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IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF ILLINOIS

EASTERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, vs. OUTBOARD MARINE CORPORATION, Defendant, Third-Party Plaintiff, and Cross-Claim Defendant, and MONSANTO COMPANY, Defendant, Third-Party Defendant, and Cross-Claim Plaintiff.	)	No. 78 C 1004

DEPOSITION OF THOMAS H. MILBY, M.D., MPH

May 27-28, 1982

Reported by:
ROBERT A. FORTINI
C.S.R. 146

PHONE 982-6008

ROBERT A. FORTINI, C.S.R.
DEPOSITION REPORTER & NOTARY
110 SUTTER STREET
SAN FRANCISCO, CA. 94104

I N D E X

EXHIBITS:

BE IT REMEMBERED that, pursuant to agreement between the parties and pursuant to the Federal Rules of Civil Procedure, and on Thursday, the 27th day of May, 1982, commencing at the hour of 10:00 A.M. thereof, at One Embarcadero Center, San Francisco, California, before me, ROBERT A. FORTINI, a Notary Public in and for the City and County of San Francisco, State of California, there personally appeared

THOMAS H. MILBY, M.D., MPH,

called as a witness herein, and who, being by me first duly sworn, was thereupon examined and interrogated as hereinafter set forth.

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ELIZABETH STEIN, Attorney at Law, U. S. Department of Justice, Land and Natural Resources Division, Tenth and Pennsylvania Avenue, N.W., Washington, D.C. 20530, appeared as counsel on behalf of the plaintiff.

MICHAEL A. POPE, Esq., and RICHARD J. PHELAN, Esq., representing the Law Offices of PHELAN, POPE & JOHN, 30 North LaSalle Street, Chicago, Illinois 60602, and RICHARD J. KISSEL, Esq., representing the Law Offices of MARTIN, CRAIG, CHESTER & SONNENSCHEIN, 115 South LaSalle Street, Chicago, Illinois 60603, appeared as counsel on behalf of the defendant Outboard Marine Corporation.

BRUCE A. FEATHERSTONE, Esq., and JAMES H. SCHNIK, Esq., representing the Law Offices of KIRKLAND & ELLIS, 200 East Randolph Drive, Chicago, Illinois 60601, appeared as counsel on behalf of the defendant Monsanto Company.

Also Present: Hugh B. Thomas, Esq., Associate Counsel and Assistant Secretary, Outboard Marine Corporation, Waukegan, Illinois.

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MS. STEIN: Before we begin, I would like to go on the record and summarize the conversation that we had when we were off the record, among counsel.

I indicated to the other parties' counsel that there were a number of documents that were identified in a letter from Mr. Hynes, dated May 19, 1982, and that a number of those documents counsel for the government has not been able to obtain prior to the deposition and that as a result, with respect to those items, we would like to leave the deposition open and I will identify for the record the specific items that we have been unable to obtain.

One is item 6, the Alexander Smith article, dated 11/81, concerning Metabolic and Health Consequences of PCBs, apparently discussed in Dr. Kimbrough's deposition.

I am not clear as to how that could be since it was after the date of her deposition.

Item 11, Articles recently published concerning Yusho.

I understand that was requested during Mr. Hynes's conversation with Ms. Oliver.

In the package that I received those were not included.

Item 16, an article dated 2/79 by Kodama on the transfer of PCB's to infants from mothers.

Item 14, comments submitted by the CMA to USEPA in response to two advance notices on rulemaking on PCBs.

Item 5, CMA report dated 1/19/82 concerning health effects of PCBs.

MR. POPE: There are two reports mentioned. Do you have the other one?

MS. STEIN: I do have the other one.

Item 19, PCB Contamination in Mothers's Milk in Michigan, by Thomas Wichizer, 4/20/80.

MR. POPE: Are you through?

MS. STEIN: Yes.

MR. POPE: Why not submit the letter as an exhibit, and then allow me to make a comment?

MS. STEIN: Why don't we just go ahead and --

MR. POPE: Unless we are in agreement -- well, let's mark this.

(Copy of Letter addressed to Roseann Oliver, dated May 19, 1982, marked as Exhibit No. 1.)

MR. POPE: Ms. Stein, in response to your statement, we have marked as an exhibit, Exhibit No. 1 in this deposition, a letter from Mr. Hynes to Roseann Oliver, dated May 19, 1982.

It appears clearly from the letter that Mr. Hynes made requests for five aspects of those 20 items listed in his letter, four of those requested items were provided to Mr. Hynes I believe the same day in accordance with his request and Ms. Oliver advised him that as to No. 11, which is referred to as "Articles Recently Published Concerning Yusho," she did not have such documents in her possession, she could not provide them to him, and in addition to that, it's a generic term, there are tons of articles on Yusho, as you very well know.

It is our position that we have provided you with

far more than the Court has ever required us to do. Many of the materials that you are asking for, and referred to here, are not materials that we provided to Dr. Milby, but rather materials that he comes in contact with and has used as a part of his practice in the public health field, and it would be absolutely absurd for you to think that we could come up here and provide you with every document that a practicing physician and toxicologist and epidemiologist is going to rely on in part of his testimony when he is practicing in the field and is on top of the current literature.

So, what you are requesting is totally beyond me; but you made a request on May 29th, we complied with it, and at no time has there been any indication that you were not prepared to proceed with this deposition. We certainly could have rescheduled this deposition if Mr. Hynes on May 19th said he wasn't ready to go or that you were not ready to go, we all have problems with our deposition schedules, we are about as busy as you are, and for you to suggest that there has been less than full compliance or if you think that there is any reason in the world for you not to proceed with this deposition to conclusion is absolutely wrong, and we have no agreement to that effect, and I think the deposition should proceed and you should ask whatever questions you want of Dr. Milby and we should conclude the matter.

MS. STEIN: I will go forward as best I can under the circumstances, and the government does not agree with Mr. Pope's statement regarding compliance with the Court's order. The answer to the expert interrogatory, which in our

opinion was insufficient, was not provided until May 18th which was five days after the date on which it was due, and I recognize that Mr. Hynes asked for certain articles, he did that, I apologize if there was any mix-up, but there were certain items on there that I was unable to obtain, and I will do the best I can to proceed to conclusion, but I am not waiving our right, if the Court is so inclined, to reconvene if it is necessary.

MR. POPE: If so, we will ask for sanctions.

In addition, the record should reflect that Mr. Hynes and Mr. Phelan had a discussion wherein Mr. Hynes asked for a little further definition as to what Dr. Milby was going to testify to and we wrote the government a letter, hand delivered on May 18, that said that Dr. Milby will testify that PCB poses a relatively small risk to human health, imposes no serious or imminent health hazard to humans, and we previously advised you of the reports that we provided to Dr. Milby for his review, and you made two informal efforts to acquire additional information, properly so I suspect under the Federal Rules, and you at no time indicated until this morning that you were not prepared to proceed with the deposition and --

MS. STEIN: I did so indicate to Ms. Oliver yesterday, and I asked Mr. Hynes to call Mr. Phelan yesterday and so inform Mr. Phelan.

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EXAMINATION BY MS. STEIN

MS. STEIN: Q. Would you please state your full

1958 and 1959.

Q. Did you specialize during that residency?

A. I specialized in occupational medicine.

Q. Will you tell me what occupational medicine is?

A. Occupational medicine is a specialty which is principally concerned with the diseases of the workplace.

Q. Doctor, are you a member of any professional societies?

A. Yes.

Q. What are those?

A. I am a Fellow of the Academy of Occupational Medicine, a Fellow of the American Occupational Medical Society, a member of the New York Academy of Sciences.

Q. Are there any certification or membership requirements to become a Fellow of the Academy of Occupational Medicine?

A. It requires Board certification in occupational medicine.

Q. Are there any membership or certification requirements to become a Fellow of the American Occupational Medical Association?

A. It requires only interest in the practice of occupational medicine, no certification is required.

Q. And are there any membership or certification requirements to become a member of the New York Academy of Sciences?

A. No.

MS. STEIN: Let's mark this as Exhibit No. 2.

(Curriculum Vitae of Thomas H. Milby, M.D., marked as Exhibit No. 2.)

MS. STEIN: Doctor, I am going to show you a document that has been marked as Milby Deposition Exhibit 2 and ask you if you can identify that document?

A. Yes, that is my curriculum vitae, current.

Q. On page 2, under the heading Other Professional Activities, the first item is Adjunct Associate Professor of Occupational Health, University of California, Berkeley, California.

Can you tell me what it is that you teach in that capacity?

A. Yes, I have been an Adjunct Associate Professor at the University of California at Berkeley for approximately ten years.

I teach medical toxicology and epidemiology and occupational medicine practice.

Q. Are those all in one course or are they separate courses?

A. Over the years they have been generally in a single course.

Q. What is the difference between occupational medicine, toxicology, and epidemiology? I want you to define each one.

A. Epidemiology is the study of the distribution and determinates of diseases and populations.

Toxicology is broadly defined as the study of the health effects of toxic substances.

Occupational medicine is a Board certification requiring practice of occupational medicine and specialty training.

Q. Could you generally outline for me the substance of these courses that you have taught over the years?

A. Yes. Because occupational medicine as it is practiced by many in the field, including myself, involves to a large extent the understanding of the epidemiology of occupational diseases, I emphasize that subject in my classes, and have at one time or another devoted my entire teaching experience during a given year to teaching occupational disease and epidemiology, it's an important part of the practice of occupational medicine.

Toxicology as I have taught it is principally concerned with the effect of toxins found in the workplace upon the health of the worker.

Q. Have you taught courses involving epidemiology, other than in the context of occupational diseases?

A. Epidemiology as it is practiced in many phases of occupational medicine also includes the environment, and so I teach the epidemiology of environmental diseases, as well.

Q. How would you define environmental diseases?

A. Environmental diseases as I would define it are diseases in which the principal toxic agent is one which is distributed in the general environment as opposed to strictly the occupational situation.

Q. Have you taught toxicology other than in the context of toxicology in the workplace and its effect on the -- well,

toxins found in the workplace and the effect on the health of workers?

A. With the exception of toxicology of environmental problems, no, I have not taught toxicology in its other context which is laboratory, or experimental animal toxicology.

Q. Would you consider toxicology in terms of being the effect of toxins found in the workplace on the health of the worker as a subset of environmental toxicology, or toxicology of environmental problems?

A. In actual fact, it's the other way around, environmental problems are a subset of what one sees in the occupation, for the most part.

Q. Why is that?

A. Because in general, substances which find their way into the environment and cause concern, have already been identified in the workplace as problems.

This is usually the case.

Q. What exceptions are there?

MR. POPE: Exceptions?

MS. STEIN: Yes, that's correct.

THE WITNESS: Offhand, I can't think of any.

MS. STEIN: Q. Is your definition that environmental problems, toxicology of environmental problems are a subset of occupational toxicology, is that a generally-accepted view among toxicologists?

A. I think so, yes.

Q. The second item listed under Other Professional Activities on your curriculum vitae is Department Editor,

Clinical Case Reports, Journal of Occupational Medicine.

Can you describe what work you engage in in that capacity?

A. In that capacity, which is no longer current, I am no longer the clinical case editor. For a number of years I was editor of case reports for the Journal of Occupational Medicine, which is essentially the house organ for the American Academy of Occupational Medicine, and in that capacity it was my job to review articles that were submitted for publication which fell under the category of case reports.

Q. What was the nature of your review that you conducted of these articles?

A. Primarily to see whether they were adequate for publication in the Journal of Occupational Medicine.

Q. What were the criteria that you used in evaluating the articles that were submitted?

A. Whether in my opinion they were timely, were they accurate, properly described, reasonably interpreted.

Q. What are the criteria that you used in determining whether or not the study properly described whatever the event was that it discussed?

A. I had no specific criteria, it was simply whether based on my experience and whether in my opinion they were indeed reliable.

Q. What were the criteria that you used in ascertaining whether or not the reports submitted reasonably interpreted the data?

A. That was a matter of my experience.

Q. How long did you serve as the Department Editor, Clinical Case Reports, Journal of Occupational Medicine?

A. Probably seven or eight years.

Q. What were those years?

A. I think that 1973 or 1974 was my last year, so sometime prior to that I started, five or six or seven years before that.

