upon the animal to which it was subjected or injected or exposed, how many more times is it more toxic than the 2,3 Dioxin?

A Over 2,000,000,000 times as toxic.

Q Now, Doctor, on the scale of toxicity have there been experiments and studies carried out to indicate how toxic Dioxin is as compared to other types of poisons that can be encountered in the world?

A Yes, there have been a number of rankings for various toxic effects.

Q And are there certain naturally occurring toxins that are extremely poisonous, extremely hazardous?

A Yes, there are.

MR. CARR: Would you mark this 231 please.

Q Now, Dr. Silbergeld, with regard to Exhibit 230 is the information that's contained on Plaintiffs' Exhibit 230 is this known public information, known in the health world and in the chemical industry?

A Yes, it is.

Q And was it known before January the 10th, 1979?

A Yes, it was.

Q Now, Dr. Silbergeld, I'll hand you -- I won't hand it to you but I'll push it over towards you -- what's been marked Plaintiffs' Exhibit No. 231 and ask you to look at that and study that if you will. Is this a chart accepted as authoritative in the world of toxicology as to the relative toxicities of certain poisons?

A It is.

Q All right. And is this chart something that has been published and is known in the health world and in the chemical industry?

A Yes.

Q And is this -- is the toxicity of these various poisons, was this something that was known by the chemical industry and by the health profession before January 10th, 1979?

A Yes, it was.

Q All right. Now, Dr. Silbergeld, can you see that all right?

A Umhm.

MR. CARR: Can you all see that?

Q Directing your attention to the substance at the

very top, what is that?

A Botulina toxin A is the lethal ingredient in botulism or food poison, which is what makes food poison so dangerous. It's secreted by a micro organism and as is shown here for its weight, that is, for the size of the molecule, it's probably one of the most toxic things we know of.

Q Now is that a toxin that occurs in nature?

A Yes, it does.

Q All right. It's not made by man?

A No.

Q All right. And the second column where it has molecular weight, 9.0 times ten times to the fifth. What does that mean?

A That's the size of the molecule, how big it is, and this indicates that it's a very big, complex molecule as are many naturally occurring poisons.

Q All right. And on the third column where it says minimum lethal dose moles/KG, what does the words minimum lethal dose mean?

A That's the smallest amount of this substance which will kill an animal when given once.

Q And what do the words moles/KG mean?

A That indicates the dose of this chemical which causes this. It's expressed in terms of moles rather than milligrams.

Q What is a mole? It's an animal to me that goes in and ruins your lawn, but what is it in chemistry and toxicology?

A A mole is a way of describing a quantity of a chemical which takes into account its molecular size, so it's just not a milligram. That's a mass weight. It indicates that within a milligram of botulina toxin and a milligram of sodium cyanide you'll have much fewer molecules of the botulina toxin because each molecule weighs much more, so it's a much more accurate indication of the potency or hazard of these poisons rather than just listing milligrams.

Q I guess I understand that. And, Doctor, 3.3 times ten to the minus seventeen. What does that mean?

A That means that it takes about three, I think, femtograms --

Q Femtogram?

A Or possibly even less of this stuff to kill an animal. It's a very, very, small amount.

Q The seventeen means zeros behind that ten, doesn't it?

A It means in front of the ten.

Q In front of the ten.

A That's right. It means there are seventeen zeros in front of that ten.

Q So if we were to describe this in decimal form,

you would put seventeen zeros in front of ten, is that correct? You'd put a decimal point --

A Decimal point, seventeen zeros.

Q -- seventeen zeros.

A That's right.

Q And you multiply that times 3.3 to show the weight --

A The molecular weight.

Q Minus weight?

A -- that you'd need.

Q And the next one is tetanus toxin. That is -- again is that a naturally occurring substance, a toxin in nature?

A It is.

Q Not made by man?

A No.

Q But it's for that toxin that we have to get tetanus shots?

A That's right. We developed antibodies to it and we have vaccination to prevent tetanus, which before vaccination, of course, was a very deadly disease for young children. Tetanus toxin is the active principal in the tetanus infection which causes death.

Q And its relative molecular weight is shown in Column

2 and its miminum lethal dosage shown in Column 3?

A That's right.

Q And it's one times ten to the minus fifteen that appears to be -- in other words, it would be fifteen zeros after a decimal point to indicate how you arrive at its weight?

A That's right.

Q The next one is diptheria toxin. Again is that a naturally occurring substance?

A Yes, it is.

Q And again we have vaccinations against diptheria, we can protect ourselves against that?

A That's right.

Q So of these three toxins so far we can protect ourselves against two of them but not the botulism except other than make sure we don't eat spoiled food?

A We can give some emergency treatment for botulism. We can't inoculate ourselves against it, but people who have botulism poisoning can be put on respirators, maintained with certain drugs until the botulism toxin, botulism toxin is degraded by the body, but in most cases people die.

THE COURT: Gentlemen, could I see you at the bench for a minute please.

(A short conference was had at the bench off the

record.)

THE COURT: Ladies and gentlemen, we're going to take a break in the proceedings for lunch. Court will resume again at 1:30. The admonishments that I've previously given to you will apply throughout this lunch break. Court's in recess.

(At this time Court recessed for lunch.)

THE COURT: Mr. Carr.

Q Dr. Silbergeld, we had at the lunch recess, I think just been discussing the diptheria toxin for which there can be a vaccination, and this again indicates as far as it's the minimum lethal dose it's a minus twelve which would indicate it means twelve zeros after a decimal point and before the 4.2, correct?

A Before the ten, yes.

Q All right. Now the next substance on this chart of selected poisons is the 2,3,7,8 TCDD Dioxin. What do the -- is that correct, ma'am?

A Yes, it is.

Q What does the TCDD stand for?

A Tetrachlorodibenzo-para-dioxin.

Q Now tetra means what?

A Four.

Q And does that refer to the four chlorine molecules?

A It does.

Q And the C stands for --

A Chloro.

Q Again that's referring to the fact that there are chlorine molecules, four in number, attached to this molecule as you previously described?

A That's right.

Q And the next letter, the D stands for what?

A Dibenzo.

Q And that on the chart indicates that there are two -- the di stands for two, does it not?

A That's right.

Q All right. And that means there are two benzine molecules?

A That's right.

Q All right. Is it atoms or molecules?

A Molecules.

Q Molecules, all right. The other D stands for what?

A Dioxin.

Q All right. It's that last D then that stands for Dioxin?

A That's right.

Q So this -- and this is a description of a particular isomer known as a tetrachloro isomer?

A That's right.

Q All right. Now of the tetrachloro isomers and that would -- on this chart of these Dioxins there are two tetrachloro -- would you have to have -- you would have to have those four numbers or four numbers describing the chlorine molecules for it to be tetra, is that correct?

A There would be four chlorines attached to the Dioxin molecule, that's correct.

Q And that's signified in the number -- in the word tetra meaning four?

A That's right.

Q Now of these tetra Dioxins, tetrachloro-dioxin how many isomers are there of the tetrachloro-dioxins?

A I believe there are 22.

Q All right. Now and of those 22 -- of those 22 isomers it is on this chart at least there's two shown, that is, 2,3,7,9 and the 2,3,7,8 Dioxin?

A That's right.

Q -- isomer, is that correct?

A That's right.

Q And by this chart for the record I mean Exhibit 230. Now of these 22 isomers it is the 2,3,7,8 isomer that is shown on the relative scale of toxicity in chart, Plaintiffs' Exhibit 231, is that correct?

A That's right.

Q Now the 322, what does that stand for that's in the second column under the word molecular weight?

A That is the weight of the compound in terms of the atoms, the elements that make it up.

Q And does the 322 indicate that it's a much lighter substance than the substances above it, if I'm saying it correctly?

A It means it's much smaller --

Q Much smaller.

A -- it has fewer atoms in its structure.

Q Just for instance, the diptheria toxin, the number of atoms would be indicated by multiplying ten with four zeros behind it and that would be -- four zeros would be what, a hundred -- 10,000, I guess.

A No, not strictly speaking. You have to transform that number by Avogardro's number to get the atomic weight.

Q You could have gone all afternoon and not said that. Do the -- which is the smallest molecule, the diptheria toxin or the 2,3,7,8 molecule?

A 2,3,7,8 TCDD is a smaller molecule, which you can tell by its smaller molecular weight.

Q And this would be something multipled times 7.2 and enter Avogardo or whatever it is would be thrown in there

somewhere, right?

A Right.

Q And so by molecular weight that all of these substances below here would be -- have lesser molecular weight than the naturally occurring toxins, is that correct?

A All of them do, yes.

Q Now over on the third column, the 3.1 times ten to the minus nine for the 2,3,7,8 Dioxin that again would be nine zeros following a decimal -- it would be .000000 etc. times 3.1, is that correct?

A That's right.

Q Now, Dr. Silbergeld, these are the poisons that are below there, what is saxitoxin?

A Saxitoxin is another naturally occurring poison which is in a fish, contained in the poison gland of that fish known as the puffer fish.

Q And it is less toxic according to this scale than Dioxin 2,3,7,8?

A That's correct.

Q Have you worked with saxitoxin?

A I have.

Q In your laboratory?

A Yes.

Q The next one, tetro--

A Tatrodotoxin.

Q Tetrodotoxin. And what is that?

A It is another naturally occurring poison in a species of frog.

Q And it is less poisonous than 2,3,7,8?

A It is.

Q And have you worked with that?

A I have.

Q The next one is bufotoxin.

A Bufotcxin.

Q Bufotoxin. What is that?

A That's another naturally occurring poison which is in a frog. I think that's the poison that some of the South American head hunters dipped their arrows in to kill people.

Q All right. Have you worked with that?

A No, I haven't.

Q The next one is curare. I've heard of that. That is a -- indeed is -- well, you tell me what it is.

A Curare is a naturally occurring poison extracted from certain plants and is also quite toxic.

Q And strychnine, we've all heard of strychnine.

A Yes, that's another naturally occurring plant substance.

Q And on the scale of toxicity of strychnine relating

to Dioxin there -- it's kind of blurred, what is that? Six zeros behind the -- no, no, I'm in the wrong column. That would be six zeros behind the 1.5 for strychnine, is that correct?

A Yes.

Q As far as lethality is concerned, Dioxin having nine zeros behind the decimal point would be more toxic than strychnine which has six zeros behind it?

A It would be a thousand times more toxic.

Q Dioxin is a thousand times more toxic than strychnine?

A That's right.

Q All right. And the next one is -- strychnine, that is a substance found in nature?

A That's right.

Q Have you worked with that?

A Yes.

Q How about the next one, muscarin?

A Muscarin.

Q Muscarin, what is that?

A That's another naturally occurring substance in mushrooms, amanita muscaria, which many people know as the most deadly mushrooms you can eat, and it's also quite toxic.

Q How many times more -- that looks like 5, I guess, or 6 behind the ten. That would again -- how many times more

toxic is Dioxin than muscarin?

A I guess it would be a thousand to ten thousand times more toxic.

Q And the next one, diisopropyl fluorophosphate.

A That's a synthetic substance, and it has been used as a pesticide, commonly known as DFP. It's also acutely toxic.

Q It's ten with five zeros, minus five zeros. And the last one is what's known as cyanide.

A That's right.

Q The word sodium is commonly dropped when you describe it and you just call it cyanide is what we all know as cyanide.

A That's a certain salt or form of cyanide, right.

Q And it's got ten to the minus four. So Dioxin is how many times more lethal than cyanide?

A A hundred thousand times more lethal.

Q Now, Doctor, when we talk about the effects of poison and in particular the poison that we're talking about in this case, Dioxin, is lethality -- that's not the right word -- lethal -- is the lethality of these substances or more particularly Dioxin to animals or to humans, is that a particularly relevant point when we're discussing about how Dioxin affects human beings?

A No, it's certainly not the sole or perhaps the most important consideration for human toxicity of Dioxin.

Q Has there been established for human beings a level toxicity for human beings insofar as Dioxin is concerned?

A Insofar as the lethal dose, that is the dose that would cause fairly rapid death obviously no one has conducted experiments to try to determine that, but if you look at the data from the industrial exposure and if you look at Dow's experiments on the prisoners at Holmberg Prison in Philadelphia it's pretty clear that Dioxin fortunately is not that acutely lethal to human beings.

Q Then, Doctor, if it is not lethal as such to human beings -- and is apparently lethal to animals, is that correct?

A To certain species of animals, yes.

Q All right. Why are we concerned about Dioxin then? Why are toxicologists concerned about Dioxin?

A The major effect, biological effect of Dioxin which concerns toxicologists, human toxicologists as well as experimental toxicologists, is its very great potency to cause cancer, to affect the liver and to affect the reproductive system.

Q Doctor, is what you're saying that while it may not -- or the amount that it would take to kill one has not been

established, is not relevant, what is relevant is the fact that it had other effects on human beings other than causing their death?

A That's right.

Q Now in the course of determining what effects TCDD has on human beings has it been necessary as you earlier indicated to conduct studies on animals for the purpose of demonstrating how it might affect or will affect human beings?

A Yes.

Q When did these studies with animals and Dioxin first start occurring?

A Well, I suppose some of the first was the studies conducted by BASF after that accident we talked about.

Q With the rabbits?

A With the rabbits. And then other studies by Dow and Monsanto to try and determine the chemical which was causing both the liver effect and the chloracne, the skin reaction which they had all observed in workers, but the very detailed experiments specifically directed 2,3,7,8 TCDD in its pure identified form probably began in the early '70s.

Q Now in the early '70s was it necessary in order for scientists to determine the effect of Dioxin on animals and thereby on human beings, was it necessary that the 2,3,7,8 isomer be isolated and identified?

A For many of the studies it was indeed necessary.

Q And sometime in the '70s, early '70s they started working with that substance with animals, is that what you just said?

A That's right.

Q What did these animal studies, and if you would, -- first of all, who are the major scientists who have worked with TCDD and animals?

A Dr. Richard Kociba of Dow Chemical, Dr. Ranata Kimbrough of the Center for Disease Control, Dr. Allen Poland and Dr. Henry Pitot of the McCardle Cancer Research Institute, Dr. Daniel Nebert of the National Institute of Health, Dr. Dieter Neubert from the University of Berlin, Dr. Andrew Kende, who works with Dr. Poland, Dr. Robert Neal at Vanderbilt and is now at the chemical industry's Institute of Toxicology, Dr. Thomas Gasiewitz of the University of Rochester, Dr. John Moore, who until very recently was at NIH and is the Assistant Adminstrator of the E.P.A. for toxic substances, Dr. Voss of the National Institutes of Health of the Netherlands, Dr. Crow from England who studied a great deal of the chloracne symptoms, Dr. Jacob Blaiberg, who I believe was at the State Department of Health in New Jersey when he did most of his research. There are others I'm sure I'm forgetting.

Q Now, Doctor, in these early studies what were they

attempting to discover and what in fact did they discover in the first published works dealing with Dioxin and animals?

A The early work was to determine the range of effects with Dioxin -- and here I'm speaking of TCDD -- could produce. Very soon after that it became very important to determine the specific molecule,which of these 22 four chlorine isomers of Dioxin was so toxic, and so in the early '70s there was a great deal of effort around what is known as structure activity studies in which --

Q Doctor, what I want to direct your attention to is the animal studies themselves. What was it that they were trying to find out with what animals and who was the pioneer, I guess you might say, in these studies and what was he trying to discover?

A There was early work attempting to discover why these -- why TCDD was so toxic to the liver. I think the pioneer there is really Dr. Allen Poland.

Q And what animal or what species of animals did he work with or in another way what did he discover occurred with respect to the liver?

A He worked mainly with rats and mice, also with guinea pigs and hamsters, and he discovered the great potency of TCDD and shortly thereafter the specific potency of 2,3,7,8 TCDD to cause chemical porphyria.

Q All right. And that chemical porphyria is what we have been referred to by Dr. Ellefson as intoxication porphyria?

A Yes.

Q And what did Dr. Poland discover 2,3,7,8 TCDD would do to these porphyrins or what did he discover with the relation to the induction of chemical or intoxication porphyria?

A He found that 2,3,7,8 TCDD was the most potent inducer of a family of enzymes in the liver, and one of the consequences of that induction of enzyme was a huge drain on the heme synthesizing system of the liver. In response to that huge demand for heme the entire porphyrin pathway was shifted into a state of biochemical abnormality.

Q Now this enzyme induction, when you're using the word enzyme could you tell us what -- what you mean and what scientists mean when you say enzyme?

A An enzyme is a biological molecule which converts one substance into another in the body.

Q And do we have enzymes, do all of us have enzymes in our bodies?

A Thousands and millions of enzymes.

Q Of different kinds of enzymes?

A Different kinds of enzymes.

Q Not just thousands and millions of molecules but thousands and millions different kinds of enzymes?

A Yes, very specific enzymes.

Q Doing specific jobs?

A That's right.

Q Can our body -- can we function as living beings without these enzymes?

A Without any enzymes we would be dead. Certain enzymes are particularly critical for life so that the specific inhibition or blockade of those enzymes which is done by some of the chemicals on that list is indeed lethal.

Q Now we all know -- at least my experience with enzymes is what you sprinkle on meat to make it tender, Accent. That is an enzyme, is it?

A It contains an enzyme preparation from papaya, I think.

Q And that -- when you say enzyme, that is just then one small kind or one specific kind of enzyme that we have some use for outside the human body?

A One set of enzymes, yes.

Q And when you're talking about enzymes in the human body, you're not talking about that particular enzyme, but you're talking about thousands and millions of other kinds of enzymes?

A Well, an analog to that kind of enzyme does exist in the human body, but the human body,of course, contains many

other types of enzymes.

Q When you say analog, what do you mean, one like it, an analogy?

A One that performs the same function.

Q In human beings?

A Yes.

Q But now these enzymes that are working with -- there's a particular kind of enzyme in the liver that works to make this substance called heme?

A There is a whole family of enzymes, which working together one after the other, in a series of related reactions or steps make heme.

Q And Dr. Poland discovered that TCDD or 2,3,7,8 had an effect upon that particular enzyme?

A It had an effect on that system. There's no one particular enzyme in the heme synthetic pathway. This effect he noted was through its action to induce another set of enzymes which contained heme in them and when their activity was greatly increased by 2,3,7,8 TCDD the body made, that is the body made more and more of this set of enzymes, which are known as the aryl hydrocarbon hydroxylases. In order to keep up with the demand for making more of this set of enzymes the heme system was switched on to produce more and more heme.

Q Well, and would that be bad necessarily, bad in the

body to have more heme? Isn't that a good substance to have?

A Heme itself is a good substance, but the consequence of switching on to a pathological extent the porphyrin pathway has a number of pathologic consequences.

Q And what are these consequences, Doctor?

A As we discussed earlier, it has consequences for the nervous system, it has consequences for mitochondrial function, that is, the ability of these compartments with themselves to contain and move oxygen and energy supplies in the cell and it may well have effects on the membrane of the cell which are related to cancer.

Q And that's occurring because of the effect upon the enzymes that act upon heme in the liver?

A As a second stage effect, because of the direct effect of Dioxon on the hydroxylase enzymes.

Q All right. Now, Doctor, did Dr. Poland discover that 2,3,7,8 has that effect on the livers of all these various animals that he worked with or was there discrimination?

A There was relatively little difference across species for this effect.

Q When did Dr. Poland publish in this area on that point?

A Starting in about 1973 Dr. Poland began publishing on this subject.

Q Has his -- has the result that he discovered relative to the effects on these enzymes and upon the liver and upon heme in animals, has that been subsequently confirmed as to occur in humans?

A Yes, it has.

Q And who confirmed that or how has that been confirmed?

A It's been confirmed in two ways. Dr. Poland, along with Dr. Blaiberg, investigated some workers from the Diamond Alkylate Plant in New Jersey who were exposed to trichlorophenols and 2,3,7,8 TCDD and found symptoms of chemical porphyria consistent with what he had produced in animals. In addition, Dr. Howard Eisen and others at the National Institutes of Health had actually taken human cells, placed them in culture, that is, in a small dish and allowed them to grow and live and exposed those human cells to 2,3,7,8 TCDD and they have reported that those human cells have exactly the same response as animal cells, that is, the cells from other mammals.

Q Now, as a general statement do all animals, all these animal species -- you mentioned a word -- the liver result, the heme results were consistent that Poland found in all these animals, but as we go along here and study some of these other effects have all animals subjected to TCDD experimentation reacted in the same way to TCDD or has there been a difference in their reactions?

A There have been slight differences in the particular expression. For example, when mice are treated -- pregnant mice are treated with 2,3,7,8 TCDD, they tend to produce offspring with cleft palate. When rhesus monkeys are exposed to 2,3,7,8 TCDD, they tend to produce dead offspring, but in the sense that all the animals which have been tested for reproductive toxicology show a similar effect at similar doses, the answer is yes. The same thing goes for cancer and for immune effects.

Q All right. Now, Doctor, after Dr. Poland worked in the area of the liver and it was an enzyme induction effect that caused this porphyria, am I correct in that statement?

A That was the primary lesion which he identified.

Q All right. Now this -- were there other works by other scientists to confirm, not just in humans but with the other animals and follow up studies that this indeed, his conclusions were indeed correct with regard to 2,3,7,8 and how it affects the hepatic system or the liver?

A Yes, there have been a number of papers which all confirm Dr. Poland's work.

Q And when we use -- when I use the word that has been used in Dr. Ellefson's deposition, hepatic, is that another word for liver?

A Yes, it is.

Q All right. So one could say hepatic or one could say liver and could mean the same thing?

A That's right.

Q Why don't you all just say liver? We all know liver, we don't know hepatic. Why do you do that? You've got no answer for that, have you, Doctor? All right. Now, Doctor, this hepatic effect, this effect upon the liver, has it been discovered that it will cause a particular kind of porphyria, and I'm not referring to what we've all learned to know as porphyria cutanea tarda?

A It does cause a very specific pattern of biochemical changes in the exposed animal or person, and that pattern has been called porphyria cutanea tarda, because there are a number of porphyrias, that is, the one porphyria just means a disturbance in the porphyrin system.

Q All right. Now, Doctor, in addition to the -- strike that. Is there anywhere that you are aware of any disputation or any disagreement with the findings of Dr. Poland and others that 2,3,7,8 TCDD causes these liver enzyme hepatic problem or porphyria problems?

A No, I'm not aware of any disagreement.

Q Is there any reputable scientist anywhere that disputes this occurrence?

A Not that I know of.

Q And how long has it been that this specific disability, this specific affliction is caused by exposure to 2,3,7,8 TCDD?

A It certainly was well established by 1974 and 1975.

Q No question but what it was known in January and February of 1979?

A None at all.

Q Now what other areas of TCDD effects have toxicologists and doctors for that matter and other people discovered with respect to 2,3,7,8?

A It's very great potency as a reproductive toxin.