Q. Did you ever send any of the articles that were submitted to you to anyone else for any kind of evaluation?

A. I am sure I did, I don't remember specifically, but that was often required, or necessary, to have another opinion, yes.

Q. And what would be the circumstances in which that would be necessary or required?

A. It would be generally necessary if I felt that in my experience I was unable to provide an evaluation of it because I had had no experience in that particular area.

Q. At the time that you were the Department Editor what were the areas in which you had not had experience?

A. I don't remember.

Q. Were there any other reasons why a second opinion might have been sought with respect to articles that were submitted to the Journal of Occupational Medicine at the time that you were the Department Editor of Clinical Case Reports?

MR. POPE: Are you asking for specific instances, or were there any other possibilities?

MS. STEIN: Any other possibilities?

MR. POPE: It's a very subjective question and I

object to the form of the question.

MS. STEIN: You may answer. I am not asking for specific instances, I am only asking for circumstances.

THE WITNESS: Not that I can recall.

MS. STEIN: Q. Was there any kind of policy or guidance in the Journal of Occupational Medicine indicating circumstances where a second opinion might or might not be required?

A. There was no policy. The way it operated was that if the editor asked me to seek a second opinion I would do that. That probably happened periodically.

Q. Did you review them and then submit them to the editor who then gave you the feedback? Is that the way it was done?

A. Yes.

Q. The third item listed under Other Professional Activities is Member, Secretary of Health, Education, and Welfare's Commission of Pesticides and Their Relationship to Environmental Health.

Is that a current item?

A. In 1969, when Robert Finch was Secretary of Health, Education and Welfare, he convened a special commission to examine the issue of pesticides and their environmental impact.

A report was written by this commission, of which I was a member, and that report was published in around 1969 I believe, and that terminated the mandate of the commission.

Q. Do you recall what the findings of that report were?

A. It was a very voluminous report and it had many findings and recommendations regarding the whole area of environmental pollution with pesticides, and the recommendations to the federal government on what kind of regulations would be appropriate, that sort of thing.

Q. Were you responsible for any particular part of that report?

A. Yes. My special assignment was to review and report on the occupational and environmental health aspects of pesticides as opposed to, for example, the assignment of other commission members might be to report on the contamination of lakes, contamination of air, contamination of wildlife, my assignment was specifically to discuss the effects on humans of pesticides.

Q. The fourth item under Other Professional Activities is Member, Study Section, Environmental Control Administration Department of Health, Education and Welfare.

Is that a current professional activity?

A. No, that was a four-year appointment to the Grant Study Section of it, what is now the National Institute for Occupational Safety and Health. At one time it had a different name, and that was a four-year appointment which was in the early '70s.

Q. What work did you do in that capacity?

A. I reviewed an endless number of grant proposals from various universities that were sent to the government for funding, and evaluated those proposals along with other members of the Study Section, discussed them, and made

recommendations as to whether they should be accepted or rejected.

Q. Were you employed by the government at that time?

A. As a consultant, yes.

Q. In other words, you were in private practice, but you had a contract with the government to be a consultant?

A. Yes, that is correct.

Q. Were the proposals that you reviewed and evaluated limited in terms of subject matter?

A. Yes, to the extent that this study section was principally concerned with occupational health, and therefore the subject matter was principally limited to occupational health problems.

Q. Was there any policy guidance on the criteria for you to use in evaluating these proposals?

A. I am sure there were some guidelines that were provided, it was many years ago, and I can't state precisely what those were now.

Q. But you do recall that there were guidelines?

A. Yes, there were.

Q. Were you involved in developing the guidelines, or were they something that preexisted your employment as a consultant to the Study Section?

A. They preexisted by consultancy.

Q. The next item under Other Professional Activities is Special Consultant, World Health Organization, India (DDT Epidemiology).

Could you tell me how long you had that position,

and what you did in that capacity?

A. That was a three-month assignment in, I believe in about 1970, plus or minus a year, where I was asked by the World Health Organization in Geneva, Switzerland, to act as a special consultant in the epidemiology of the human health effects of DDT. The problem was that at that time the United States Government was anticipating some sort of ban on that particular pesticidal agent and the World Health Organization was concerned because DDT at that time was an important malaria eradication agent throughout the world, and that if the United States banned that compound then other countries that were dependent on it because of its efficacy and low cost, would tend to be concerned and perhaps even change to different pesticides which would cost more money and would be a negative development in malaria eradication throughout the world; therefore, they proposed to develop a cohort of individuals who had been exposed to DDT over many years and to carry out medical examinations of those individuals to see whether DDT had affected their health.

The only viable cohort that WHO in their experience could find was a cohort of mosquito abatement control people in India, and they sent me to India to determine whether from an epidemiologist's standpoint such a cohort could be put together and could such a study be carried out.

Q. And were you able to put together such a study?

A. Yes.

Q. Before we go to what you found in your study, can you tell me what you meant by a viable cohort for the purposes

of this study?

A. By a viable cohort I meant a cohort, a group of individuals who, number one, you could find, that is, they were identifiable and able to locate such people, and two that you could make some estimate of DDT exposure over the years, and three, whether you carry out the study.

Q. What factors influenced whether you could carry out the study?

A. The government policies towards the practice of medicine in India, the budgetary restrictions of the World Health Organization, the availability of qualified physicians in India, and the availability of employment records for mosquito abatement district employees in India.

Q. With respect to those four items, government policies in India, budgetary constraints of the World Health Organization, the availability of qualified physicians in India, and the availability of employment records of mosquito abatement spray men, what were the answers to those questions in terms of your study?

A. My assignment was to go to India and to determine whether a study could be carried out, and these were the factors that I looked at. I then came back to Geneva, to the headquarters of WHO, after about a four-week stay, and travels around India, and wrote a report for the World Health Organization, assessing each of these points, and probably others.

That was the end of my assignment.

Q. Do you know whether or not the study was ever

carried out?

A. Yes, the study was undertaken by WHO approximately a year after I left. Because I was not on the scene I am not exactly sure what happened, but I know that there were investigators in India from WHO for six or eight months. Eventually they determined that the problems that they encountered, which were mostly as I understand it, problems such as the inability to import certain kinds of medical equipment into India, which simply made the study impossible, and after six or eight months they abandoned the study.

Q. The next item is Special Consultant, U.S. Food & Drug Administration, Japan (Polychlorinated Biphenyls).

Can you tell me when you had that job, how long it lasted, and what you did?

A. Yes. That was in October of 1971. The assignment lasted about two weeks and the circumstances surrounding the assignment was that the United States government, including the Drug Administration, Food & Drug Administration, was concerned about the information they had received from Japan in connection with the -- what is now called the Yusho epidemic of poisoning that occurred in Kyushu in Western Japan. They asked me, as their consultant, to go to Japan and to speak with the Japanese investigators, Japanese government scientists, and to come back with information specifically regarding the medical aspects of that outbreak, and they were particularly, the Food & Drug Administration, was particularly interested in the dose of toxic agent that was received by the individuals who suffered the medical problems, as well as the

numbers of people involved, the kinds of medical problems, the diagnostic criteria, the prognosis, the treatment, and such things.

Q. Can you tell me everything that you remember about the work as a special consultant to the USFDA in October of 1971 involving PCB's?

MR. FEATHERSTONE: I object to the form of the question. Can you be more specific?

MS. STEIN: I am being specific about the item that is listed on his curriculum vitae as Special Consultant, U.S. Food & Drug Administration, Japan (Polychlorinated Biphenyls).

MR. FEATHERSTONE: Your question asks for everything that he can remember about that.

MS. STEIN: You may answer, Doctor Milby.

MR. POPE: Are you able to deal with that?

THE WITNESS: I think I can answer that, as best I can remember.

I visited Japan with a toxicologist from the U.S. Food & Drug Administration, Dr. Blumenthal.

We first spent several days in the Tokyo area discussing the situation with the Ministers of Health and Agriculture.

We then traveled to Fukuoka, which is in Western Japan, where the outbreak was centered. This was in 1971. The outbreak principally occurred in 1968, so this was some three years later.

There in Fukuoka we spoke to the principal Japanese

scientists who were involved in that. Our principal contact there was Dr. Mansanori Karatsune, he is Professor of Epidemiology at the University of Fukuoka.

We spoke also with other people there at the University whose names I do not recall, pharmacologists, determatologists, and perhaps others.

We found that the number of individuals involved was a little uncertain because the diagnosis of Yusho, which means oil disease, varied to some extent from year to year and so therefore the number of victims was never clearly known because the number of individuals who ingested the contaminated oil was never clearly and fully verified.

The kinds of problems that were recognized at that time were those which are described throughout the literature even to this day, involving primarily manifestations of intoxication, including pigmentations of the skin, chloracne, swelling, and secretions from the eye glands, neurological effects such as fatigue, headache, numbness, and tingling of the extremities, gastrointestinal upsets, and among pregnant women children were born and there were as I recall during the epidemic year, that is to say the year of 1968, in which most of the cases were recorded at that time there were some 13 women who delivered children, 11 of these women were classified as Yusho patients because of their various manifestations that they exhibited, and two were wives of husbands who were described as Yusho patients.

Among these 13 pregnancies that came to delivery, ten were normal deliveries, two were stillbirths, one very

premature child, and the other child had come to term but was born dead because of a strangulation by the umbilical cord, and the 13th child was delivered by Caesarean at approximately term.

Both of these children, with the apparent exception of the two women who had not suffered, were not classified as Yusho patients. The children of the other mothers generally showed dark discoloration of the skin, and the Japanese called them Coca-Cola babies. They showed a discoloration of the mucous membrane, and the nail beds as well.

Several were born and their birth weight was somewhat less than would be expected. Several had teeth that had erupted in utero, which is uncommon, they suffered from secretions of the eye glands and some facial edema.

Q. Edema is swelling, is that right?

A. Yes, swelling, of the face. They subsequently all recovered as far as the Japanese investigators could tell us, in the sense that these manifestations disappeared, the discolorations went away, they gained weight and were normal within the first six months or so of their birth.

At that time we also discussed various manifestations of Yusho disease with the investigators and most of what I learned has subsequently been published and I can review it for you if you wish, in regard to the symptoms and that sort of thing.

The other aspect that we were sent to investigate was the matter of dose, how much of the dose that was found to be contaminated did it take to cause symptomatic Yusho disease.

At that time, there was a good deal of confusion about this problem because it was the first one on record. The signs and symptoms of poisoning were not generally considered as those attributable to Polychlorinated Biphenyls.

The dose of oil -- during this discussion I would like to refer to it as the Yusho oil as opposed to PCB fluid, in other words, the oil was contaminated with heat transferred fluid, and the heat transferred fluid contained PCBs.

The amount of oil, the actual cooking oil that was ingested, averaged or ranged I should say, ranged from perhaps half a liter to a liter and a half over a period of perhaps three months.

The symptoms that were demonstrated were clearly dose dependent, that is to say, the more oil that was ingested the worse the symptoms. That was clear. The amount of PCBs that were in that oil due to the contamination events, at that time was estimated to be between one and two grams.

Q. Per liter?

A. No, total amount, to cause the disease. The contamination was about, at that time, estimated to be something like 2,000 to 2500 parts per million of fluid, PCB fluid, in the oil, in the edible oil, and when you calculate the volume of fluid in the oil, calculate the amount of edible oil that was ingested, the dose of PCB's came out to be somewhere between a half and two grams, or between half a gram and two grams. Subsequent investigations refined those numbers somewhat, but they are still in the ballpark, and actually when we were there Dr. Blumenthal and I dictated a report which was

eventually sent to me in draft, which I corrected slightly and sent back to the Food & Drug Administration. My file, my personal file, does not contain a copy of that final report. The contact at the U.S. Food & Drug Administration is Dr. Albert Kolybe who is still there.

Q. Was that report ever published?

A. Not to my knowledge.

Q. Do you know how far if it was used by the USFDA in any way?

A. I don't know.

Q. Earlier, during the response to the question regarding your investigation of the Yusho disease, you said that the diagnosis of Yusho varied from year to year.

Will you explain what you mean by that?

A. Yes. The occurrence of symptoms of this type in a large group of people was of course puzzling and so the initial identification of a population, there were 150 or so people initially identified as having these problems. As the investigators became aware that there was some, obviously some underlying cause for these skin outbreaks and puffiness of the face, swelling of the face, and neurological and gastrointestinal problems, it became aware that this was a toxic substance, as opposed to an infectious disease or some other kind of problem.

Then they began to look elsewhere for individuals who might have suffered from these problems, and it turned out that some 20 different prefectures in that part of Japan had individuals in them who were suffering from this kind of thing;

so as time went on and the investigation widened more and more people were included as Yusho patients.

Also, the diagnosis became more complete and better understood, and that is what I was trying to get across.

So, if you look in the literature you will find that the initial number of patients was thought to be only 160 but that has grown now to some 1600.

Q. Did the symptoms change in terms of the analysis that was made?

MR. POPE: As to a particular patient, or in terms of point in time, as in get better?

MS. STEIN: Let me rephrase the question.

Q. Did the criteria for diagnosing victims of Yusho disease change during this period of expanding investigation?

MR. POPE: You are assuming that there was a criteria at least in the beginning?

MS. STEIN: Let me ask first whether there were criteria in the beginning for diagnosing Yusho disease.

THE WITNESS: To my knowledge indeed there were. I can't tell you specifically what they were because they were never told to me, I assume that is because I didn't ask, perhaps; it was clear what the constellation of signs and symptoms were, however, and I mentioned most of those previously here.

MS. STEIN: Q. Then let me ask you this, do you know whether this constellation of symptoms changed during the course of the widening investigation?

A. The constellation of symptoms grew, it became apparent that there were more than just dermatitis and discoloration and headaches, that there were neurological problems, that there were gastrointestinal problems, that there were other kinds of things that were identified, other kinds of problems that were identified as the investigation widened.

Q. And these were the gastrointestinal --

A. I am not sure exactly in what order they were identified, the initial symptoms were fatigue and headache and dermatitis.

Q. You mentioned that the signs and symptoms of Yusho disease were not those that were generally attributed to PCBs.. Can you tell me what you meant by that?

A. Yes. PCBs as a family of chemicals have been around for a long time in industry, probably 40 or 50 years, perhaps a bit longer, and observations have been made and published in connection with the capacity of these chemicals to cause health problems in workers, and these health problems have been generally limited to dermatitis, in fact the name chloracne is a rather specific term for the rather stubborn and lasting kind of acne that one gets from exposure to a PCB and other polychlorinated compounds which have been used in industry for a long time. Holowaxes for example have been used and have been around for a long time; so the fact that these agents can cause dermatitis has been known for a long time.

The Yusho patients had problems which went well beyond dermatitis, the neurological symptoms, for example headaches, fatigue ability, numbness, are not signs and symptoms

that were described previously in PCB intoxication. That is what I was getting at, that based on the knowledge of PCB intoxication that we had in 1968, 1969 and 1970, these intoxications were simply not consistent with what one would expect with pure PCB intoxication. On the other hand, there was no other information at the time as to what they might have been.

Q. All right. Now, just for clarification, this constellation of signs and symptoms were those that were reported in the literature, including the edema, gastrointestinal, pigmentation, secretion of the eye, swelling of the eye?

A. Yes.

Q. And the effects on the children?

A. Yes.

MR. POPE: Are you referring to temporary effects?

MS. STEIN: I am referring to the effects as described by Dr. Milby, rather than as characterized by you.

Q. As of the date that you went to Japan had their been any studies involving PCB effects other than those on workers exposed to PCBs?

MR. POPE: Is your question, was he aware of any when he went to Japan?

MS. STEIN: That's right, was he aware of any.

THE WITNESS: No, I was not.

MR. FEATHERSTONE: May I have the question read back?

(Record read as requested.)

MS. STEIN: Q. Did you do any follow-up work on the trip to Japan and the report that resulted from it?

MR. POPE: For the FDA?

MS. STEIN: Yes, for the FDA.

THE WITNESS: No.

MS. STEIN: Q. Now, the next item on your curriculum vitae under Other Professional Activities is Editorial Board, Western Journal of Medicine.

Is that a current position?

A. Yes.

Q. How long have you had that position?

A. Eight years.

Q. What are your duties, or what jobs do you perform on the editorial board of the Western Journal of Medicine?

A. I am the -- on the editorial board I am responsible for industrial medicine and toxicology, which means that papers which come to the Western Journal of Medicine, which is a medical journal published in the Western States --

MS. STEIN: Excuse me for a moment, Doctor. I am having trouble hearing the witness with these conversations that are going on.

Please continue, Dr. Milby.

THE WITNESS: The Western Journal of Medicine is a regional journal of medicine which is published in San Francisco and is distributed to the Western United States.

The papers which are received by the editor which involve toxicology, occupational health, occupational medicine, problems such as that, are sent to me for review and for a recommendation as to whether they should be published, or what action should be taken, should they be sent back, that sort of

thing.

Q. Do you ever solicit a second opinion with respect to the papers that you review for the Western Journal of Medicine?

A. Yes.

Q. And what would be the circumstances under which you would solicit a second opinion?

A. If it was a subject that I felt that I was not fully qualified to assess.

Q. Can you give me an example of an area that you don't feel qualified to assess, any examples that you can think of?

A. I'm afraid offhand I can't.

Q. Have there been any occasions during the eight years that you have been on the editorial board of the Western Journal of Medicine where you have solicited a second opinion?

A. I am sure there have been but I would have to admit that I can't recall those to mind.

Q. The next item on your curriculum vitae under Other Professional Activities is Chairman, Task Group on Occupational Exposure to Pesticides, Federal Working Group on Pesticide Management.

Is that a current appointment or position?

A. No, that was an assignment that I accepted in the early 1970's that went on for probably a year and a half.

The problem was a special kind of occupational pesticide poisoning that we had described in California, and the federal government was concerned that that problem might be prominent in other parts of the country, and the Council on

Environmental Quality had a group at that time called the Working Group on Pesticide Management, I believe was the name of it, it's an interagency group of pesticide scientists and I chaired an ad hoc committee, a working group if you will, of scientists from other parts of the country to discuss this particular problem and to publish a report, which was published.

Q. What was the special kind of poisoning that you were working on?

A. It was called worker residue poisoning.

Q. Could you describe what that is?

A. Yes. It's a problem that we discovered in California that we attributed to the very heavy use of organophosphate pesticides, such as parathion.

The situation was that with increasing heavy use of these agents, individuals who came into the fields to pick crops such as oranges, peaches, that sort of thing, weeks, days and weeks after the last application of some of the agents suchas parathion, received a sufficient dose from simply coming into contact with the leaves to produce organophosphate intoxication.

This had not been described elsewhere as a general health problem, as an occupational health problem.

Q. What are the symptoms of organophosphate poisoning?

A. The symptoms of organophosphate poisoning are weakness, nausea, vomitting, pinpoint pupils, muscle weakness, muscle fasciculation, abdominal cramping, nausea, diarrhea, slow heartbeat, swelling, salivation, difficulty in breathing

and death is through respiratory paralysis.

Q. And the report that was published described all of these symptoms?

A. That's correct.

Q. Did you have any findings or recommendations in that report?

A. Yes, in general the recommendations were that the use of this particular class of pesticides, the organophosphates, the repeated use of these compounds potentially posed a problem in areas such as California and some of the Southwestern States in this country because the pesticides did not break down, did not dissolve in the environment if you will, as readily as one thought. These agents are considered to be evanescent in the environment, and it was felt that after a few days of their application they were no longer a hazard, and we found that not to be the case, and made recommendations to protect the workers, which were not to spray so much, that sort of thing, and wait a period that we called a re-entry period between the last application of pesticides and re-entry into the field by people who wished to pick or cultivate or whatever, and we actually established re-entry periods for each pesticide because some disappeared more quickly than others, and it would be possible to go into the field within a few days, and other pesticides lasted longer and you had to stay out for a period of two weeks perhaps,

Q. Do you recall what the factors were that determined which pesticides broke down more quickly than others?

A. In general, yes, although that is not totally

understood yet. It had to do with the chemical makeup of that pesticide, some were more quickly degraded than others because of the chemical nature of it. It had to do with the amount of dust on the ground because pesticides which adhere to the dust were protected from destruction by the environment and to some extent it had to do with the amount of moisture and the amount of sunlight and perhaps smog had an effect on the pesticide which made it more toxic.

Q. In terms of chemical makeup making the difference with respect to the degradability of these organophosphate pesticides, what were the specific factors that related to that degradability?

MR. POPE: On the study he did some years ago?

MS. STEIN: Yes, in the study that he did as Chairman of the Task Force, that's correct.

THE WITNESS: That information was never determined, we simply knew that certain agents, certain pesticides, were less degradable than others, and the chemical nature of that, the chemical explanation for that, is not understood.

MS. STEIN: Q. Did you investigate that?

A. Some of my colleagues at the University of California investigated that and were never able to come to a satisfactory answer.

Q. The next item on your curriculum vitae under Other Professional Activities is Member, Subcommittee on Hydrogen Sulfide, National Research Council, National Academy of Sciences.

Could you describe how long you were involved in that

work and what it consisted of?

A. In about 1974, or perhaps 1975, I was asked to become a member of a group, a task group, established by the National Academy of Sciences, National Research Council, National Academy of Sciences in order to participate in the development of a document on the health effects of hydrogen sulfide gas and this was to be one of many monographs prepared by the National Academy of Sciences.

My role was to develop a chapter on human health effects of hydrogen sulfide, which I did, and the monograph has been published. The entire assignment lasted a year or 18 months, and is now completed.

Q. When was that work completed?

A. In about 1975.

Q. What were your findings on the human health effects of hydrogen sulfide?

A. They generally had to do with the fact that hydrogen sulfide is a highly toxic gas, that insofar as we knew produced no long-term effects, but that it was very acutely toxic, and that is it essentially.

Q. The last item under Other Professional Activities in your curriculum vitae is Technical Advisor/Editor. Environmental Health Criteria. Hydrogen Sulfide. World Health Organization, Geneva, Switzerland.

Can you tell me how long you worked in that capacity and what you did?

A. That was a special assignment from about 1978 through 1980, when I was asked by the World Health Organization in

Geneva, Switzerland to develop for them a document called Environmental Health Criteria for Hydrogen Sulfide.

I spent a number of weeks in Geneva on several occasions with experts on epidemiology and toxicology, from New Zealand, Russia, Great Britain, France, Germany, and other countries in the world to discuss the problem of hydrogen sulfide both as an environmental and as an occupational hazard.

We prepared a report, which to my knowledge has not yet been published; however, eventually I'm sure it will be.

Q. Can you give me a general description of the findings discussed in your report?

A. They are largely similar to the results and recommendations that I discussed earlier on the National Academy of Sciences document, principally involving the acute toxicology of hydrogen sulfide, the lack of long-term effects, and a discussion of the physiological effects of odor.

Q. What were the findings relating to the physiological effects of odor?

A. It turns out that the physiological effects of odor is a very difficult thing to describe, and not particularly well understood or generally accepted. I'm afraid I can't say much more.

MR. POPE: Nor is it at all relevant to this lawsuit.

MS. STEIN: Q. Dr. Milby, in the field of epidemiology is there some sort of review procedure that individuals go through for having documents published, studies published?

A. All reputable medical journals of which I am aware have what we call peer review; therefore, when a manuscript is submitted for publication, that manuscript is sent out by the editor to various experts in the field for review and recommendations regarding publication, suitability for publication.

Q. Doctor, I am going to hand you your curriculum vitae. There are 40 publications listed on there and if you would please identify just by item number those publications which have been subject to peer review.

A. The following numbers, indicating publications which have been submitted to peer review. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, through 40, they all have been peer-reviewed.

Q. Doctor, can you tell me what the specific training is to become a epidemiologist?

A. Yes. That varies to some extent. There are various levels of training, of academic training. There is training at the Masters level, primarily for a Masters degree in Public Health an MPH. Then many schools, many universities, will provide an opportunity for doctoral training in epidemiolo and will provide a candidate, a successful candidate, with a Ph.D. or S.C.D. in the subject.

Q. What does S.C.D. stand for?

A. It's a doctoral degree, a science doctor.

Q. What are the specific subjects that are studied in training to become an epidemiologist?

A. Specifically, epidemiology as an academic course, biostatistics, and then the candidate takes other courses, but

those are the major courses that all epidemiologists must take, epidemiology and biostatistics.

Q. Doctor, what does the study of biostatistics consist of?

A. Biostatistics is -- I will have to give you a layman's definition since I am not a biostatistician -- it is the science of evaluating numbers, and especially as to how those observations refer to biological events.