Q Now does that concern itself with metabolism or enzyme induction or lipids?

A It may include enzyme induction as one of the mechanisms of action.

Q In the -- as far as a general effect is concerned you mentioned that TCDD affects or induces enzyme production in animals and in humans. Is there other system wide effects such as metabolism that are affected by 2,3,7,8 TCDD or the lipid system or lipids?

A Well, by affecting those enzymes, by inducing their activity as a consequence there's a kind of cascade effect throughout the body and among those effects are alteration in liver metabolism of a number of compounds, as I mentioned,

including sex hormones, drugs, therapeutic drugs that people might take and other chemicals. The metabolism of lipids by the liver is altered, but those are all the result of the first step, which is this powerful induction of enzymes.

Q Now this metabolism you mentioned, does that occur then in the living being just in the liver?

A No, this same metabolism also occurs in other organs of the body.

Q And do the -- does the metabolism in these other organs, is it -- are they affected by 2,3,7,8 TCDD?

A They are to a varying extent.

Q And who worked in and who discovered that to occur?

A I believe Dr. Robert Neal was one of the pioneers who demonstrated the changes in metabolism in the lung and in certain other organs. Dr. Thorgiersson and Dr. Madison, my colleague at N.I.H., were among the first to show that this change in metabolism occurs in the sex organs, that is, the ovaries and the testes. I believe Dr. Voss was one of the first to show that it occurs in the thymus, that is, the major gland involved in regulating immune function.

Q All right. Now, Dr. Silbergeld, tell us please what is meant when you say metabolism, what actually occurs, what is this metabolism?

A Metabolism generally refers to the conversion of

one substance or chemical into another usually by a series of enzymes.

Q All right. Is this metabolism, is this important in the functioning of mammals, of living beings?

A It's absolutely essential. It's how we convert our food into energy, how we regulate and handle the various chemicals the body secretes in order to communicate from one organ to another. It's how we regulate things such as sexual function, how we handle chemicals that come into our body from the outside world.

Q You said it's how we handle -- when we -- when one digests one's food in the digestive process, are we really metabolizing that food?

A We are.

Q In more than one organ or in more than one process?

A Yes, in very complex processes.

Q And if instead of using the word metabolism if I were to say change, would I be saying the same thing?

A Not quite, I guess.

Q Well --

A Converting perhaps.

Q Converting?

A I'd use.

Q All right. Metabolism means convert then?

A Yes.

Q So if I say convert food into whatever food is converted into, calories, I guess, -- no, that's not right.

A Muscle.

Q Muscle? All right. Really when food is converted into muscle the body is converting or changing that food into muscle through a series of complicated processes, is that right?

A That's right.

Q All right. Now what else is metabolized or converted or changed in the human body?

A As I mentioned, a variety of substances which various organs secrete.

Q Well --

A For instance --

Q Give me an example.

A For instance, the ovary secretes estrogen, and that estrogen is very important obviously in human reproduction, but that estrogen has to be broken down, cleared by the body regularly or else it would build up and become quite toxic.

Q The body then metabolizes this estrogen, is that correct?

A The body takes certain chemicals and metabolizes into estrogen. Then it takes the estrogen and metabolizes

that into substances which can either be reused or excreted.

Q It's excreted if the body doesn't want it or if it's deleterious, can't use it or it's used if the body wants it?

A More or less, yes.

Q All right. What else besides estrogen is metabolized or converted or changed in the body?

A Almost all the various chemicals that our cells make are metabolized into being. They are created from simple molecules such as amino acids and they are then broken down by other metabolic processes or recycled and reused, and it's by that process, sometimes known as physiological homeostasis that the body continues to function in a more or less even manner.

Q And then what? Is it fair to say that the entire operation of our body, the creation of skin and muscle and hair and toenails and everything else is really a form of metabolism?

A That's right. Everything in our body is constantly being metabolized, even bone is being resorbed, that is, becoming dilute and then put back down again, reestablished.

Q All right. So when -- what we're most commonly acquainted with when we're trying to lose weight some people have a different metabolism than others and therefore, they use up the energy or use up the food and it won't turn into

fat. When we say metabolism that's just one little bitty aspect of metabolism in the human body?

A That's right.

Q Do these rates of metabolism or conversion or changes, do they vary from person to person then in these other areas just as one's metabolism with reference to the ability to gain or lose weight varies from person to person?

A Probably to a varying extent, yes.

Q Some people can eat food just like mad all the time and you hate them for doing it and they always stay thin?

A That's right.

Q Other people can get close to a milkshake, just smell and they get fat?

A I don't think that's metabolism.

Q That isn't metabolism? All right. Now, Dr. Silbergeld, is that the process then that's going on throughout the human body and that to some extent varies from person to person?

A That's right.

Q Now, and isn't that a fact that science has discovered it's changed or influenced by 2,3,7,8 TCDD in all of these aspects?

A No, only certain highly specific parts of metabolism appear to be affected by 2,3,7,8 TCDD.

Q All right. What are those effects, which ones are affected? What metabolism rates or conversions in our body or animals for that matter are affected by 2,3,7,8 TCDD?

A Well, that's a two level question. The first level is, as I mentioned, this rapid and extreme induction that is the --

Q Induction means --

A Increase in the amount of an enzyme. That's that AHH or aryl hydrocarbon hydroxylases set of enzymes. As a result of that many metabolic processes which use those enzymes -- enzymes are kind of like tools and various functions in the body reach in and grab a tool when they need it and then put it down when they're through. Another function will come in and use the same set of enzymes so that, for example, if you were taking phenobarbital because you had epilepsy, these enzymes would be called into action to break down the phenobarbital so you wouldn't be killed by it. If you had a surge of a sex hormone as men and women do during the day and during the month, those same enzymes would be called into play to break those substances down. As lipids, cholesterol build up in the blood those same enzymes would have to come into play to take care of those substances as well.

Q All right. Now, Dr. Silbergeld, as far as this --

the specific effects of metabolism, what metabolic processes are known to be affected by 2,3,7,8 TCDD in the animal and who discovered it?

A Basically all those processes that use that set of enzyme are known to be affected and a range of workers have studied this, starting with Dr. Poland but covering many of the people I mentioned before and others as well.

Q All right. Now this effect of 2,3,7,8 upon this metabolic process has this been published from the mid '70s onward?

A Yes, it has.

Q And has it been published in journals that are available to the -- to I suppose anybody that wants to go to a store and buy this particular magazine that's published and sold?

A Yes.

Q Something that's known to the chemical industry and the health professionals?

A Certainly some members of the chemical industry contributed greatly to the research, yes.

Q Now the word lipid has been used from time to time in this case. What is a lipid?

A A lipid is a fat, a certain type of molecule.

Q The fat that I have on my body, another name for

that is lipid?

A That is a type of lipid, yes.

Q And there are other types of lipids other than fat?

A Other than body epidermal fat.

Q All right. And what role do lipids play in the healthy functions of animals and human beings?

A Lipids are essential, because all the membranes, that is, the outer layers of all of our cells contain lipids, and they indeed provide, many people think, the barrier which keeps cells from leaking their contents out into the water and blood that surrounds them.

Q Now have -- has science established that these lipids are affected by 2,3,7,8 TCDD either directly or indirectly?

A Lipid metabolism, certain lipid metabolism is affected by 2,3,7,8 TCDD.

Q In what animals was that first discovered?

A I'm not certain. It was described, I think, by some of the occupational physicians looking at humans who reported hyperlipidemia, that is, increases in lipids in blood, but the complete explanation and examination of this effect was, of course, done in animals, I think probably rodents.

Q Probably what?

A Rodents and guinea pigs.

Q All right. And when was that work going on with the lipids?

A From the mid '70s to the present time.

Q It's still going on, I take it?

A There's still a great deal of research on 2,3,7,8 TCDD.

Q Now, Dr. Silbergeld, is there any -- has there been any dispute or question in the scientific world that TCDD, 2,3,7,8 TCDD has this effect upon the lipids in the animal and human body?

A Well, there was a question at one point raised as to whether the effects of TCDD to increase the levels of lipids in blood might be the result of another action of this chemical to cause an anorexia, a failure to eat and a wasting away of the body, and as the body was not taking in enough nutrients from outside, it was burning itself, if you will, and releasing a lot of lipids from broken down cells, but Dr. Robert Neal, who is now the head of the chemical industry's Institute of Toxicology conducted some very elegant experiments, I think about 1976, in which he showed that even if you control very carefully the food intake and body weight of animals -- obviously this could only be done with animals -- there was an additional, separate, important effect of 2,3,7,8 TCDD on

lipid metabolism. I don't think that's in any dispute.

Q Is what you're saying that TCDD could cause one to have an increased number of lipids and in some other person or under other circumstances cause a decrease in lipids?

A No, in general it seems to cause an increase in circulating lipids in the blood, but it also causes in many types of animals a wasting away syndrome or lack of appetite known as anorexia. Now lack of appetite, severe lack of appetite, will itself increase circulating lipids, so it was important to distinguish an effect of Dioxin on the 2,3,7,8 TCDD on lipid metabolism separate from its effect on appetite, and this has been done.

Q Now at the time Dr. Neal discovered this effect and published in this area what was his position?

A He was a professor of pharmacology and toxicology at Vanderbilt University.

Q And he published in it, and at the present time, however, after that publication or at some chronological time after that he became Director, Executive Director of the Chemical Institute on Toxicology?

A That's right.

Q This jury has had a deposition, or portions of a deposition of Dr. Neal read, so they are familiar with the name, all right. This work though was done before he became

the head of that industrial organization?

A As far as I know, yes.

Q All right. Now has anyone disputed these results that Dr. Neal and others in the same vein discovered insofar as lipids and anorexia is concerned?

A I don't believe so, no.

Q Now is there a difference between -- you've used the words and others have used the words between acute effect and chronic effects?

A Yes, there is.

Q What is known as an acute effect?

A Generally speaking, an acute effect is one that occurs shortly after administration or exposure to a toxic substance or it is an effect which occurs after very limited exposure.

Q All right. An acute effect then of a poison, say, that one is given, if you've given a large enough dose can cause his death immediately. That would be called an acute effect?

A That's right.

Q But if he's given that dose, that poison in small doses over a period of time so that it doesn't kill him but -- and say in the case of lead poisoning, for instance, makes him sick and tired all the time and not enough to kill

him, but enough to make him sick, the effect of making him sick and tired would be considered a chronic effect because it didn't kill him and it took place over a long period of time? Would that be correct?

A Well, in part the use of the word chronic like the use of the word acute describes both the type of exposure, that is, in your example the exposure of was a series of sub-toxic, sublethal doses and also that the effects observed occurred over a period of time, but there is a warning. When you're dealing with substances like 2,3,7,8 TCDD or into lead, which are accumulated in the body, it's sometimes difficult to make these distinctions between acute and chronic, because a series of small doses will accumulate in the body and it is possible to achieve a level at which acute effect will occur, that is, you will suddenly start to see a different type of very severe toxicity at the point you give the last little dose.

Q That would be like you can -- you could kill somebody with little doses of arsenic, for instance, over a long period of time. It's that last dose that accumulated along with the arsenic stored up in his body, I take it, that caused the acute effect of death?

A I believe that's been known to happen in murder trials.

Q That's what I was thinking about, Arsenic and Old Lace and that sort of thing. Or you could cause that acute

effect by one large dose at the beginning?

A In general terms, yes.

Q Now has TCDD known to have -- to accumulate in the human body and in the body of animals?

A It is known to accumulate in the body of animals.

Q What animals?