Q. Are there particular methodologies for relating observations to biological events? Are there any particular models or methods of any sort?

A. Yes.

Q. Could you tell me what those are?

A. I could tell you some of them, yes.

Q. All right.

A. There are a number of techniques that biostatisticians use to evaluate observations of biological events.

These include multiple reversion analysis, Chi square analysis, analysis of variants, and there are others which are used that I can't recall to my mind at this point.

Q. Have you had training in any of these techniques to evaluate observations of health effects and relate them to biological events?

A. Yes.

Q. Which ones, Doctor?

A. When I received my training in public health I took several courses in biostatistics, as was required. Most of my experience with biostatistics has been as an epidemiologist,

and not as a biostatistician, actually performing epidemiological studies for which biostatistical techniques need to be applied.

In the actual course of events, to undertake complex studies, the usual approach is to work in collaboration with a biostatistician, which I always do. The biostatistician's role is to be sure that the proper techniques are used. I am generally familiar with the assumptions behind most of those, but I am not a biostatistician by specialization.

Q. Doctor, could you briefly describe what multiple regression analysis is, and how it works?

MR. POPE: I object to the question. Where are we going? Multiple regression analysis?

MS. STEIN: It's one of the techniques used in conjunction with epidemiological studies.

MR. POPE: Ms. Stein, might we move forward in this deposition?

MS. STEIN: We are.

MR. POPE: I suggest that we are moving sideways.

THE WITNESS: Multiple regression analysis is a biostatistical technique that numerically assesses the impact of various variables on a statistical assumption.

MS. STEIN: Q. What is Chi square analysis?

A. Chi square analysis is a simple biostatistical technique that is utilized to examine the association between two events.

Q. Are there any specific criteria that it uses, or assumptions, or is it a numerical --

A. That is a numerical formula.

Q. Okay. And the analysis of variants?

A. The analysis of variants is a biostatistical technique utilized to examine the difference between two means, to determine whether --

MS. STEIN: Excuse me, Doctor, I am having trouble hearing you due to the conversation at the end of the table.

THE WITNESS: The mean age of one population could be compared to the mean age of another population, using the analysis of variants techniques.

MS. STEIN: Q. What is the difference in training for an epidemiologist and for a toxicologist, if there are any differences?

A. There are substantial differences.

Q. Could you tell me what they are?

A. A toxicologist is one who is trained in the response of animals to toxic substances. The animal may be a primate or it may be a lower form of animal life.

An epidemiologist is one who is trained in understanding the distribution, and the importance of the distribution and determinates of disease in populations.

Q. Do epidemiologists ever do biop studies of any sort?

A. Yes, in the sense that epidemiologists and biostatisticians both are involved in drug evaluations, clinical trials, and I believe that is about as close to a laboratory kind of test that epidemiologists will get involved in.

Q. Do epidemiologists do field studies then, going out and looking at populations primarily?

A. Yes.

Q. What are the different kinds of studies that epidemiologists do?

If you don't understand the question, I will rephrase it.

A. I think I can respond to that.

Epidemiologists primarily are involved in two kinds of studies, morbidity and mortality.

A study of morbidity uses as an end point any measure of health that is appropriate, which may include sickness, over sickness, which may include subclinical disease, which may include nothing more than physiological function, or it may include even less and it may include nothing more than the storage of a compound in the body.

All these are measurements of morbidity as defined by the epidemiologist.

Mortality studies deal with death as an end point.

All studies of epidemiology can be subsumed under those two major headings.

Q. Can you define what you mean by a subclinical disease?

A. A subclinical disease is a disease which has not yet become apparent to the victim or to the clinician.

Q. What is the way of gathering information in a morbidity study?

A. There are host of ways of gathering information in a morbidity study. They vary from examining records of past illnesses, past and present illnesses, along a spectrum all the

way to conducting clinical examinations of individuals, and in between are gathering of biological fluids for analysis, and gathering other kinds of health data for analysis.

Q. Do you gather other than biological fluids, for example do you gather tissue samples?

A. Yes.

Q. In clinical examinations what are the kinds of things that you look for in a morbidity study?

A. The kinds of things one looks for in a morbidity study can be very specific if indeed one suspects that the reason for the morbidity study is to examine a specific organ, for example the liver.

On the other hand, such an examination can be very general if there is no clear understanding of what effects might be looked for, but it's more of a fact finding kind of examination.

Q. Would it be fair to say that the type of clinical examination that might be performed is dependent on the specific item that you may be looking for, a specific disease or a specific response to a specific compound?

MR. FEATHERSTONE: I object to that insofar as you are attempting to characterize the witness's testimony. He just told you that it depends on whether you are looking for something specific or something general. That is how I understood his testimony.

THE WITNESS: May I have the question?

(Record read as requested.)

THE WITNESS: The answer is yes, in that if one has

an idea which organ system to focus on, one will do that; but many examinations go well beyond a single organ system.

MS. STEIN: Q. Doctor, have you ever designed any morbidity studies?

A. Yes.

Q. What are the variables that you take into account in designing a morbidity study?

A. The variables depend to some extent on what the purpose of the morbidity study is, so the variables could be included under a number of headings: one, examination of the environment or exposure; two, the examination of the individual; three, perhaps the examination of the mechanism by which the environment impacts on the individual.

Q. In designing morbidity studies, do you take into account the route of exposure, is that one of the things that you could include under the third item you just mentioned?

MR. POPE: Could include?

THE WITNESS: Yes.

MS. STEIN: Q. Are there accepted methodologies or criteria in the field of epidemiology that are used in designing morbidity studies?

A. Each morbidity study is designed with an understanding of what the problems in mind might be, what the hypothesis might be, and then from there a host of considerations are important, such as available population for study, available analytical tests for identification of the presence or the effect of an agent, and a host of other items.

Q. Can you tell me what those are?

A. It varies from study to study.

If you would like to give me a "for instance" I would be glad to attempt that. Textbooks have been written on the subject and I'm afraid that --

Q. Are there any standard texts on that subject?

MR. POPE: The subject of what?

MS. STEIN: The design of morbidity studies.

THE WITNESS: The subject is included in most textbooks on epidemiology, of which there are several.

MS. STEIN: Q. What are the standard texts in epidemiology?

A. The standard texts, most recent texts I should say, is a text on Occupational Epidemiology, by Richard Monsonn.

Historically there have been many other textbooks upon epidemiology, they come out every several years.

Q. Are there any others that you recall the titles of?

A. There's a textbook by Bryon McMahon on Principles of Epidemiology.

There's a textbook by Gary Freeman on The Principles of Epidemiology.

Primarily however, the epidemiologist who is practicing from day to day doesn't rely on textbooks, he or she relies on ongoing publications and the literature on what are the current concepts of how one conducts a morbidity or mortality analysis. The criteria keeps changing all the time, and the textbooks are out of date before they reach you.

Q. What are some of the journals that a practitioner would consult to find the up-to-date information on

epidemiological studies and their design?

A. My curriculum vitae, listing the publications, has most of them. Would you like me to enumerate some of them?

Q. Yes, please.

A. The American Journal of Epidemiology; Journal of Occupational Medicines; Archives of Environmental Health Sciences; The Journal of the American Medical Association; The British Journal of Industrial Medicine; The Scandanavian Archives of Work Physiology; and there are others but those come to my mind.

Q. What are the factors that you consider in designing a mortality study? Let me back up one step. What is a mortality study, first of all?

A. A mortality study is a study which examines the causes of death in a population, the exposures of the members of that population to various environmental factors, and the comparison of the experience of death in that population with another population that we call a control population, which is generally the United States population.

Q. What is a standard mortality ratio?

A. A standard mortality ratio, a so-called S.M.R., is the ratio of the cause, age, time in a specific mortality in a study population, divided by the same number in a comparison population. It is generally called observed over expected, times 100, so that if the mortality experience in the population under observation is exactly the same as the comparison population, then the S.M.R. would be 100.

Q. With respect to the comparison population, is there

published data somewhere that you can refer to?

A. Yes.

Q. Who prepares that data, and where is it published?

A. There are a number of sources for comparison data for a mortality analysis. There is national data which is collected by the National Center for Health Statistics, and made available on age, sex, time, race, cause, specific mortality, and similar data are available from most states and from many counties, and from some industries.

Q. Is that published, or do they just make it available apart from the National Center for Health Statistics, is the information regarding comparison populations published somewhere, or does one write to a specific agency or industry and ask for the statistics?

A. Some is published, and some one has to ask for, and some is confidential, I suppose.

Q. When evaluating data in mortality studies, are there ways of ranking what it is that is observed, for example if it is statistically significant, not negative, can you describe what the classifications are, if you will, for observations in a mortality studies?

A. In a mortality study where the statistical end point is a standardized mortality ratio, S.M.R.'s are compared between an exposed, or the observation population, and the control population, and a statistical calculation is made as to whether there is a stastically significant difference at some predetermined level of significance, generally considered to be, by the shorthand of biostatisticians, as the .05 level of

significance.

Q. What does the .05 level of significance mean?

A. It's stastical shorthand for reporting a calculation which compares the observed S.M.R. with the expected. The observed number of deaths or the expected number of deaths, and based on the standard deviation of both of those numbers, whether the means of those numbers fall in different populations, and the statistical calculation is one which I can't give you because I am not a biostatistician, but it is a routinely used comparison statistic.

Q. In other words, it is generally accepted?

A. It is generally accepted, a generally accepted comparison statistic, that's right.

Q. Can you tell me what a negative study is when talking about a mortality study?

A. A negative study is -- to begin with, the definition of a negative study is -- it must remain the individual determination of every investigator, there is no definition of a negative study. A negative study might be defined as a study which shows no positive results, that is to say, there are no S.M.R.'s for example which are statistically in excess of expected.

Q. What if there are positive results that are not statistically significant, is that possible?

A. There are positive results because an S.M.R. is a statistical calculation, anything over the 100 that I described before is considered to be in excess.

In general, an S.M.R. which is over 100 but has not

yet reached the level of statistical significance is considered -- the consideration has to be dependent on what you are looking for. For example, if you are looking for lung cancer in a population and you find an S.M.R. which is above 100 but not yet reached the level of statistical significance, that may be of interest to you; but in general, S.M.R.'s which have not reached statistical significance are given considerably less weight than those which have reached the level of statistical significance.

Q. But are they considered negative in terms of health effects by the epidemiologists?

A. It depends. It depends on a lot of things such as what you are looking for or what the nature of the effect is, how well the study was done, if a study was not done very well, that is if the population under observation is very small, the number of deaths that were ascertained was much fewer than the number of deaths that could have been ascertained, then the S.M.R. has less importance perhaps.

Q. Could you explain what you mean by the number of deaths was less than could have been ascertained?

A. Yes. In any mortality analysis the investigator must go through the exercise of determining the number of deaths that occurred in the study population over the period of observation. For example, many mortality analyses observe a population for 20 years. It is important that all deaths that occurred in that population during that 20-year period be identified or ascertained. Not only must they be identified, but the cause of death must be identified, usually through

obtaining a death certificate.

If it is determined that there are a thousand deaths during that 20-year period and only 500 causes of death were ascertained through death certificate analysis, that study would be considered inadequate.

Q. Is anything other than the death certificate consulted in mortality studies?

MR. FEATHERSTONE: For the purpose of determining whether somebody died?

MS. STEIN: For the purposes of epidemiological studies.

THE WITNESS: In order to be comparable to other epidemiological studies and even have more importance to national statistics, no other source of information needs to be considered, and indeed death certificates must be coded in a very uniform way so that one can compare the exposed population, the study population, to the control population. However, in many cases after the comparison is made in a uniform way, then we are interested in pursuing further the diagnosis of the cause of death by looking at, obtaining and looking at doctors's records, hospital records, and other causes of death. But for the initial comparison and calculation of standardized mortality ratio, one must depend uniformly on death certificates.

MS. STEIN: Q. Is there any disagreement in the epidemiological community regarding the validity of death certificates for ascertaining the cause of death?

A. I don't know whether one would call it a disagreement, it's generally known that death certificates are an imperfect

indicator of cause of deaths. A misdiagnosis may find its way to the death certificate, or an incorrect diagnosis, or an improperly coded diagnosis; so, death certificates are not uniformly reliable.

Nonetheless, the assumption is that the same errors would be made in a study that would be made to determine the cause of death as determined by the National Center for Health Statistics, since their statistics, that is, the National Center's statistics, are only those statistics which are collected by the state and by the county. The point is that the National Center uses the same data that the epidemiologist uses, and therefore they should be comparable even though there are errors on both data bases so the assumption is made that they can be compared because the random errors that occur occur in both data bases, and the errors are at random.

Q. By random errors, will you explain what you mean? I'm trying to ascertain whether they go to who performs, who actually signs the death certificate, whether there may be differences that way or there may be a random error because a wrong number was put down.

MR. POPE: You stated that it could be either or both of those circumstances that arise from time to time, and the point is is if you are comparing one set of statistics to another set of statistics, then you are assuming that those same errors, whatever they are, are in both.

MS. STEIN: I would like to find out what the sources of the errors are.

MR. FEATHERSTONE: You mean the random errors?

THE WITNESS: There are various sources, there can be an error in diagnosis by the physician, there can be an error in transcribing the diagnosis to the death certificate, there can be an error in coding the death certificate because that is done by the state, by a state coder, there can be an error in transcribing that code to a tape later, to a national statistical tape, there can be mistakes and errors all along the time. The concept is that those errors are the same in both data bases and that they are random in nature and not systematic so that they cancel each other out.

MS. STEIN: Q. Is there an accepted definition in the field of epidemiology as to a positive study? Let's talk now just about mortality studies.

A. There is no black and white for either positive or negative studies, each study must be interpreted by someone who knows the strength and weaknesses of that study and so what one expert may call positive, a positive study, others may disagree.

Q. In terms of studies being interpreted by one familiar with the strengths and weaknesses of the study, would the best person to evaluate whether a study is positive or negative be the person who actually did the study?

MR. POPE: I object to the form of the question. That doesn't make any sense.

MS. STEIN: Q. Do you understand the question, Dr. Milby?

A. I can try to answer it.

The person who did the study is not necessarily the

best judge of whether it is positive or negative, although that person could have an opinion on that matter. That opinion may not always be shared by others.

Q. What would the reasons be that the person who performed the study is not necessarily the best one to evaluate whether it is positive or negative?

A. It is conceivable that the person who did the study is not as experienced in epidemiology as someone who is criticizing the study, or maybe the investigator who carried out the study may be ignorant of certain principles that the more experienced person is aware of.

Q. What would be in your opinion a negative study, a negative morbidity study?

A. There is no way for me to answer that because there are so many variables that must be considered, and I would have to look at a study to determine whether I would consider it to be negative, so I can't specifically answer that for you.

Q. What would be the factors that you would look for in evaluating a morbidity study to see whether or not it was negative?

A. I would start with the hypothesis as to what the investigator was looking for, and I would look at the interpretation, what did the investigator feel that he or she found? Then I would look at the study design so that I would understand the number of individuals examined or observed in some way, what methods of observation were used, the size of the study population, the nature of the comparison population, the sensitivity of the analytical methods used,

such as laboratory studies, x-rays, pulmonary function studies, and other measures of health or disease. I would examine the way that those measures of health or disease were assessed by the investigator. Then I would attempt to reach my own conclusion as to whether those things were all, in my opinion, properly measured and properly assessed.

Q. And with respect to a mortality study, what are the factors that you would look at in ascertaining whether it was negative or positive?

A. I would be interested in whether the study was considered to be hypothesis generating or hypothesis testing, or what the hypothesis might be, what the interpretations were, what the study design was in terms of the population studied, the comparison population, the total ascertainment of death figures, that is to say whether 90 percent of the deaths were ascertained or some smaller number. I would be interested in the statistical methods reported. I think that covers most of it.

Q. Can you tell me what you mean by hypothesis generated, as opposed to hypothesis testing?

A. Hypothesis generated is a study which essentially is a study that is undertaken to see whether there are any health problems in the population. There is no hypothesis. There is something wrong with that population, for example.

Hypothesis testing study is a study which already has an hypothesis before it starts. The hypothesis may be that there is more lung cancer in the population under study than there is in the general population.

MR. FEATHERSTONE: Can we go off the record?

MS. STEIN: Yes.

(Off the record.)

MS. STEIN: Back on the record.

Q. Dr. Milby, with respect to the publications that are listed on your curriculum vitae, did you know in advance who was going to be the peer review group for those publications?

A. Generally not, no.

Q. You have been retained by Outboard Marine Corporation as an expert witness in the case. What is your understanding of the subject matter that you will be testifying to?

A. My understanding of the material that I will be testifying to is that I will be discussing the general health effects of PCB's in humans, and the medical implications of such exposures.

Q. Do you have an opinion as to what the general health effects of PCB's in humans are, and the medical implications of such exposures?

A. Yes, I have opinions on those matters.

Q. Can you tell me what those opinions are please?

A. Well, I can summarize my opinions on the matter in a very general way.

Q. All right.

A. Based on my long interest in this subject, beginning even before the days of the Yusho problem --

Q. Excuse me, this subject, meaning specifically PCBs?

A. Yes.

Q. All right. Please continue.

A. And my interest in the Yusho problem, both because of my specific personal involvement, together with my interest in PCBs as an occupational and environmental exposure situation; based upon further my experience with PCB in my medical practice, in which I see patients who have been exposed to PCBs, or believe they have been exposed to PCBs in one form or another; based upon my experience with other clients with whom I consult, it's my opinion that PCBs are a minimal health problem, that their health significance is considerably overemphasized, that their acute toxicity is not especially important from a health standpoint, and that their implications in connection with long-term chronic health effects are also minimal.

I also believe that the issue of PCBs has been greatly overemphasized and that many of the problems that I see in my own practice involving people who have been exposed or believe they have been exposed, to PCBs, I put in the area of excessive concern by these people, by these patients, because of what they have read or what they have been told about these compounds, and I am prepared to discuss these matters specifically, but in general that is my impression.

Q. All right. Let's start with the patients that you have observed who believe that they have been exposed to PCBs. Without violating the privileges that may be available in terms of doctor and patient, could you describe what you have observed over the length of time in which you have made

these observations, and the number of patients that you observed?

A. During the last eight to twelve months perhaps I have seen patients that have been referred to me either by a local industry or who have sought me out for other reasons, who have either been exposed to PCBs in the course of their work, or believe that they may have been exposed because of the occurrence of an event near their home, for example, a capacitor may have erupted and they felt that they may have been exposed; or, a transformer may have exploded nearby, and they saw the smoke and feel that they might have been exposed to PCBs, and I have seen such patients, I have see less than a dozen of these in this period, probably close six or eight, and these have been adults, male and fema who have come to me because of their concern that they been exposed to PCBs. I have conducted examinations, questionnaires, that sort of thing, and have done medical examinations on these individuals, including when I feel it is indicated, I have done liver function studies and PCB's serum analyses, that is, I have caused these laboratory studies to be done.

Q. Can you tell me what the occupations are of those who are occupationally exposed?

A. Yes, these have been electrical utility workers, and I might add, since I was permitted to mention it earlier, that in addition to seeing eight or so patients, I am named on the consultant list of some 500 doctors that are on what is called the panel for the local utility company, the local

utility company that serves most of Northern California, and the panel of doctors are doctors that this utility sends their employees to should they become ill on the job, if they have an occupational problem.

When these problems occur, if they involve PCBs, my name is on the panel list to be consulted by other physicians should such events occur, so not only do I see patients, but I receive inquiries from other physicians who do see patients as well who have such problems, and so my experience is not only with my own small group of patients that I have seen, but many dozens of physicians throughout the Northern California area.

Q. Have you actually seen any of those patients that you have discussed with other physicians?

A. On one or two occasions they have sent them to me, but generally no, I have not seen them.

Q. When you conducted examinations of the six to eight patients that you have seen --

MR. POPE: Within the past 12 months?

MS. STEIN: Within the past 8 to 12 months, what did you examine these individuals for?

THE WITNESS: I conducted general examinations, keeping in mind the alleged exposures, and if I felt that there was a problem then I conducted laboratory studies. The problem could have been, for example, had I seen an overt manifestation of a problem, such as dermatitis, skin irritation, that sort of thing, then I would have been more likely to have ordered blood studies.

As it turns out, in none of these individuals have I found anything of any nature during a medical examination, which in some cases includes blood studies, but not all of them, because I didn't feel it was indicated.

These blood studies sometimes included liver function studies, but only in a few cases because I didn't think it was indicated on others, and on a few occasions had done plasma PCB levels and none of those cases did I find any medical problem, and I might add that with perhaps a single exception of the many phone calls I have received in consultation from other physicians that there has never been an overt problem that has been described to me by these physicians, not even dermatitis, which would be the principal thing that one would look for in a patient who had truly been exposed to PCBs. So, I have seen no dermatitis, and only one time was it described to me on the telephone consultation.

Q. With respect to the six or eight patients that you examined in the last 8 to 12 months, were you able to ascertain whether in fact any or all of these individuals had been exposed to PCBs?

A. By history, that is, what the patient told me, they all believed that they had been exposed to PCBs in one way or another. I have never been able to verify that by finding PCBs in the blood in excess of the amount that we consider to be background in the population.

Q. What do you consider to be background in the population?

A. We consider, and when I say we I mean the State

Department of Health in California, and others knowledgeable in this particular area of PCB exposures, consider 20 parts per billion in the serum to be just about the maximum one would find in a population of individuals exposed only through diet and other ways, that is, people who do not have exposure to PCBs at their work.

Q. On how many of the six to eight patients that you examined in the last 8 to 12 months did you do a serum analysis for PCBs?

A. I believe three, three times.

Q. And what did you find?

A. The laboratory to which I sent samples for this analysis, a laboratory which I have been referred to by the State Department of Public Health, reports only as less than 20 parts per billion, or if an analysis shows greater than 20 parts per billion, will give the direct number, so they have all been less than 20 parts per billion. That is what the laboratory slip says when it comes back to me, so I don't know whether it's 10 or 15 or 2.

Q. Do you know what the standard is that this laboratory uses to measure PCBs in blood levels?

A. The standard that they use I am told by them is the standard set out by the American College of Pathology. This is a group that sends out samples to analytical laboratories, and I believe that is the one they use. They do use a standard, and they may use the Health Department standard. The State Health Department also sets up standards and I am not sure of which one they use, perhaps both.

Q. Do you know whether the standard is defined in terms of a specific Aroclor?

A. I don't know.

Q. Do you know what specific analytical technique this laboratory uses to ascertain serum levels of PCBs?

A. The gas chromatographic technique.

Q. Gas chromatographic, and is it coupled with anything else?

A. It is coupled with an electron capture device. I was referred to the laboratory by the State Department of Health who looks after these things and I am aware of the analysis requiring any gas chromatographic technique and electron capture device.

Q. Do you know whether they used packed columns or capillaries?

A. No, I don't.

Q. You mentioned with respect to the patients that you have examined, I believe in the last 8 to 12 months that you used a questionnaire, is that correct?

A. Whenever we do an examination of someone we fill out a form as well as do an examination, and that is what I meant, a medical history, if you will.

Q. With respect to the six to eight patients that you examined in the last 8 to 12 months for PCBs, how many liver function studies did you do?

A. I believe I did one, perhaps two.

Q. What were the specific liver functions that you were looking for?

A. In this medical community we order studies, laboratory studies, in groups, as do most other physicians in other medical communities, so that we order a sequential multiple analyzer study which includes a number of studies which we consider to be studies of liver function, and these include SGOT, SGPT, and GGTP, alkaline phosphatase, bilirubin, and essentially that is it for liver function studies.

Q. Can you tell me what the letters stand for when you mention those letters? I will go through them individually and then ask you what each test is measuring.

What does SGOT stand for?

A. Serum glutamic-oxaloacetic transaminase.

Q. Is that sort of a --

A. That is a -- what is measured there is an enzyme in the blood which is elaborated by a number of tissues, especially when they are damaged, and a liver which is damaged or injured releases this enzyme and it can be elevated in the blood, so it's a standard test for, not so much liver function really, but liver involvement, a liver injury, by a toxic substance.