A A whole range of animals from invertebrates, frogs, fish, all the way through mammals, primates, monkeys.

Q And can the effect of those -- of that accumulation over a longer period of time be the same as a larger dose at the beginning of that period of time?

A It may be for certain effects.

Q All right. Now -- Doctor, that's another point that I want to explore subsequently, but as far as the acute versus chronic toxicity, when you talk about chronic toxicity, then you're talking about the effects over a long period of time, so to speak, or a longer period of time, is that correct?

A That's right.

Q All right. Now insofar as other organs of the body are concerned, for instance, the kidney had, have there -- has there been work to demonstrate that 2,3,7,8 TCDD has deleterious or harmful effects upon the kidney?

A Yes, there has.

Q And what -- in what -- who demonstrated that

and in what animal or animals or humans?

A The animal work was begun by Dr. Richard Kociba of the Dow Chemical Company in which he showed a variety of biochemical and pathological effects in the kidneys of rats he exposed to 2,3,7,8 TCDD.

Q Now is the word renal the same as saying kidney?

A Yes, it is.

Q All right. We got hepatic means liver and renal means kidney?

A Right.

Q So if I say effect upon the kidney, you'll know I'm talking about renal and if you say renal, I'll know you're talking about kidney.

A Right.

Q All right. Now what effects has been known or demonstrate renal or kidney effects with 2,3,7,8 TCDD?

A As I said, changes in the biochemistry of the kidney particularly the porphyrin synthetic pathway --

Q Porphyrins are involved in the kidney as well as the liver?

A Yes. Porphyrins synthesis is an important metabolic pathway in many cells, including nerve cells. In addition, treatment with 2,3,7,8 TCDD also has pathological damage to the kidneys, that is, actual destruction of kidney cells.

Q All right. Not just talking about then affecting the kidney in its function, but you're talking about destruction of the kidney cells itself?

A That's right.

Q Is that correct?

A That's right.

Q And this was demonstrated as to be an effect from 2,3,7,8 how long ago?

A I think as early as 1976, 1977 by Dr. Kociba.

Q And when these scientists for Dow, for instance, when they discovered that, again was it published or was it kept secret?

A Oh, no, it was presented at international meetings and published in prestigious journals.

Q Meetings that you might, if you had been a toxicologist at that time that you might have attended or that medical directors of various corporations might attend, they would be privy to that information?

A Certainly.

Q Now what is the system known as the endocrine system? What is that, what does endocrine mean?

A Endocrine describes a set of organs which secrete chemicals, naturally formed chemicals and direct metabolism and other functions in the body by means of these chemicals.

Q Now, I don't know that I understand that. I know we've got an endocrine system and I know it does something, but I really don't understand what you're saying. Could you explain that a little bit, what is the endocrine system and what it does to us on a practical basis?

A Well, I can give you an example of an endocrine system. There are many such systems in the body.

Q There's more than one endocrine system in the body?

A Well, there are a number of organs which can all be called part of the endocrine system, but usually scientists distinguish a particular endocrine system. For example, the endocrine system which controls reproduction or the endocrine system which controls insulin production, they are all part of the endocrine system. But, for instance, the reproductive system involved in endocrine network which includes a part of the brain known as the hypothalamus. It includes the pituitary, which is another part of the brain.

Q The pituitary, that's also known as the growth gland, is it not?

A One of the things the pituitary does is secrete a hormone known as growth hormone, so it's then an endocrine system controlling growth.

Q All right. So the pituitary gland is part of the endocrine system?

A That's right.

Q All right.

A The pituitary secretes chemicals, prolactin which induces milk in women shortly after they deliver babies and does other things. Those hormones travel through the blood to the sex organs, the ovary or the testes and cause cellular changes to occur in those organs. Those organs themselves then secrete chemicals. They are endocrine organs also in this sense. Those chemicals go back up to the pituitary through the blood stream and to the part of the brain, the hypothalamus, and regulate the entire function. So that's an endocrine system.

Q Well, I think I heard what you said, but I must confess I'm not really sure that I know what you said. The endocrine system, I take it, is an important part of the living being's functioning the way we're functioning?

A That's right.

Q Growing and changing and everything like that?

A That's right.

Q All right. Now has there been work done in animals to demonstrate whether or not 2,3,7,8 TCDD affects the endocrine system?

A Yes, there has.

Q And who did that and when?

A I think probably Dr. Kociba again was one of the first to do these studies.

Q And again he's the toxicologist working for Dow Chemical?

A That's right.

Q All right.

A This would be in the mid '70s, and there have been a number of other people working in this area, including myself.

Q You have worked in this area of the endocrine system?

A Yes.

Q When we read off these papers dealing with the reproductive work that you did that was in fact work in the endocrine system?

A That's correct.

Q And has it been established then that 2,3,7,8 TCDD does have a harmful effect on the functioning of the endocrine system?

A Yes, it has.

Q And that's been known since the mid '70s?

A Yes, it has.

Q Is there any one scientist or group of scientists that dispute the effect of 2,3,7,8 TCDD upon some aspects or parts of the endocrine system?

A There is no dispute that 2,3,7,8 TCDD can affect aspects of the endocrine system. The entire range of its effects on that system is, of course, not presently known.

Q Why isn't it known, Doctor?

A These are very complex systems and, as I mentioned, they exist in a relationship with each other. For example, we found that 2,3,7,8 TCDD stops ovulation in female mice. Now that effect could be because the chemical is affecting the ovary directly or the chemical could just be changing hormone metabolism in the liver or it could be acting on the pituitary or the hypothalamus.

Q You know that it's doing something to cause these ovaries not to function; just exactly the mechanism how it's doing it you don't know?

A That's right.

Q All right. Now, Doctor, is the reproduction of the species then, is that the net result of the functioning of a lot of these systems that we're talking about?

A That's one of the results, yes.

Q Now in the work in reproduction in what species have definitive or experimental work been done to determine whether or not 2,3,7,8 TCDD affects reproduction?

A In mice, rats, guinea pigs, hamsters, rhesus monkeys and there have been epidemiological surveys of humans.

Q Now when you say epidemiological surveys you people went out and checked with humans that had been exposed to 2,3,7,8 and found out whether they had some effects upon their capacity to reproduce, is that correct?

A That's right. They didn't go out and expose people to 2,3,7,8 TCDD, but they went out and tried to find people whom you could assume might have been exposed. For instance, the Defense Department's study of Air Force people involved in the packaging and dropping of Agent Orange in Viet-Nam.

Q And what about the Seveso people? Would they be part of the study groups?

A That would be another such study.

Q All right. Now that's study with humans. Insofar as the study with animals is concerned, is there -- is there any species of animal who have been discovered that 2,3,7,8 TCDD does not affect their or its reproductive system?

A No. As I mentioned before, there are some variations in just how the effect occurs, but I'm not aware of any species which is resistant in terms of the reproductive effects of 2,3,7,8 TCDD.

Q Now is this something that has been published and is known at large by the health professionals and by the chemical industry that deals with these substances that may contain 2,3,7,8 TCDD?

A Yes.

Q Doctor, a system known as the immune system, has there been work done in laboratory and elsewhere to ascertain what effects 2,3,7,8 TCDD has upon the immune system of animals?

A Yes, there has.

Q Who's done that work and when?

A I think that work was started by Dr. Voss of the Netherlands, also Dr. John Moore from NIEHS, now at the E.P.A.

Q NIEHS means what?

A National Institute of Environmental and Health Sciences. It's part of the NIH. It's a Federal agency.

Q And the NIH is the National Institute of Health, a Federal agency?

A That's right.

Q Go ahead. I didn't mean to interrupt you.

A Dr. Voss, Dr. Bekesi and Dr. Nebert. A variety of people have worked on this subject.

Q Now, Dr. Silbergeld, we will have after you testify an immunologist that will testify in depth and in detail about the immune system, but for our purposes of presenting your testimony as a toxicologist I'd like for you to explain to the jury what is the immune system, how it functions.

A The immune system is basically the body's defense system against agents which cause certain types of disease.

It includes certain organs and circulating cells in the blood.

Q And how does the immune system operate to prevent you and I from being sick? If I've got a cold and I come and breathe upon you, you might get sick and then the next guy might not get sick with that cold. Somebody's immune system, I take it, is operating to prevent the cold being -- to affect him. Could you tell us please how that occurs?

A Basically in two fundamental ways; obviously it's a very complex system as we're discovering, but the body makes cells which can actually chew up substances such as germs and substances that produce allergies or irritations in the body. Also, through another series of very special cells secretes chemicals which are known as antigens or antibodies, and these actually bind the substance which causes the disease and neutralize it.

Q Now, Doctor, have there been scientists who have worked with animals to determine whether or not 2,3,7,8 TCDD affects the immune system?

A Yes, as I mentioned, there have.

Q And how long ago was the work taking place? When did it start with 2,3,7,8 TCDD?

A About 1973.

Q And have science concluded that 2,3,7,8 does affect the immune system?

A Yes. Most scientists agree that 2,3,7,8 TCDD is a very potent toxin to the immune system.

Q And how does that occur?

A One way in which it occurs is by attacking the thymus gland itself, which is one of the glands which produces cells which give us our immune competent or our defense against these agents. There may also be other effects on the production of white cells and on the ability of these cells once they're produced to actually engage in the warfare against infectious agents.

Q When you say these white blood cells, when I was a kid and I'd get a cut and there was yellow substance, pus, around that cut if I wasn't too clean, and I was told at least that that pus is really the good white cells fighting those germs. Is that correct?

A In part, yes.

Q Just in part, correct?

A Yes.

Q How is it wrong?

A Well, it's a more much complex reaction than just white cells grouping together to fight an infection. There are also chemicals secreted by endocrine organs and other parts of the body which participate in this as well as factors from the red cells.

Q All right. Now in what animals has it been discovered that their immune system could be affected or is affected by 2,3,7,8 TCDD?

A Again a range of animals from mice and rats and hamsters and guinea pigs and humans.

Q And again has that been published and is it known?

A Yes, it is.

Q Is there any dispute about that fact, that it does have an effect upon the human immune system?

A I don't believe so.

MR. CARR: Your Honor, it's -- if the Court's willing, this would be a good time for a refreshing break.

THE COURT: Fine. Court will be in a short recess.

(At this time a short recess was taken.)

Q Dr. Silbergeld, we were discussing at the break the demonstrated effects upon the immune system. When you use the words thymus or thymus. Is it thymus?

A Thymus.

Q Is that the gland or organ that produces the cells known as T-cells?

A Yes, it is.

Q And is it the T-cell that -- among others that works in the immune system to make us immune to certain things?

A That is one of the important cells in the immune

system defense systems, yes.

Q Now has there been experiments performed upon animals to demonstrate that the T-cell is affected by 2,3,7,8 TCDD?

A Yes, there have.

Q And who did that work?

A Dr. Voss has done some of that work. Dr. McConnell, Dr. Moore, both of them are at NIH, Dr. Nebert at NIH, Dr. Goldstein and others.

Q And is the work in that area as to the extent of the effect upon the immune system by 2,3,7,8, is that work still ongoing to this day?

A Yes, it is.

Q Now, Doctor, has TCDD been demonstrated in animals and otherwise to have a hematologic effect?

A Yes, it has.

Q And is hematologic effect the same as saying, as you have described earlier, as the effect upon heme or is that a different effect?

A It's part of that effect. It's one expression, if you will, of that effect.

Q All right. What has -- what has it been demonstrated -- what hematologic effect has been demonstrated as being associated or caused by 2,3,7,8 TCDD?

A An effect on the stability of the red cell and upon the availability of heme for incorporation into hemoglobin.