Q. And this is done with a blood sample?

A. This is done with a blood sample.

Q. And not a tissue specimen?

A. No tissue, just blood.

Q. Are all these tests done with blood, as opposed to a liver tissue specimen?

A. Correct, they are all done with blood.

Q. The second one was SGPT.

A. That is serum glutamic-pyruvic transaminase. It is similar to the other, it's an enzyme study similar to the other, it too is released by certain tissues, including the liver, when they are injured.

Q. Let me back up a minute. With the SGOT test, what is the function that is involved, serum glutamic-oxaloacetic transaminase, I'm not sure exactly what you are looking at there and --

A. Both SGOT and SGPT are enzymes which are normally found in various tissues, the liver, muscle, heart, and upon damage of these organs, for example in a heart attack, these enzymes are elevated, but SGPT may be elevated more so one must exert some kind of clinical judgment based on the elevation and the differential between the two, that sort of thing, but there are several enzymes which are released from various tissues upon damage, and normally if there is no damaged tissue there are no levels. With damage they can be very high, and so they are used as an indicator of damage.

Q. Is there a normal range?

A. Yes.

Q. What is that?

A. SGOT, by our laboratory, the laboratory I use, is as high as 50 units, and SGPT is as high as 75 units.

Q. And this is the normal?

A. This is the upper range of normals the two numbers I gave you.

Q. What is the margin of error in doing this test, how accurate are these tests?

A. For the SGOT and SGPT they are sufficiently accurate for clinical purposes. By that I mean that before one sees an elevation in the tissue, the liver, heart or whatever will have undergone substantial injury. If you are asking me what the laboratory error is in carrying out those studies, I don't know because it is unimportant, it probably runs 10 percent, which most laboratory studies do, and the clinical variation in the individual is much higher than that, so it's not very important.

Q. The next one you mentioned was GGPT.

A. That is gamma,glutyml transpeptidase. It's another liver function study, it's an enzyme, and it is also released from the liver, it is fairly specific to the liver, it's a very sensitive study and is a good indicator of liver injury.

The upper limits of normal in that test is 100.

Q. With respect to alkaline phosphatase, what is that?

A. Alkaline phosphatase is a substance, a chemical, released by tissues which are damaged. It's a rather non-specific test when looked at for liver function. A damaged liver has high alkaline phosphatase in many cases. It's a nonspecific indicator of damage to the liver.

Q. Is there a normal range on that one, as well?

A. Yes, the upper limit of normal of alkaline phosphatase in our laboratory, in the laboratory we use is 12.

Q. I believe the last one you mentioned was bilirubin?

A. Yes.

Q. What is that?

A. Bilirubin is a pigment in the blood which builds up when the liver is severely damaged, it's normally metabolized and excreted through the liver when the liver is functioning normally. When the liver is not functioning normally the bilirubin builds up in the blood and indicates a poorly functioning liver.

Q. Is there an upper limit that is normal?

A. The upper limit that is normal is 1.5.

Q. With respect to the liver function test or tests that you carried out with respect to the patients who were examined for PCB exposure in the last 8 to 12 months, what were the results of the liver function battery of tests?

A. The one or two cases I looked at, the studies were all normal, all within normal limits, indicating to me that there was no clinically significant injury to the liver.

Q. Has any other laboratory tests been performed with respect to any of these six to eight patients?

A. No.

Q. Were there any physical symptoms of any kind that you observed with respect to the six or eight patients?

A. Only anxiety about the possibility that they had been exposed to a very dangerous chemical.

Q. When you did your medical history of these patients, did you examine their dietary habits?

A. In a general way.

Q. Did you look at whether they ate a lot of fish?

A. That is not normally a question I would ask, but with patients who believe that they have been exposed to PCB,

and on whom I take a blood study, yes, I asked that question and no, they were not particularly heavy fish eaters.

Q. Can you be a little more specific about what you mean by not particularly heavy fish eaters, the number of meals per week, or whatever?

A. I believe I asked the question how often do you have fish as a meal, and the answers I received as I recall were the kind of answers that I would expect from someone who doesn't eat a lot of fish, occasionally I eat fish, that sort of thing, and I didn't try to quantitate it in terms of meals or grams or anything like that.

Q. Did you ask about specific kinds of fish?

A. No.

Q. Did you examine any of these patients before you were retained by OMC to testify in this matter?

A. Yes.

Q. How many of those patients did you examine before you were retained by OMC?

A. Most of them. I am not sure exactly how many.

Q. With regard to your activities as a consultant to the panel for the utility company, do you have a standard list of questions that you ask a physician who has a patient complaining of possible PCB exposures?

A. No, I don't have a standard list of questions, I listen to the problem and attempt to respond in a medical way, and generally I end up discussing the toxicology of PCBs to some extent and what the clinical implications are, and what kinds of studies one might wish to do if he seriously suspects

PCB exposure, what to look for.

Q. What do you tell these physicians who call you with regard to the toxicology of PCBs?

A. It depends to some extent on how interested that physician might be and what it is that he or she has seen. As I testified earlier, there was only one case in my memory that was actually something to see from the physician's eyes, and that was a case of mild dermatitis.

So, in many cases, although as I indicated I don't have a routine presentation to make on the telephone, I simply discuss with the physician the kinds of laboratory studies he might wish to consider in assessing that exposure, where you get the tests done, how much it costs, what it means, what the implications are of exposure to long-term health, that kind of thing.

Q. Have you had any follow-up calls from any of these physicians?

A. One or two times, yes.

Q. Can you recall what the follow-up consisted of?

A. In one case it consisted of a further question or two on a case. That is the only one specifically that I recall.

Q. Earlier you indicated that one of the bases for your opinion is your experience with other clients with whom you consult.

Is that the same thing as being on this panel for the utility corporation?

A. It's the same company, and I was referring to that company, yes.

Q. Is there anything that would come within that item as a basis for your opinion regarding PCBs?

A. You mean, other experience?

Q. Other experience with clients with whom you consult.

A. No, I think not.

MS. STEIN: This is a document DEFENDANT OUTBOARD MARINE CORPORATION'S PARTIAL RESPONSE TO PLAINTIFF'S INTERROGATORY REGARDING EXPERT WITNESSES and we'll mark that as Exhibit No. 3.

(Document DEFENDANT OUTBOARD MARINE CORPORATION'S PARTIAL RESPONSE TO PLAINTIFF'S INTERROGATORY REGARDING EXPERT WITNESSES, marked as Exhibit No. 3.)

MS. STEIN: Q. Dr. Milby, in response to an interrogatory submitted to Outboard Marine Corporation, item c, a response to the government's interrogatory, it is stated: "Dr. Milby will testify concerning published literature relating to the effects of PCBs on human health, and the risks to human health presented by PCBs."

In formulating your opinion on the health risks posed by PCBs, have you reviewed or consulted any documents that are not published?

A. I have examined several depositions in this case, and I have read -- I have reviewed such as this, reviewed the Chemical Manufacturers Association documents which are not published in the literature, and I believe that is all, an open, available published literature.

Q. I guess we had better define what you mean by

published.

MR. POPE: Just ask your questions.

MS. STEIN: Q. Let me ask you this, Dr. Milby, let me ask you to look at what has been marked as Exhibit No. 1. Can you tell me if that is all of the literature that you have reviewed?

A. No, I review things all the time. I have read dozens and dozens of articles on PCBs. As I said, I have been interested in the subject for a long time, and so I have read many, many papers on PCBs, I read them all the time, I keep track of many of them.

Other documents that suddenly pop into my mind which I have looked at and read and which would not be in the realm of being published are Dr. Humphrey's report on Great Lakes Fish, and one or two other reports such as that and most of those or all of those are on here.

Q. Would you like to look at that to confirm that?

MR. POPE: That, being Deposition Exhibit No. 1.

THE WITNESS: Dr. Humphrey's report, that is item number 2.

The Greta Fine infant study has not been published, but I read that. And that is item number 3.

Item 4 has not been published and that is this document, the 2/19/82 Drill, Friess, Hays & Loomis study.

Item 5, two CMA reports.

Item number 6, Dr. Gaffey's article, dated 11/81 I read and that has not been published I don't believe.

Item 9, a report dated 10/81 from George Levinscus

produced by Monsanto.

Item 13, an article entitled Toxicology of PCBs, by the State of California, 1/81, is an unpublished document.

Item 15, process notes by Dr. Puffer.

The other documents have been published.

MS. STEIN: Q. Are there any other unpublished documents that you have referred to as a basis for your testimony?

MR. POPE: Wait just a minute, please. In response to your last question, Dr. Milby told you the articles on your list that are not published that he has reviewed. Whether or not there are other materials that he has reviewed in connection with his opinion or whether any of those articles were reviewed by him in connection with this opinion in this case, are two different things. For somebody who is practicing in the field he may be reviewing these articles for purposes of treating his patients or doing various work in the epidemiology field.

I don't want you to assume that there is a list of documents that he has reviewed for purposes of giving his testimony in this case because that is not true. That is what I was trying to indicate to you earlier, there are a number of materials some of which he sent to us and some of which we sent to him, but the question has got to be differentiated as to whether you are talking about materials that he reviewed for purposes of this case. There may not be any.

MS. STEIN: I will differentiate.

Q. Are there any materials that you have reviewed

for the purpose of -- specifically for the purpose of this case, as distinguished from your general practice?

A. Yes, and many of those, in fact most of those, I just cited from this list. In fact, I think that is a pretty good list of the things that I reviewed specifically for this case, which I probably wouldn't have seen otherwise.

Q. Are there any materials that are not listed on Exhibit No. 1 that you recall that you may have reviewed for your opinion in this case?

MR. POPE: In addition to depositions?

MS. STEIN: In addition to Exhibit No. 1.

MR. POPE: In addition to the depositions that he told you about. I don't think they are on the list.

MS. STEIN: No, they are not on the list, and I will ask about them.

THE WITNESS: I reviewed many, many documents which are not on this list for other purposes in my interest in PCBs. It is likely that some of those documents provided information to me on which I have come to base an opinion, my general opinion, about PCBs. I'm sure that is the case. Many of these documents are not on this list, but I reviewed them for other purposes, not for this case specifically.

MS. STEIN: Q. You indicated that you had reviewed depositions as part of your preparation for your opinion in this case, is that correct?

A. That's correct.

Q. What were those depositions?

A. I reviewed Dr. Humphrey's deposition; I reviewed

Dr. Ringer's deposition.

Q. Any other depositions?

A. I don't recall, there may be, but I don't recall them so obviously I didn't spend too much time on those; I don't recall any others at this time.

Q. Were you also provided with copies of all of the exhibits to those two depositions?

A. No.

Q. Just the transcript?

A. Just the transcripts, yes.

Q. About how many hours did you spend preparing for this deposition today?

MR. POPE: For this deposition, as opposed to his general preparation for the trial in October?

MS. STEIN: That's right.

THE WITNESS: During the last week or two I suppose I spent 10 or 15 hours.

MS. STEIN: Q. And apart from that 10 or 15 hours, how much time have you spent preparing for the testimony that you will give in this case?

A. Probably another 100 hours.

Q. In terms of that approximately 100 hours, what were the activities that you engaged in?

A. Most of the hours were spent reading various documents. I visited the Waukegan OMC facility. I was shown through that facility. I was shown around the grounds of this facility, walked through the plant, spoke with Mr. Thomas and several other attorneys involved in this case. I have had

several other meetings with Mr. Phelan, Mr. Pope, Mr. Thomas, Mr. Kissel, and some phone calls back and forth primarily having to do with documents that they asked me about, whether I have seen them, and I said yes or no.

Specifically I think that covers most of the hours.

Q. Did you have meetings with anyone other than attorneys for Outboard Marine Corporation and the site visit in connection with preparation for your testimony?

A. No.

Q. Did you have any phone calls other than with the attorneys for Outboard Marine in connection with your preparation for your testimony?

A. No.

Q. Did you talk to anyone who has been identified as a witness in this case?

A. No, I don't believe so.

MS. STEIN: Shall we take a lunch break?

MR. POPE: Okay.

(Noon recess.)

THURSDAY, MAY 27, 1982 AFTERNOON SESSION 2:00 P.M.

EXAMINATION BY MS. STEIN (Resumed)

MS. STEIN: Q. Dr. Milby, would you describe for me the visit you made to the Outboard Marine Corporation, the Waukegan facility?

A. Yes. The visit took most of one day. I drove to -- I was driven to Waukegan by Roseann Oliver from Chicago, where I had flown in the night before.

We spent several hours in the latter part of the morning with Mr. Thomas, we being Roseann Oliver and Mr. Kissel and Mr. Pope, talking about PCB matters.

I asked a number of questions that I was curious about with regard to Outboard Marine, the layout of their company, the kind of work that was done there, and after several hours of discussion I was then, after lunch, shown around the grounds, and I asked if I could be shown through the die cast plant since I had never seen such a facility, and that was done, and essentially that was it, and then I left.

Q. Have you seen any sampling or test results that were done in the Waukegan area for PCBs?

A. No, I don't believe I have seen any. I have been told in generalities about things like fish and that sort of thing, but I don't know anything about people or food or environment or workplace or anything like that.

Q. What have you been told about fish?

A. As I recall, because it was only a passing comment, that there was a time when the fish in Waukegan Harbor had levels of PCBs that were above the lake fish and were in the

10 or 15 parts per million range, something like that, I really didn't pay a whole lot of attention to that.

Q. Have you had any publications dealing with PCBs?

A. No.

Q. Can you tell me what a dose-response relationship is?

A. A dose-response relationship as used in toxicology is, simply stated as more of a toxic substance is absorbed into the body the greater response to that toxic substance by the body.

Q. Is there such a thing as a linear relationship in toxicology?

MR. POPE: In connection with -- are you talking about dose-response relationships, or something totally different?

MS. STEIN: I'm talking about the subject matter of dose-response.

THE WITNESS: Yes, there is such a phenomenon as a linear relationship, yes.

MS. STEIN: Q. What is that?

A. That simply is that even with increasing doses, either a level in the body or a response by the body, whether that response be an enzyme response or a clinical response, is not increased or decreased even though the amount of toxin is increased.

That is a linear response.

Q. What is the difference between an enzyme or a clinical response?

A. We were talking this morning about SGOT and SGPT and the possibility of those enzymes showing an increased concentration in the blood under certain conditions, such as liver damage and heart damage. That is enzyme response because there could be, there are situations, indeed there are situations in which there is no apparent illness and yet an enzyme level in the blood is found to be increased, and that would be an enzyme response, for example.

Q. Is an enzyme response the same thing as increased enzyme induction?

A. No, those are two different phenomena.

Q. Okay. Could you describe the difference please?

A. An enzyme response is what I just described where SGOT or SGPT is elevated for example, enzyme in the blood is elevated in concentration because of some organic damage, for example liver or heart. That is an enzyme response.

Enzyme induction is an entirely different phenomenon. Enzyme induction is generally, when we are talking about enzyme induction in toxicology, we are talking about the capacity of a drug or a chemical to stimulate the liver to produce -- to stimulate the liver, an enzyme or drug to stimulate or to induce the production of an enzyme in the liver, and the liver enzymes we are usually talking about are generally called mixed function oxydase enzymes, and these -- the liver can be stimulated to produce these enzymes which are responsible for metabolizing various drugs and various chemicals, and the number of drugs and chemicals will indeed induce these enzymes to higher activities.

Q. Is it fair to state that an enzyme response indicates a malfunction in the organism?

A. An enzyme response is not an indicator of function.

Q. What is it an indicator of?

A. It's an indicator of damage.

Q. And what is enzyme induction an indicator of, if anything?

A. There are many enzymes in the liver which can be induced so that to find that a given enzyme is induced in the liver, say one of the mixed function oxydase enzymes, could be of absolutely no health significance.

On the other hand it could indicate that the liver is being stimulated by a drug or a chemical and in many ways that is a defense mechanism because the mixed function oxydase enzymes are responsible for the detoxification of a huge number of drugs and chemicals, and therefore to induce the enzyme system may improve the body's capability to detoxify and metabolize undesirable chemicals.

Q. Would enzyme induction as a health effect, whether classified as adverse health effects or not, would that relate to the specific enzyme being induced?

MR. POPE: I will object to the form of the question, I think you just asked whether the enzyme being induced would relate to the enzyme being induced but if the doctor understands --

MS. STEIN: If Dr. Milby can't understand it --

MR. POPE: I'm sure he will understand it.

THE WITNESS: May I have it again?

(Record read as requested.)

THE WITNESS: In situations involving humans as opposed to experimental or wild animals, I cannot think of a clinically important example of where enzyme induction is important, is significant. There are situations in which one can demonstrate that enzymes in the liver are induced. That is possible to demonstrate. The significance of that in terms of health is another matter. One can speculate about that, but in terms of real situations I don't know of any.

MS. STEIN: Q. Can you tell me what you meant by the phrase clinically important in your last answer?

A. Yes, whether it makes someone ill or not, it does have a significant impact on health. Is the person less or more healthy, does it make you less healthy to have your enzymes induced.

Q. Less healthy as measured by observed symptoms?

A. Yes.

Q. As part of your work do you prepare risk assessments?

A. The definition of the term risk assessment is one that -- I'm not totally clear on what you mean, we do indeed assess the risk of various situations, various exposures, yes, we do that all the time.

Q. What are the tools that you use or techniques that you use in assessing risks of exposures?

A. Our knowledge of clinical medicine, toxicology, epidemiology, and occupational and environmental exposure parameters.

Q. Do you use some mathematical models in that work?

A. No, we do not.

Q. What are the environmental exposure parameters that you examine in assessing the risk from that exposure?

A. Concentration of the toxins in the environment, in the air, water, food, soil, that sort of thing, the nature of that toxicant, the possibilities for exposure, of significant exposure, the kinds of people involved, age, sex, race, medical predispositions, a whole series of things.

Q. Smoking or nonsmoking?

A. Yes.

Q. Alcohol consumption?

A. That would be a possibility, yes.

Q. In terms of medical predispositions, do you look at family members as well?

A. Sometimes you do. By medical predispositions, I was principally referring to special hypersensitivities, that kind of thing.

Q. Do you look at route of exposure?

A. Yes.

Q. Does route of exposure have an impact on the clinical or subclinical impacts in an individual?

MR. POPE: I object to the form of the question as being incomprehensive.

MS. STEIN: I was using terms that Dr. Milby used,

MR. FEATHERSTONE: That doesn't mean that you put them together in a sensible manner.

MR. POPE: Are you talking about generally, or are you talking with respect to --

MS. STEIN: I am talking generally now, whether route exposure --

MR. POPE: Will always be, or would sometimes be, is that your question?

MS. STEIN: Generally, and if there are exceptions I would be happy for Dr. Milby to tell me what they are. What I am trying to get at is whether or not route of exposure is one of the parameters examined.

MR. FEATHERSTONE: In risk assessments?

MS. STEIN: In risk exposure.

MR. POPE: Exposure to what?

MS. STEIN: The toxicant.

THE WITNESS: Yes, route of exposure is considered.

MS. STEIN: Q. Is geography a factor that is considered in assessing the risk of exposure also?

A. It may be, yes.

Q. Obesity?

A. It may be, yes.

Q. Stress.

MR. POPE: What about stress? Is that a question?'

MS. STEIN: Yes, that is a question.

MR. POPE: No, it's just a word. And I object to the form of the statement.

MS. STEIN: Q. All right.

Is stress one of the parameters that you consider?

A. We do sometimes.

MR. POPE: In what?

MS. STEIN: In assessing risk of exposure to toxicants.

THE WITNESS: Yes.

MS. STEIN: Q. Is social class a parameter that you consider?

A. Yes, we may.

Q. Are there standard methods for controlling, for smoking as a variable in assessing the risk of exposure to a toxicant?

A. There are standard methods for controlling, for any confounding variable, of which smoking certainly is often one.

Q. Let's go through separate confounding variables. What is the way in which epidemiologists control for smoking as a confounding variable in assessing risk from exposure to a toxicant?

A. You assure that the smoking habits of the exposed population and the control population, or the comparison population, are the same.

Q. Is social class a parameter that you consider in assessing the risk of exposure to a toxicant?

MR. POPE: That has been asked and answered.

THE WITNESS: You asked it already.

MS. STEIN: Did I? Okay.

Q. How do you control for social class as a confounding variable in assessing the risk of exposure to the toxicant?

A. As a general principle in epidemiology controls for confounding variables is accomplished by assuring insofar as possible that that confounder is present in both the study

population and the comparison population.

Social class, smoking, and other confounders are generally handled that way.

Q. In your experience as an epidemiologist, have you found in your work with PCBs that the route of exposure to humans has an impact on the effects observed in humans?

A. No.

Q. Can you tell me what the basis for your negative answer is?

A. The basis for my saying that in my experience the route of entry of PCBs into the body is not determined or in any significant way affect the response to PCBs, is based upon the fact that PCBs may enter the body through ingestion, inhalation, or through the skin. Either ingestion, inhalation, or skin absorption changes the PCB chemically or toxicologically. Therefore, once the PCB is in the body it really makes no difference how it got there; so the toxicology, once it's in there, is the same.

Q. Could you tell me what you mean by the route of exposure doesn't change the PCB chemically?

A. Sure. For the most part, most toxic chemicals, the route of entry does not affect the toxicity of the chemical. Sometimes it does. For example, the skin does affect the toxic nature of certain pesticides, that is when they are absorbed through the skin the skin changes to some extent to make them more or less toxic, depending upon the compounds. But for the most part no matter which route of entry a toxicant uses, that route of entry doesn't change its toxicity.

Now, it is true to say of course that most compounds are more quickly absorbed if they are swallowed or inhaled than if placed on the skin and absorbed; therefore, the speed with which they cause a reaction may differ, but the nature of that reaction generally doesn't differ.

Q. Does the duration of exposure have an impact on assessing the risk of exposure from a toxicant?

A. Could you define for me, duration of exposure? It's used in different ways.

Q. All right. Why don't you tell me the ways in which it is used?

A. From an epidemiological standpoint, the duration of exposure is the period from the time that an individual in a study group is hired until the time he leaves work, is either terminated, fired, or has died, or just disappears.

That is your duration of exposure, a very specific definition of duration.

In other situations, if we are talking about someone who lives near an environmental source of a toxicant, then duration is something else, it may be how long the person has lived there, how long the person has come in direct contact, that sort of thing.

Now, duration of exposure, if you mean, as to the first definition, that it is limited to occupational -- well, in my mind for the purpose of this discussion I am trying to so that I can keep them straight.

Q. All right.

A. So the duration of exposure as we use it in the

epidemiology of occupational mortality studies is significant because in many cases we are talking about compounds which are either absorbed and stored in the body or we are talking about compounds which may have a long-term effect based on the fact that exposure is repeated day in and day out, so duration of exposure is especially important for example in occupational exposure while looking at cancer and its relationship to exposure during occupational activities.

Generally that definition is not one that I use for other kinds of exposures, and duration generally doesn't mean a lot to me outside of that rather specific definition.

Q. Then let me ask you, if duration has a specific meaning for you, and it is limited to the occupational context, how can I discuss with you the concept of time with relation to environmental exposures, other than in the occupational context?

A. It would help me to understand what you mean. If a person lives, for example, near a source of pollution and is exposed daily for years, then I would accept that as duration, if that is what you mean. By duration I wasn't sure whether you meant how many times someone is taking an aspirin, that would be confusing to me.

Q. I guess I would have said how many times a person takes an aspirin is frequency, as opposed to duration.

A. All right, we can work on that definition.

Q. All right?

A. Yes, sure.

Q. The next question is how does the frequency of

exposure affect assessing the risk of exposure from a toxicant, if it does.

MR. POPE: The question is how?

MS. STEIN: Yes.

THE WITNESS: I am not sure that I can generalize on that, frequency can be important in some cases and not very important in others, so it is safe to generalize it that most of the time both frequency and duration of exposure bear on the toxicology of the substance, and the toxicity of that compound.

MS. STEIN: Q. Does the recentness of the last exposure factor into an analysis in assessing the risk of exposure to a toxicant?

A. It can, yes.

Q. Could you tell me, could you define the term biomagnification?

A. Biomagnification is a term that is used to describe the phenomenon in which tissues absorb a chemical, a substance, and the exposure continues at a rate which is greater than the excretion of that compound, so that more comes in than goes out, and that result is an increasing body burden of that chemical and that is called biomagnification.

Q. Is that also referred to as either bioconcentration or bioaccumulation?

A. I believe it is, yes.

Q. Are we talking about increasing the body burden in a specific individual, as opposed to increasing concentrations as one moves up a food chain?