Q And is hemoglobin essential to healthy animals, including human beings?

A Hemoglobin is that part of the red cell that carries oxygen from our lungs to all body organs and cells. It is absolutely essential for life.

Q All right. Now has it been demonstrated that 2,3,7,8 has an adverse or harmful effect upon the hematologic system?

A It's been shown that 2,3,7,8 TCDD reduces the function of the red cell system or hematologic system.

Q In what animals has that been demonstrated?

A A range of rodents, and I believe also rhesus monkeys. I think also cows and horses.

Q Has it been confirmed that similar effects occur in human beings?

A It has.

Q And who did the confirmatory work and where has it been confirmed?

A It's been confirmed, I believe, in some of the studies on the Seveso population and I think some of the industrial workers in some of the industrial settings where there was high exposure.

Q Now again has -- is there any dispute about the

fact that TCDD can have such an adverse effect in animals and in humans?

A There is no real dispute. There is discussion as to the extent of this effect, but no dispute that TCDD can actually affect this system.

Q And was this something known prior to January 10th, '79 or February 8th, 1979?

A Yes, it was.

Q Dr. Silbergeld, has there been work done in animals and work with human beings as to the effect of 2,3,7,8 on the neurological system and on the neuropsychiatric system at least insofar as it affects humans, if not animals?

A Yes, there have.

Q In the original industrial accident in 1949 at Nitro, West Virginia was there reported and demonstrated in the very first group of workers that were exposed neuropsychiatric effects?

A Yes, there were.

Q What were these neuropsychiatric effects that were demonstrated back in '49?

A There were a variety of signs indicating damage to the peripheral and central nervous system, that is, to the nerves outside the brain and spinal cord as well as to the brain. They included sensations of burning, fatigue, and

muscle -- neuromuscular weakness. In terms of the central nervous system, psychiatric kinds of effects, insomnia, that is, inability to fall asleep, suppression of appetite, depression, lethargy, and tiredness, a range of neuropsychiatric effects.

Q And did, as far as the published literature is concerned, did those doctors and scientists working for Monsanto at that time in '49 and thereafter, did they publish and was it known from that time forward that the exposure to this 2,4,5 trichlorophenol which had the 2,3,7,8 contaminant, that these neuropsychiatric effects did occur?

A I don't think the medical officers associated with Monsanto published much of their findings, but there were findings published by Bleiberg and Poland on the Diamond workers and some of the incidents in Germany as well as work from Czechoslovakia, which was sufficient to demonstrate by the mid '70s that there were significant neurologic effects of these compounds.

Q Doctor, what is a peripheral neuropathy?

A Peripheral neuropathy is damage to the nerves outside the brain and spinal cord.

Q Has there been work to demonstrate that 2,3,7,8 has such an effect?

A Yes, there has.

Q By whom and when?

A The clinical studies we've touched on. The animal studies have been done by Strik's Group in the Netherlands, by Elovaara's Group in Finland and by the workers at NEIHS and Dr. Moore's Group, among others.

Q What is a peripheral neuropathy?

A It's, as I said, damage to the nerves of the peripheral system.

Q Which would be the arms or the legs or the fingers?

A Those would be some of them. There are other nerves which control our heart, stomach, and a variety of other organs and systems in the body which are part of the peripheral nervous sytem.

Q Dr. Silbergeld, a significant amount of your work, your publication work has been dealing with neurotoxic effects of different substances?

A That's right.

Q Have you been able to demonstrate or have others demonstrated just what it is that 2,3,7,8 does to nerves?

A My work has focused on the consequences for the nerves of altering porphyrins biochemistry, and what I've shown is that there are several effects associated with that ultimate mechanism which are particularly dangerous for the nervous system. First off, since the porphyrin system produces

heme, that molecule which carries oxygen in the body, a reduction in the amount of heme through the draining off into that enzyme system that's induced, a reduction in that amount of heme deprives cells of their oxygen carrier, if you will. Nerve cells have the highest need for energy, for oxygen of all cells in the body because they're always active and therefore, they are among the first to die or be affected when there's a lack of oxygen. We all know the syndrome, the dangers of drowning or short periods of submersion in water, the organ that's affected most severely is the brain. That's because of its high demand for oxygen. The same thing happens if the cells can't get oxygen because they don't have a carrier for oxygen, heme. Another way in which altering porphyrin chemistry affects the nervous system is this insulation, this fatty wrapping around the nerves which is made out of lipids, is very dependent on active porphyrin system in those same cells and its porphyrin system is deranged as has been shown by workers at Rockefeller University and elsewhere, some of the first cells to die are these wrapping cells, what's known as myolin around nerves. Then the nerve becomes like an electric wire that's been stripped of its insulation, and as you know from short circuits and other problems in electrical appliances, this means that the system can't really work very well. That's known as demye-

lination neuropathy and indead has been described as a consequence of exposure to 2,3,7,8 TCDD. The final way in which altering porphrin pathways can affect the brain or nervous system very specifically is that some of the chemical in the porphyrin pathway are themselves neuroactive, that is, they have properties like drugs to affect certain parts of the nervous system with a very great deal of specificity and action.

Q All right. Then those persons that may have chemical or intoxication porphyria or for that matter inherited form of porphyria are having something done to their systems that would affect this covering on the nerve?

A Yes. As a matter of fact, that's why I became interested in this problem as a researcher because of the very complete descriptions of the neuropsychiatric and neuropathologic signs which have been described in many types of porphyria, yet no one really knew why these diseases, which are primarily diseases of the liver or of the kidney or both could really be affecting the nervous system so sensitively, and that's why I became interested and have devoted a great deal of research to this issue of connections between altering porphyrin metabolism even outside the brain and the very sensitive response of the brain to that alteration.

Q And in this effect of 2,3,7,8 TCDD upon the peripheral

nervous system on this lining around these nerves had that been published?

A Yes, it has.

Q How long ago were the first articles appearing dealing with this demyelination or porphyria effect upon the nerves and the lining of the nerves?

A Of TCDD?

Q Yes.

A I think starting around the mid 1970s.

Q All right. And again were these articles published so that anyone that wanted to read them could find them?

A Yes. I would add also that for anyone concerned about 2,3,7,8 TCDD, anyone who knew anything of the literature on porphyria, both the genetic inherited porphyrias and the other kinds of chemical porphyrias produced by hexachlorobenzene, by lead, by a variety of chemicals although they're all slightly different. Anyone who knew about the porphyrias would have been able to suspect reasonably that an agent which was so powerful a porphyringen, that is, a substance that produces porphyria, would be a very powerful neurotoxic agent.

Q All right.

A And indeed that had been speculated and discussed by a number of workers in the '60s.

Q Now, Dr. Silbergeld, what does the word teratogenicity mean?

A That's a property of a substance or an exposure which causes deformities or alterations in a fetus.

Q Now you mentioned in passing the cleft palate in the mice?

A Yes.

Q Is that a teratogenic effect?

A Yes, it is.

Q And has there been considerable work done as to the teratogenicity of 2,3,7,8 TCDD?

A Yes, there has.

Q Beginning when?

A I believe starting in the early '70s the work of Dr. Courtney and others.

Q And has it been demonstrated that TCDD can cause genetic defects to pass from one generation to another or cause these teratogenic effects that you have described?

A Teratogenic effects are not genetic effects. The words are slightly similar.

Q All right. But they're not the same?

A They're not the same. Teratogenic means producing or capable of acting. It means producing literally a monster, a deformed offspring. It may involve effects on the genetic

component of the body system, the developing fetus, or it may not.

Q All right. What you're saying is that -- if I understand you correctly then, is the toxic substance causes the fetus or the embryo in the animal or whatever the living being may be to become deformed or to have defects?

A That's right. That's a teratogen.

Q And those defects are not necessarily a genetic defect, that is, passed from father to son or mother to son or through parents, is that correct?

A That's correct.

Q It is a direct effect then by exposure of the embryo or the fetus to the substance or is it an effect by exposing the parent to the substance that this defect occurs in the offspring?

A It is usually -- the word teratogen is usually restricted to exposures with occurred during the development of the embryo or fetus so it would be restricted to a direct exposure of that embryo or fetus --

Q All right.

A -- or the exposure of the mother. It doesn't mean that's the only way birth defects are produced but that is the strict definition of a teratogen.

Q Is what you're saying then a mother, not pregnant,

being exposed to this toxic substance that that could cause her offspring to be deformed?

A Yes, that is a mechanism of action by which birth defects can, of course, occur, and the best example of that is Down's syndrome or mongolism in which the defect is in the mother's eggs and comes out when reproduction occurs, but -- and Dioxin may well have such effect on cells in the human ovaries as well as other animals, but a teratogenic effect is usually used to describe effects after reproduction is started, gestation is ongoing and the fetus is developing.

Q All right. So ordinarily when you use the term, you mean the effect upon the embryo or the unborn child or offspring, is that correct?

A That's right.

Q Now in how many different varieties of animals has it been demonstrated that 2,3,7,8 TCDD will have these -- will cause a defect in the offspring?

A In a wide range of species, many rodents, primates, monkeys, and there have again been epidemiologic studies in humans.

Q Now what does -- again has all this been published, this ability of 2,3,7,8 TCDD to do that?

A Yes, it has.

Q What's meant by the word fetotoxicity or embryo

toxicity?

A Those are toxic effects which are specifically occurring in the embryo or fetus. They might include teratogenic affect, but they would be more general as well. For instance, 2,3,7,8 TCDD exposure of pregnant females is known to alter the livers of their unborn offspring. That would be a fetotoxic or embryo toxic, depending on the time and development effect as opposed to a teratogenic effect, which is defined as involving a real structural change in the embryo or the fetus.

Q And has it been demonstrated that 2,3,7,8 TCDD has a fetotoxic effect?

A Yes, it has.

Q And has that been published?

A Yes, it has.

Q How long has it been known that 2,3,7,8 has such an effect?

A I think since 1976, 1977.

Q All right. Now, Doctor, what does cocarcinogenicity?

A Carcinogenicity means the property to produce cancer, that is, a tumor or leukemia.

Q All right. Now has there been work done in the area of producing cancers with 2,3,7,8 TCDD?

A Yes, there has.

Q When was this work started?

A I believe about 1976 or 1977 by Dow Chemical.

Q Now, have -- has it been demonstrated that 2,3,7,8 TCDD can cause cancer itself?

A Yes. It is generally stated that 2,3,7,8 TCDD is the most powerful chemical carcinogen identified.

Q Now, Dr. Silbergeld, are there certain substances that while they may not necessarily cause a cancer by itself, in itself, can -- that is, won't initiate the cancer or can initiate a cancer but also promote other substances in the creation or growth of cancers?

A Well, it's customarily accepted in molecular biology now that the progress of developing a cancer involves several stages, whereby a normal cell is changed into an abnormal cell and then that abnormal cell begins to divide and proliferate rapidly and abnormally and that's what forms the visible, operable, we hope, cancer. In that process there are a number of biological events which occur. Now the studies from Dow show quite clearly that exposure of animals to 2,3,7,8 TCDD alone can cause cancer; that is, 2,3,7,8 TCDD is a complete carcinogen. It does everything to the animal that's necessary to go from a healthy animal without a cancer to an animal with a cancer. In addition, people have looked at animals in which various preceding steps in the

progress of cancer have already been done to these animals. The animals have had cells initiated, as it's usually called in molecular biology, and then Dioxin is applied to the animal. Under those conditions of what's called two-stage carcinogenises Dioxin has been shown to be the most powerful second stage or promoter type carcinogen we have ever identified.

Q Doctor, in this promotion of a cancer has it been demonstrated that certain substances and many substances for that matter do in fact or can in some individuals and in some persons depending upon their immune system, upon their genetic makeup, that these carcinogens, these substances can cause cancers in some people and not cause cancers in others? If my question is unclear, I'll try to rephrase it, Doctor.

A It's true that there are some people born with, for instance, genetic defects in the skin who already exist with some of the stages of cancer, skin cancer unfortunately already having taken place in them. These people are very sensitive to UV light. Now --

Q UV light meaning sunlight?

A Sunlight or a sunlamp. Now prolonged exposure to sunlight, as we know, is not recommended for anyone and there is concern about skin cancers in people who spend a lot of time trying to be suntanned all the time, but in these people

it takes very little exposure to sunlight to make them progress very rapidly into a melanoma or skin cancer. So there are differences of that type, but when dealing with a compound like 2,3,7,8 TCDD, which is a complete carcinogen, I'm not aware that there would be expected to be people who wouldn't develop a cancer. Now the other possible variation in response to this chemical, 2,3,7,8 TCDD, relates to a mechanism of cancer we haven't talked about yet, and this is the involvement of the immune system in cancer. It's recognized that a number of cancers, including human cancers are actually caused by viruses. Many of us have these viruses in our body all the time. Fortunately our immune system is able to take care of them and they don't manage to invade cells, transform these cells and insert their malignant genetic information into our own genetic information and cause the cells to become cancerous. However, if the immune system is depressed severely these cancer causing viruses then are unchecked by the body's defense system and can cause a cancer. A very good example of this is the concern that we all have about Acquired Immune Deficiency Syndrome or AIDS and the incidence of certain types of sarcoma or cancer in people who have AIDS. They get that sarcoma because their immune system has been totally wiped out by the disease.

Q Now, Doctor, insofar as the ability of 2,3,7,8 TCDD

to promote cancer, does that take place when there is already something in the body, be it a germ or a virus or a chemical or a foreign substance that does by itself cause cancer, does the existence of that with the 2,3,7,8 TCDD have an accelerating effect upon the ability of the initial carcinogen to cause cancer?

A It has a greatly increasing effect.

Q All right. Could you -- and is that effect known as the ability of 2,3,7,8 TCDD to promote cancer rather than to initiate it?

A That is its promotional power. That's right.

Q Could you explain that please? What does it do to promote or to permit these other substances that aren't by themselves causing cancer at that point in time, what does 2,3,7,8 TCDD do to cause that other substance or to promote that other substance in the growth of cancer?

A Well, that's an area of very great research. I don't think anyone doubts that TCDD has this property. This is work primarily by Dr. Henry Pitot and his colleagues, and it is indeed a very powerful promoter in animals who have already been exposed to these initiating carcinogens. How it does this is an area of very great active research. My own colleague, Dr. Nebert, at NIH believes it is connected very closely with the ability of 2,3,7,8 TCDD to induce that set

of enzymes which we talked about a while ago, those AHH enzymes, because he's shown that a variety of chemicals which induce those enzymes are promoters and indeed based on their potency to induce these enzymes to have a similar rank order of potency in being promotional carcinogens.

Q Now again is this -- you mentioned your colleague and others -- is this ability of Dioxin to promote cancer, promote other organisms or other materials to cause cancer is this quality of it known and has it been known for a period of time?

A Yes, it is.

Q -- by the health professionals and by the chemical industry for some time?

A Yes, it has.

Q How long has it been known, and by known I mean published, that 2,3,7,8 TCDD is a promoter of cancer?

A I think from about 1977, '78.

Q Dr. Silbergeld, I have had some charts prepared over here. Before I get to that, has there been an area relating to either the acute toxicity of 2,3,7,8 or chronic toxic effects of 2,3,7,8 that I haven't asked you about, that I may have missed?

A We haven't talked about the other types of reproductive effects of 2,3,7,8 TCDD in addition to the effects on the

pregnant woman at the time after the fetus and embryo begins to develop, but there is considerable evidence in the animal literature and some evidence now coming from epidemiologic studies that exposure of the male or female parent prior to conception can also have effects which show up in the offspring of the child and those are very different kinds of effects, although the end result might be quite similar, as we discussed above.

In addition, we haven't talked about chloracne, which is a very characteristic reaction of dermal cells to exposure to 2,3,7,8 TCDD and indeed was one of the earlier effects described under conditions of very high dose exposure in the occupational setting primarily.

Q That would be relating to a high dose exposure, chloracne?

A The human evidence certainly suggests that it takes a rather high acute dose of 2,3,7,8 TCDD to produce chloracne. It is not a reliable indicator of exposure and certainly not an indicator of low exposure or chronic exposure.

Q You mentioned these other reproductive effects. Have you explained that reproductive effect so that we understand it now, Doctor?

A Well, there appeared to be effects -- there are effects which have been reported in animals primarily on the

cells which are involved in reproduction, which is the sperm of the male and the oocyte or egg cells of the female, and these effects occur before reproduction occurs, before the male and female get together and produce a child, and depending on the dose and the timing of these effects they can indeed be expressed as damage in the child. Now with the woman, with the female this is particularly important, because women are born into the world with all the egg cells they are going to have. We don't turn them over and make new ones.

Q They're there all the time?

A They're there from birth. That's it.

Q The total supply?

A The total supply is there from birth.

Q One a month -- one a month until menopause?

A That's it.

Q It's all there?

A It's all there.

Q All right. Go ahead.

A So anything that happens to that population of egg cells from birth onward is going to be with the woman for her life, and if that damaged egg cell is ovulated and fertilized by a sperm, then that damage will be expressed in her children.

Now with the male, the male is constantly producing new sperm in a cycle of somewhere under a month in the human

male, but the male is also born into this world with the machinery that makes sperm and that isn't renewed, and so damage to those cells which has been shown to occur in animals with 2,3,7,8 TCDD is also kind of a permanent reproductive effect on the male.

Q Dr. Silbergeld, does this damage now to the egg cells in the female, are you talking about the female in all kinds of animals, including the human?

A Yes.

Q And has it been demonstrated in these animal studies and others that 2,3,7,8 TCDD can and does damage these egg cells?

A That's indeed the subject of my own research.

Q What did you do to -- could you explain please how you discovered that or found that or demonstrated that effect in your research? What did you do?

A We took animals, mice in this case, and treated them once with a single dose of 2,3,7,8 TCDD. We purposely chose very, very low doses of 2,3,7,8, because we didn't want to cause an awful lot of toxic effect in the animal and that's hard to do with this chemical, but we weren't trying to find the lowest possible dose, because, as I mentioned, we're interested in studying how these effects occur, so we took a range of doses where we knew something was going to happen to

reproduction in the female and we went over a range of those doses to explore what that might be. What we found was that for many weeks after this single exposure in these mice there is an alteration, a pathological alteration in the cells of the ovary of these animals.

Q How did you demonstrate that? What did you do to find that?

A We removed the ovaries from the animal and we did two things. We measured -- three things -- we measured the state of metabolism in the ovaries, we measured levels of hormones in the ovaries and then we actually took some ovaries and prepared them for pathology; that is, we put them in a preserving solution, made microscopic slides from these glands and then looked at the cells under a microscope.

Q And you could see with your own eye under the microscope that those cells were changed by 2,3,7,8?

A That's right.

Q Now why do you believe, Dr. Silbergeld, as obviously you do, that that which has occurred that you demonstrated occurring in this mouse will occur to human beings exposed to 2,3,7,8 TCDD?

A Well there's a tremendous amount of work in basic sciences and clincal, that is, medical sciences showing how various parameters in the mouse ovary are very similar and can

be used to predict what will happen in the human ovary.

Q Is this something that you have concluded by yourself or is this something that is an accepted scientific fact by the science community?

A As far as I know, it's an accepted scientific fact. That's why in the laboratory of reproductive toxicology at NIH we use mice. I don't know of anyone who is suggesting that there is no relationship between what happens in the mammalian reproduction in the mouse and rat and what happens in humans.

Q Well, the animal in fact, the rat, the mouse, the hamster is in fact not a human being. Why do you all conclude that doing something to that rat or that mouse is equivalent to doing something to the human being?

A Because of a large body of physiology and biochemistry which have studied in great detail the anatomy, biochemistry and functions of the reproductive system in these animals and the reproductive system in humans. Also, of course, we are not going to experiment on human beings.

Q Does the FDA require that with any drugs, new drug that comes on the market, that its safety is first demonstrated with certain animal models before they even allow it to be tried out on human beings?

A That's right.

Q And is the fact that our government requires that, is this done in other countries throughout the world as well, that is, the animal is first triad out to see whether it's safe in the animal before it's allowed in human beings?

A That's right.

Q Is that an accepted, long time accepted scientific method of discovering or demonstrating the safety or on the other hand, the unsafety, the dangerousness of drugs, chemicals and materials?

A Yes, it is.

Q Where would we be in the area of demonstrating safe drugs and manufacturing safe drugs without animals to use for this purpose? How could we do it otherwise?

A Well, I think the other point we would be nowhere obviously, but also it's important to remember, as much of my research in pharmacology was based, that we use animals to find the good properties of chemicals, too. When we're trying to develop a new drug to treat a dread disease, even cancer, we use animals so we use them for good purposes as well as toxicology testing.

Q Doctor, I had some charts made earlier. I'd like to have you explain some of them, if you will. Now, Doctor, the first one I have here --

MR. CARR: Maybe we better put a mark on it.

(At this time Plaintiffs' Exhibit 232 was marked for identification.)

Q Handing you -- pushing at you what's been marked Plaintiffs' Exhibit No. 232 and putting it on the chart, if you would -- can you see that, Doctor?

A I can.

Q All right. Would you tell us what that chart is and what it purports to demonstrate.

A This is a chart taken from the work of a colleague of mine, Dr. Howard Eisen, who's at NIH, and it's looking at the relative ability of a range of chemicals, including chemicals that are normally in the body like bilirubin and cholesterol through some common drugs like phenobarbital, progesterone through DDT, and insecticides, through some very well characterized carcinogens like benzo(a)pyrene and 3-Methyl-cholenthrene and then the Dioxin, including TCDD, by which he means 2,3,7,8 TCDD for their ability to bind to a receptor molecule in cells. Now if I might have a chart, perhaps I could explain what this has to do with the toxicity of Dioxin.

Q What, this chart on toxicities, you mean?

A Yes. Do you have something perhaps to draw on?

Q Oh, sure.

MR. CARR: We got some blank sheets left in your pad?

MR. HEINEMAN: Sure.

MR. CARR: May we use them?

MR. HEINEMAN: Help yourself.

A What this chart is about, looking at something which has been called the Dioxin receptor, which we now know exists in a variety of cells, including human cells, and is probably why TCDD, 2,3,7,8 TCDD is so extraordinarily powerful and so toxic, because a very real question to scientists who have been studying this chemical is why something that was made at the earliest in 1889 could possibly be so powerful an agent in so many different animals --

MR. CARR: We're going to have to move this up here, I'm sure. (Pause) We have some magic markers in here.

(Short discussion off the record.)

MR. HEINEMAN: Mr. Carr, do you happen to have a small sheet of that so we can make a copy of it.

MR. CARR: Small what?

MR. HEINEMAN: I mean this big chart. Do you have a small sheet?

MR. CARR: No, not me. I'm sure it's available.

MR. HEINEMAN: Is it published somewhere?

MS. WITNESS: Yes. It's published in a paper by Dr. Eisen. I think it's in the Journal of Biological Chemistry, 1983, but if one were to go to Index Medicus under Eisen you would find it.

A Now what this is about is really getting at why this material can possibly be so toxic, particularly something so recent. It's not like diptheria toxin or other poisons which have been around for so long and that is that we now know that within many cells -- this is a cell and here's its membrane, which contains lipids and other materials, that within many cells there is a molecule which is normally made by the body. This is a biological molecule which appears to be able to recognize TCDD with extraordinary ability.

If you think about the system as a kind of lock and key system, the receptor is a lock and it opens some doors which are very important in biology and in cells. Now there are keys that fit this lock more or less well, and sometimes you can take a key that doesn't fit quite that well and jiggle it around a little and get the lock to open. That's what you see up here when you see, oh, this 2,3 dichloro-dibenzo-dioxin has some activity with this receptor. That's kind of like saying it's a roughly shaped key which can enter the lock and if you wiggle it around biologically speaking you get the lock to open a little bit. But clearly the substance which opens, fits this lock the best is TCDD. In fact it fits it so well that this molecule is known to scientists as the Dioxin receptor. That's the name that's been given it because of the key that fits it the best of

of everything we know. Now what happens --

Q Is that the reason that you've got four pluses --

A That's right.

Q -- across from TCDD, because that is the best in fitting this lock, so to speak?

A That's right.

Q Of all these substances?

A Of all these substances it is the best, and that's why it got this name.

Q And is the fact that it is the best has that -- has that got a direct relationship to the fact that it can do all these things that you've been testifying to that it can do is that the key, so to speak, to its potency in this area?

A In terms of the molecular toxicology, that is, when one molecule is speaking to another this is what scientists think lies behind the extraordinary power and danger of TCDD. TCDD comes into the body, and it goes into cells pretty easily. It is lipid soluble, it can be dissolved in fat, and biological membranes are made largely out of fat so the membranes can't stop it from coming across.

Q The TCDD actually dissolves the membranes then?

A No, the membranes dissolve the TCDD, if you will, as a fat barrier. If you think of a cell as a cup of water and there are some magic tricks in kid's chemistry sets where

you can do this. You put a layer of water here, you put a layer of oil here and you put another layer of water. Sometimes they're different colors and kids generally like that a lot. This is what a cell is like. Here's the water and blood on the outside of the cell, here's the cell membrane, and here's the inside of the cell. Now something that is only dissolved in water can't get across. It sits up here in this water layer, but it can't get into the fat layer and oil layer into this bottom layer. That's exactly what the cell is like. But if you have a substance like TCDD and a wide range of materials which are called lipid soluble, they can move from water through the fatty layer. As a matter of fact, they like to be in fat better than water -- into this lower water layer or in biological terms from the outside water or the blood or water around cells through the cell wall inside the cell.

Now once inside that's where this receptor comes into play. It, as I said, recognizes Dioxin, TCDD Dioxin better than anything else we know of in the world, and so it binds it up. The lock goes -- the key goes right into the lock. Then this lock and key complex moves into the nucleus of the cell and when it's in the nucleus of the cell it associates itself with part of the nucleus known as chromatin, which is that part of the nucleus where DNA and RNA and all

the genetic machinery controls what the cell is doing is located. Now once it gets into this level -- we now got it from outside the cell through the cell wall, bound to its receptor moving into the nucleus of the cell. This is where it really starts to cause its destruction of cellular processes. One of the things that the genetic machinery of a cell does is maintain all those metabolic processes we talked about. It keeps them going at the right level, it makes new proteins as we need them, it makes new enzymes as we need them, it even repairs the membrane of the cell as we need it, and this whole process is directed by DNA through a series of steps through RNA -- these are all part of the genetic materials of the cell -- and then RNA sends the message to turn on protein synthesis, to activate certain parts of metabolism. Now what this Dioxin receptor locking key complex, which has gone into the nucleus does, is that it intervenes in this program and it changes the message. It doesn't intervene, as far as we know, directly changing DNA, but what it does --

Q DNA means a genetic material?

A That's the hereditary code.

Q Tells other cells what to do?

A No, it's the part of the cell, the genetic material which is reproduced when the cell divides but DNA, if you

will, doesn't talk directly to metabolism. DNA, if you will, has to make a telephone call to RNA, and then RNA makes a telephone call down to various parts of the cell which actually make proteins or engage in other parts of metabolism.

So using that analogy, what the Dioxin receptor complex does is gets on that telephone line -- DNA has called up RNA and said, would you please make a certain amount of this enzyme, AHH we've been talking about, but Dioxin receptor gets on the line and says, don't listen to that message. I'm going to give you a modification of the message. Don't make ten units of AHH, make ten thousand, and what happens is you get an overriding of this message and that is indeed what goes on, what we call enzyme induction.

Now this is a very, very sensitive, fine tuned process and what makes it so sensitive and so fine tuned is actually the structure of this receptor and it's been what I call structure activities studies where people have taken the basic Dioxin molecule, which looks like this, and they put things on various parts of it and seen what that does to this whole system. It's a lot of the work of Poland, of Eisen, of Nebert and others. That's where they found that when you put things here, particularly if you put chlorine there it fits the best.

Now obviously this receptor wasn't put in cells in

1890 when Dioxin was first made. It's been in cells for a long time and we can show it in the cells of a variety of life forms so we can show a kind of evolutionary presence, so it doesn't just sit there in order to do something nasty when we get exposed to Dioxin. Clearly there's something which is inside our bodies, we don't know what it is yet, which normally does this regulating. There's a reason for it. We want this enzyme system to turn on and off. As I mentioned, one of the things this enzyme system does is metabolize sex hormones. Now sex hormones rise and fall in the body over a course of a day or a month. There are great increases and decreases in the amount of sex hormones that are produced. You want more or less AHH activity to take care of these peaks and valleys so it's a metabolic system you want to have some control over, and the way in which we have control over it is through this receptor. Now there must be something in the body which normally does this kind of switching routine, binding to the receptor, going into the nucleus, getting on the line with the RNA message and changing it. We haven't identified that yet, and that is an area of great research. Now it is probably very unfortunate for us as a species that we managed to synthesize something by mistake which is so powerful at mimicking the normal key that fits into this lock.

Q What you're saying, if I understand you correctly,

Doctor, is that we haven't yet been able to discover the combination to this lock ourselves, but TCDD has?

A That's right. It is a key that we've put into the body. There's obviously another key which was always there in our body. Now there are many examples. For example, about ten years ago scientists at John Hopkins and elsewhere found a similar kind of thing, a receptor which was the lock for morphine and heroin. They called it the morphine receptor. Now obviously our bodies didn't make this receptor just to take care of morphine and heroin. You can find it in people who's never had morphine or heroin, so it served some type of normal purpose, which as you might expect, had a lot to do with responses to pain. Morphine and heroin are pain killers. It took about three more years until people isolated the substance in the body which acted with those receptors normally in the absence of morphine and heroin, and those are actually called morphinoid neurotransmitters or the brain's own opiates in honor of morphine or opium, and they are structurally very similar, and that's kind of a clue that scientists used in order to find the substances that are normally there, and people are using this receptor, which they've now purified, to find what this "X" substance might be which is normally in the body, but clearly the best tool for studying this receptor and its role that we now have is Dioxin.

Q Now, Doctor, I notice on this chart, the exhibit number I forget -- that there's another Dioxin that's got three pluses or doesn't have four as TCDD does. It's 1,2,3,4,7,8. That would be -- Dioxin is tetra -- oh, here it is.

A It has six chlorines.

Q Six chlorines?

A Right.

Q That is a Dioxin, but it's not one of the 22 --

A Tetras.

Q Tetra-dioxin, but is another form of Dioxin?

A Right, and you'll notice --

Q Is that present in these trichlorophenols or do you know?

A I'm not sure. It has been measured in some chlorinated phenol manufacture, particularly pantachlorophenol. You'll notice again it has those chlorines in the bad places, 2,3, and 7, which is probably why it's so active and yet when you get to oxtachloro, which is chlorines at every possible place, the molecule is now much too highly charged and it won't go inside this lock.

Q So octa meaning eight, so if you have a chlorine molecule at all eight positions that it's possible to have one, it becomes inert and has no potency whatsoever as an inducer,

as a key to this lock, is that correct?

A That's right.

Q But the hexachlorodibenzo-p-dioxin that has some ability -- well, right directly below the ability of TCDD so to act, is that correct?

A That's right.

Q Now --

A And also, in addition, some other very potent carcinogens like benzo(a)pyrene and Methylcholenthrene has some ability to act with this -- with this lock as well.

Q Doctor, I have another -- is there anything else on that chart or on the drawing that you want to explain, Doctor?

A Well, I think the other thing to emphasize is that kind of effect has been demonstrated in many species and indeed cells taken from human beings have been run in these kinds of experiments.

MR. CARR: Would you put a number on that one please.

(At this time the exhibit was marked for identification.)

Q Doctor, the other exhibit you mentioned where it came from. I think it was No. 232. That is published and one can get to that by going to this Index Medicus that you

mentioned, is that correct?

A That's right.

Q All right. And Eisen, he's a recognized authority in this particular field?

A He is.

Q Is what he discovered as to the ability of TCDD, that TCDD is the very best key to this lock that there is, has that been published and well known and is that disputed by anybody that you know of?

A No. It was first suggested by Dr. Poland in the -- about 1974 or '75 and what Dr. Eisen's work is a building upon and further refinement and really a very fine statement about current knowledge of this system and what it means.

Q Now, Doctor, Exhibit 233, I think it is, is that correct -- is another chart that has Dr. Eisen's name appended to it. Could you tell us please what that chart is and what it purports to show?

A Okay.

Q You can't see that, can you? Can you see that all right?

A This is an attempt by Dr. Eisen to take these events we've just been talking about and put them into a whole cell system and try to explain what this means for the whole organism, why should these kind of molecular events be associ-

ated with cancer or with suppression of the immune system? So what he's done is to take a great deal of biochemical and biological literature and integrate it together and show why exposure to these polycyclic compounds with 2,3,7,8 TCDD being the most powerful of all of them, interacting with this receptor which we just talked about, the Dioxin receptor activating genetic controlled protein synthesis we just talked about and inducing all these different substances including some of these enzymes, why this would then be connected with changes in the membrane of the cell which might well have a lot to do with the promotion of cancer and with problems in the immune system, because immune cells work by recognizing things outside them and taking care of them through recognition sites on the membranes, so anything that's going to change the membrane surface will have some very serious effect for cancer promotion and for immunosuppression.

Q Doctor, let's start up here at the beginning with these polycyclic aromatic compounds which you have previously described as being those halogenated hydrocarbons.

A Right.

Q Of which 2,3,7,8 TCDD is a contaminant?

A It is one of those compounds.

Q All right.

A Yes.

Q And the large black arrow aimed to the cytosolic Ah receptor -- is that -- is that Ah, is that the enzyme that you've just -- that we just discussed?

A That is the Dioxin receptor. It's given this name, Ah, because of some very elegant studies now showing where it's located on the --

Q You've just shown us about this receptor and how TCDD induces --

A Right.

Q -- the best. All right. It goes -- then it goes to this receptor and then it goes to the activation of structural genes. Is that also what you've just had on that little drawing of the RNA and the DNA?

A That's right. It interferes in that communication.

Q And that's shown here?

A That's this right here.

Q When it says activation, that in effect is saying it's coming in on that party line on that telephone and giving a different message? That's what's in this chart?

A Right.

Q Now there are -- there's one, two, three, four arrows going from -- after the genes have been activated it goes over to this one that says UDPG -- well, what does that mean?

A What this means is that talking through this ganetic system the Dioxin receptor complex leads to an increase in the activity of these enzymes.

Q And these UDPG transferase, ODC, DT-diaphorase are all names of enzymes?

A That's right.

Q All right.

A It leads to an increase in the level of alpha-fetoprotein.

Q And that is a protein?

A That is a protein that's specifically frequent -- commonly associated with periods of fetal development.

Q And when you say fetal development, you mean when the baby is growing in your abdomen?

A In the womb, yes.

Q Womb, thank you. Well, I've got lots of kids, five. I knew that word. All right. Anyway, when the child is growing in the mommy's tummy. That's the way I've known it for years -- it's receiving protein?

A No, it is making a very special protein, alpha-fetoprotein, but it's since been discovered that that's not the only source of this protein, and one of the things that Dioxin does is to cause an abnormal amount of this protein to be produced.

Q There's a question mark -- at least that looks like a question mark. What does that mean?

A It means that the evidence is so far limited to one species in which it's been studied.

Q All right. And the significance of this is that Dioxin has an effect upon this fetoprotein, is that correct?

A That's right. It increases levels of it.

Q All right. And does that have an adverse effect upon the fetus, on the baby?

A No one knows.

Q You don't know that?

A We don't know that. High levels of alpha-fetoprotein in pregnant women are associated with certain types of birth defects, but we don't know, because it hasn't been measured in that setting as to whether this kind of effect would have an implication for adverse effect on the fetus.

Q All right. It may have an effect, but as to what the extent is at this stage is unknown?

A That's right.

Q All right. Now the arrow aiming down here to aldehyde dehydrogenase, Y-glutam -- that's not a Y, that's Greek.

A Gamma.

Q Gamma-glutamyltranspeptidase, choline kinase --

you mentioned choline the other day, didn't you? Ethanolamine kinase, phospholipase. What are all these?

A Those are other enzymes.

Q Enzymes just like this business up at the top?

A That's right.

Q All right. Other names of other enzymes that do other things?

A That's right.

Q And what is -- it indicates by the arrow that TCDD, having given a false message to the genes, that message is then being passed on in the creation or induction of these abnormal amounts of these enzymes, is that correct?

A That's right. The false message that the Dioxin receptor complex is giving is make a lot of these enzymes and this protein, and that's not a message that the cell was giving, it's not something that was normally being called for, but it's an intervention and a false message being inserted by Dioxin.

Q All right. And do we know -- does science know the effect of this manufacturing of excessive amounts of these enzymes?

A There are some thoughts about some of them, but no one has yet -- as I said, no one's really taken these observations and put them together with the toxic effects of Dioxin

to see whether these might explain anything.

Q All right. We know the toxic effects, they've been discovered, we just haven't demonstrated whether the toxic effect is caused by this enzyme, this enzyme, this enzyme, or perhaps some other vehicle altogether?

A That's right.

Q Is that correct?

A That's right.

Q Now there's another arrow going from the activation of these genes I suppose indicating another false message to multiple forms of induced P-450. What is that?

A This is those AHH or mono-oxygenase enzymes we were talking about earlier. They're sometimes known as P-450 because you measure them in an instrument which reads when set at 450, an old fashioned name for this set of enzymes.

Q These are still enzymes then that we're talking about?

A That's right.

Q And do we know the effect of that -- there's a kind of a circular arrow going there to reactive intermediates and also an arrow coming directly from the arrow -- the polycyclic compounds to this reactive intermediates.

A That's right.

Q What does that mean?

A Well, Dr. Eisen is trying to explain why Dioxin and

other chemicals are complete carcinogens, that is, administration or exposure only to Dioxin is enough to cause cancer. And what he's showing here is that when this enzyme system is induced, one of the things it does is go back and take the Dioxin itself, metabolize it, and one of the products of that metabolism of Dioxin is a new molecule which is very reactive, that is, it can interact with DNA, with other parts of the genetic code of the cell and cause initiation, that first stage of the carcinogenic process.

Q All right. So this demonstrates that these intermediates that initiate cancer and the toxicity can come through the false message process indicated by the activation of the genes or can come directly from the Dioxin itself, is that correct?

A That's right. Moreover, it says -- this again I think helps to explain why Dioxin is so toxic. Dioxin enhances its own toxicity.

Q Well, you got me there.

A Dioxin directly has this range of effect which are toxic, but then a metabolite, a conversion product of Dioxin is also toxic and adminstration of Dioxin increases the speed at which Dioxin is made into this toxic metabolite. It's a very vicious biochemical system.

Q I guess I understand that. It not only is toxic

itself but it creates something that helps it be more toxic? Is that what you're saying?

A One of the effects that it has directly --

Q Is that what you're saying, cause I can understand that.

A Let me see if I can say it also. One of the effects of Dioxin, direct effects of Dioxin acting as Dioxin is to change itself into something even worse.

Q Change itself into something worse?

A That is, it enhances its own metabolism. One of the metabolic products, perhaps more than one, is highly reactive as shown here by Dr. Eisen. Those compounds, unlike Dioxin, can initiate cancer.

Q Okay. That which it creates by itself is more toxic than it is and can then initiate or cause cancer?

A That's right.

Q Now there is another arrow with a question mark that Dr. Eisen has put in here down to a double arrow pointing over to the -- to the enzymes that we discussed and pointing over to the cell main -- membrane surface receptor at or near EGF receptor site. What does that mean, Doctor?

A Well, what Dr. Eisen is trying to do in this whole part of this chart is to understand why Dioxin is the most potent promoter we know about. He's dealt with how it initiates,

its first stage carcinogen. He's now trying to explain on the basis of what we know about it why it's so potent at promoting second stage carcinogen and to do that he's hypothesized, and the question marks mean that this really is a hypothesis --

Q Well, it's a theory and not proven fact --

A That's right.

Q Not demonstrated in the laboratory.

A There's no disagreement that this Dioxin causes this. What we don't know is how you get from here to there.

Q All right.

A That's, of course, a main area of Dr. Eisen's research. What he's hypothesizing is that one of these metabolic products that Dioxin has caused to form itself because it enhances its own metabolism has an interaction on the membrane of the cell now EGF is epidermal growth factor and there's a great deal of research in cancer biology right now that suggests that this is what's involved in promotion and that's why Dr. Eisen thinks that that might be how this is acting. It causes the surface of the cell to proliferate, that's hyperplasia, to grow abnormally --

Q Hyperplasia means great growth?

A Abnormally great growth.

Q All right.

A That --

Q Epidermal means skin?

A Or surface. In this case it's surface of the cell, skin of the cell, if you will. It doesn't mean literally the skin of the animal or the skin of the human, but that effect is in fact promotion. In addition, if these surface receptors are on T-cells, the cells that are in the immune system, then that could lead to immunosuppression and then promotion of cancer or viral cancer or other kinds of cancer which the immune system usually takes care of.

Q But since it can't take care of it --

A That's right.

Q -- the cancer is allowed to grow?

A That's right.

Q Anything else on that, Doctor?

A Well, there's another very interesting part which Eisen didn't indicate here, but which is an area I am very interested in and others, Dr. Weinberg at MIT and others, and that is whether this effect might have something to do with cancer. It's been shown recently that the genetic material in many of our cells, whether or not we have cancer, contains parts which actually cause cancer. Fortunately, most of the time these aren't active and our cells go on as if those parts of the genetic code aren't there. Those are called oncogenes or cancer genes, and a great deal of recent,

very important discoveries have shown that when you have cancer what happens is the genetic structure doesn't change but suddenly the cell begins to read that part of the gene that it skipped over before. It's as if you had a sentence and then a word that was nonsense. You read it and said, okay, I'll go on, but in the process of cancer you read this word, you read the nonsense word, then you go on. Unfortunately, if you're a cell, reading that nonsense word means let's proliferate and become a cancer, and what Weinberg and others have shown is some chemicals which don't alter the genes, not really altering the genes, because that stuff was always there, that gobbledygook word, but some chemicals cause the cell to read that oncogene and become active.

Q And thus activate it?

A My current area of research is to look at whether Dioxin can do that. Many of these or several of these polycyclic compounds do indeed do that. They activate oncogenes.

Q But you haven't yet completed your research in order to say yes or no --

A No.

Q -- as to that situation?

A And that could be a very powerful initiation step, and then since Dioxin is also a promoter that might explain

why it by itself is such a powerful carcinogen.

Q What you're looking for is not does it cause it but why, to explain why it causes it, is that correct?

A That's right. There's no doubt in anybody's mind that cancer, cancer is an end result of Dioxin exposure. What makes Dioxin interesting for toxicologists and biologists to study is not to show that it's carcinogenic. Nobody doubts that, but to show how it does that and perhaps to gain some understanding about other compounds, other cancers as a result of this unique tool we have to study.

Q Anything else on this, Doctor?

MR. CARR: Does the Court want to continue working today?

THE COURT: Gentlemen, could I see you at the bench for a second?

(A short conference was had at the bench off the record.)

THE COURT: Okay. Ladies and gentlemen, since this is a convenient point in the testimony, we'll break the proceedings for today. We will resume at 9:30 tomorrow morning, at which time I'd like you to be here so we can resume testimony in this cause. I think I had told you before, I'll remind you again now that the testimony in this case will end at noon tomorrow, because tomorrow afternoon, due

to other responsibilities that I have, I have to try a criminal matter and it has to be tried within a certain amount of time, so it has to be tried tomorrow.

MR. CARR: Your Honor, before we recess and before I forget it could we have this marked as an exhibit so I don't forget.

THE COURT: Sure.

MR. CARR: Could you give me a number for it?

THE COURT: What number are we on?

MR. CARR: 234, your Honor.

THE COURT: Anyway, ladies and gentlemen, this criminal matter has to be taken care of. Criminal takes priority over civil so it has to be taken care of and it will be tomorrow and we will stop at noon tomorrow. As usual I admonish you the normal admonishment. You are not to discuss this matter among yourselves, discuss it with anyone outside the jury panel, or form as yet any opinions or conclusions about the matters on trial. I'd further admonish you that you are not to either read, listen to, or watch anything about this trial in particular or the subject matter of this trial in general in either the print or electronic media. Thank you for your attention, your cooperation, your artistic endeavors and the general cooperation you've given us in this trial. Court's adjourned for today.

STATE OF ILLINOIS)
) SS
COUNTY OF ST. CLAIR)

I, MARSHA SCHNIPPER, one of the Official Court Reporters in and for the Twentieth Judicial Circuit of the State of Illinois, and the Official Court Reporter who reported the proceedings had at the hearing of Frances E. Kemmer, et al. vs. Monsanto Company, et al., No. 80-L-970, on the 12th day of April, 1984, do hereby certify that the above and foregoing is a true and correct transcript of the proceedings had at said hearing, which proceedings were reported by me in shorthand and by me correctly transcribed.

Dated this 19th day of April, 1984.

Marsha Schnipper
Official Court Reporter

STATE OF ILLINOIS)
)
TWENTIETH JUDICIAL CIRCUIT) SS
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COUNTY OF ST. CLAIR)

I, RICHARD P. GOLDENHERSH, Circuit Judge in and for the Twentieth Judicial Circuit of the State of Illinois, and the sole presiding Judge in the aforesaid cause on the 12th day of April, 1984, do hereby certify that I have examined the aforesaid transcript of the proceedings and further certify that the same is a true and correct transcript of said proceedings had in said cause.

Dated this 19th day of April, 1984.

CIRCUIT JUDGE