A. The latter definition in my understanding is biomass.

Q. In your opinion Dr. Milby, do all of the commercially produced mixtures of PCBs exhibit the same degree of toxicity to humans?

A. Well, I would have to separate that into general categories, let's use acute and chronic toxicity.

It's generally assumed that the more chlorination, the higher chlorinated compounds, are less toxic than the lower chlorinated compounds.

On the other hand, the higher chlorinated compounds are more likely to be retained by the body and concentrated in the fat, than are the lower chlorinated compounds.

Because of the nature of the metabolism of these compounds, the toxicologist would predict that the lower chlorinated compounds are more likely to be carcinogenic than the higher chlorinated compounds.

Animal feeding studies have not supported this notion, so on balance it's a question for which there is no real answer, but those general statements I have just made are considered to be about where we stand on the knowledge of that.

Q. This was general, as opposed to --

A. As opposed to the acute or chronic, yes. Generally that is the case.

Q. What is the basis for saying in light of the general assumption about higher chlorinated being more toxic than the lower, is that correct, more toxic than the lower?

A. Higher chlorinated are less toxic, the more the chlorination the less the toxicity, is a general assumption.

Q. And I believe you said that as a result a toxicologist

would predict that the lower chlorinated may be or would be more likely to be more carcinogenic. Could you tell me the basis for that statement?

A. The basis for that statement is that the lower chlorinated compounds are more readily metabolized and the step through which they are metabolized produces an intermediate called arene oxide which is likely to be a carcinogen, so by that rather relatively simple assumption, that is the basis for my statement and for the general understanding in that regard.

Q. Does this basis that you just described to me, is that discussed in the published literature on PCBs?

A. Yes, I believe it is, I think so, I can't give you a citation but I wouldn't know about that if it were not published.

Q. Doctor, do all commercially produced PCB mixtures exhibit the same degree of acute toxicity in humans?

MR. POPE: Are you talking about commercially produced in this country?

MS. STEIN: That were produced in this country, that's right.

MR. POPE: As opposed to Europe?

MS. STEIN: Yes, that's right.

THE WITNESS: As a practical matter, and without regard to contaminants such as dibenzofurans, assuming we are talking about just PCBs without regard to contaminants, from a practical standpoint I am not aware of any important differences in the toxicity, although I am aware that in animals some differences can be shown.

MS. STEIN: Q. Do the differences that have been shown in animals have any relevance to human acute toxicity studies involving PCBs, again with the assumption that there are no impurities in them?

A. I have never seen any evidence to indicate that that is the case.

Q. With respect to commercial mixtures of PCBs that were produced in the United States, is there any difference in the chronic toxicity of any of those, and again for now we will take your assumption that there are no contaminants in them.

A. I have never seen any evidence of disease in humans that would bear that out, although I am aware that animal studies may show that.

Q. Do you know whether PCB commercial mixtures produced in the United States contain any degree of contaminants specifically including dibenzofurans?

A. Only what I have read, which suggests that PCBs made in this country on occasion have been found to contain very small concentrations of dibenzofurans, much smaller than have been found in Japanese PCBs, for example.

Q. What is the basis for your statement that on occasion the American PCBs have been found to contain very small amounts?

A. Because I have read that sometimes there are found to be none.

Q. Could you tell me what you read that said American PCB mixtures had no dibenzofurans in them?

A. I am trying to -- I have to remember them.

Dr. Kimbrough's book, published by the El Sevier publishers, published in 1979 I believe, perhaps 1980, discusses this subject. I know that in that book it was said that American PCBs are found to have very low levels of dibenzofurans. I believe I have read elsewhere and I cannot give you a citation that, that there have been samples of PCBs in which detectable levels of dibenzofurans have not been found.

Q. Do you know whether this other source that you refer to, that said that samples of PCBs in which detectable levels of dibenzofurans were not found, were involved in environmental samples, or were they the commercially prepared mixtures themselves before having gotten into the environment?

A. They would be commercial PCBs before entrance into the environment.

Q. Does entrance into the environment have any effect on dibenzofurans concentration in PCBs -- that is, commercially prepared PCB mixtures?

MR. FEATHERSTONE: Why don't you try the question again?

MS. STEIN: Sure. Does entrance into the environment have any effect on the presence of dibenzofurans in American commercially prepared PCB mixtures?

MR. FEATHERSTONE: I object to the question, lack of foundation.

MS. STEIN: Go ahead Doctor.

THE WITNESS: The term enters into the environment, has me a little bit confused. PCBs which are relatively free or perhaps completely free of dibenzofurans, when heated to

high levels like in the Yusho situation, may contain more dibenzofurans by virtue of the fact that the heating produced dibenzofurans from the PCBs.

That is commonly understood, and then it gets into the environment as it did in the Yusho situation, so in that case, the answer to your question is yes.

MS. STEIN: Q. Do you have an opinion as to the effect on toxicity to humans of the presence of dibenzofurans in PCBs, first in trace amounts and secondly in an instance higher than in trace amounts, that you are aware of?

A. Yes, on both counts.

Q. Okay. Can you tell me what your opinion is?

A. Dibenzofurans are perhaps 500 times more acutely toxic than PCBs. They are also likely to be much more potent carcinogens than PCBs if indeed PCBs are carcinogens.

The carcinogenicity of dibenzofurans has not been completely studied.

So, back to the question, indeed the presence of dibenzofurans in PCBs would contribute significantly and substantially to their toxicity and indeed would likely in my opinion produce manifestations that the PCBs themselves cannot produce.

Q. Can you give me the basis for that opinion, any literature?

A. Citations?

Q. Yes, or any conversations or seminars.

A. I will refer again to Dr. Kimbrough's book to which I referred earlier, which discusses the toxicity of those two

compounds. It is clearly stated in that book that the agents are quite different in their toxic nature. It has been widely speculated, and I believe I would agree, that dibenzofurans were prominant in the Yusho incident. Dibenzofurans were implicated in the Taiwan Yusho incident recently.

Q. Anything else?

A. At the moment that is all I can think of.

Q. I believe you said in response to an earlier question that dibenzofurans are perhaps 500 times more acutely toxic than PCBs. Is there a difference in the chronic toxicity between dibenzofurans and PCBs, as well?

A. I usually -- whenever I talk about chronic toxicity, I include carcinogens and it is my understanding that despite the fact that dibenzofurans have not been studied extensively for their carcinogenicity, that their mutagenicity or teratogenicity, that indeed they are more active in all three of those chronic health responses than PCBs are.

Q. Can you refer me to any specific studies?

A. I can refer you to Dr. Kimbrough's book again because these notions are described in her book.

Q. Do you have an opinion as to whether specific congeners of PCBs are more toxic than others?

A. I don't know of any evidence for that, especially in humans.

Q. How about in animals?

A. I don't know of any; there may be.

Q. Do you believe that the blood levels of PCBs in humans are an accurate indication of the duration of exposure

to PCBs as you previously defined duration, and let's start with the occupational context.

A. In humans?

Q. That's right.

A. Yes, I think that in humans duration, along with the duration of exposure, the more likelihood it is that the blood levels will be higher. The problem, however, it must be understood, is that the PCB levels in body tissues are also a function of age, as has been demonstrated repeatedly; so insofar as duration can be separated, duration of exposure can be separated from age, I would suspect that duration will contribute, but one has to separate age to begin with.

Q. By body tissues, do you include blood?

A. Yes.

Q. In your opinion are PCB blood levels in humans an accurate indicate of the recentness of exposure to PCBs?

A. They could be, yes.

Q. How about the total amount of exposure, are blood levels in humans an accurate indication of the total amount of PCBs to which the individual was exposed?

A. I can't answer that question because of the way you put it, if you mean body burden, or the total amount over a lifetime, or --

Q. The total amount of environmental exposure.

MR. POPE: Is the question, is it an accurate --

MS. STEIN: That's right, an accurate indication.

THE WITNESS: No, I don't think so, if I understand what you are saying.

MS. STEIN: Q. And do PCB blood levels in humans provide any indication of acute toxic effects?

MR. POPE: This is a different question?

MS. STEIN: That's correct.

THE WITNESS: Is there any particular toxic effect that you have in mind?

MS. STEIN: Q. I will be happy to say this, do you believe that chloracne is an acute effect?

A. There has been at least one study that suggested that blood levels in excess of around 400 parts of a billion are more likely to be associated with clinically apparent chloracne, but there are some individuals with chloracne who have levels lower than that, and some individuals who have levels higher than that, but as a general guideline, that has been suggested, 400 parts per billion.

Q. What study was that?

A. Oue, O-u-e, et al. I am not sure if I spelled it correct. It may be O-u-w, I think it's O-u-w.

Q. Yes, I think it's O-u-w. In other words, you do believe that there is a relationship between PCB blood levels and clinical indications of chloracne?

MR. POPE: I object to the form of the question, that isn't what he said, he said there has been a paper indicating that hypothesis.

MS. STEIN: I will be happy to withdraw the question and ask another question.

Q. Do you agree with the paper you previously mentioned that appears to state that blood levels of PCBs in

humans may be an indication of chloracne?

MR. FEATHERSTONE: I object to the form of that question, it is not how he described it at all.

MS. STEIN: Q. Doctor?

A. I have no experience with looking at chloracne in blood levels of PCBs, so I don't know, all I can do is cite that paper.

Q. Do you have an opinion as to whether or not PCB blood levels in humans are an indication of any chronic toxic effects on humans?

A. No, I know of no evidence that would suggest that.

Q. Do you have an opinion as to whether adipose tissue concentration of PCBs are an accurate indication of the duration of exposure to PCBs as you previously defined it?

A. Yes, I have an opinion.

Q. What is your opinion?

A. My opinion is that the adipose levels could be an indication of duration of exposures, assuming that that exposure duration had not ended a long time ago and the body had a chance to clear the PCBs from the tissues.

Q. What is the basis for that opinion?

A. The basis is twofold. One is that PCBs do accumulate in the tissues and therefore it would make sense to suggest that the longer the exposure the more accumulation.

Secondly, PCBs do eventually leave the adipose tissues; therefore, if there were no exposures for a long period of time then I would expect that the level of PCBs in adipose tissue would not necessarily reflect duration.

Q. What is the basis for your opinion that PCBs do leave adipose tissue after exposure has ceased? Is that a correct statement of your testimony?

A. Yes. There's some specific examples, and some general comments in connection with that question that I would make.

It has been shown in experimental animals given a single dose of PCBs that with time the adipose tissue levels drop.

Also as a generality, since PCBs and DDT share many similarities with regard to their ability to store in fat tissues, it's well known that DDT levels in the fat drop with time, and I would expect the same thing would likely happen with PCBs, and I think that has been demonstrated by animal experiments.

Q. Is it fair to state that it is your opinion that with respect to retention time in human adipose tissues, animal studies relating to retention time in animal adipose tissues are relevant?

A. In principle, I believe they are relevant, that is to say, that if PCBs are stored in animal tissue and with time are excreted from the animal tissue, then I would expect that to happen in humans, yes.

Q. Do you know whether there are any studies involving the retention time of PCBs in human adipose tissue?

A. There have been some studies, at least one study that I have read, that has attempted to address that question, and that was the Humphrey study, but upon examining the results

that he described and shown in his report, I am not at all sure that he demonstrated that indeed adipose tissue levels fell, but I think that is because his observation period was very short, it was only a matter of 12 months or so at the longest.

Q. Is the Humphrey study to which you referred in your answer Item No. 2 on Exhibit No. 1?

A. Yes.

Q. With regard to Dr. Humphrey's study, I believe you -- is it correct to state that you believe that the duration of the study was too short to reach a definite conclusion regarding retention time of PCBs in adipose tissue in humans?

A. It is my testimony that the data presented in his study, that in those data the observation period was too short to clearly demonstrate a drop in adipose tissue because he only described a few patients, a few subjects, rather, in which these observations were made.

Q. I am not sure that I understand. I believe you said that the period of time was too short, and then you mentioned that there were too few subjects. Are those two different factors to consider in evaluating Dr. Humphrey's study?

A. Yes. As far as I could tell from reading Dr. Humphrey's study, only six patients were observed as individuals. He looked at groups and observed groups over a time, but that has too many problems, which we may discuss later; but the six individuals for which he gave chronological PCB data in their blood, it's not for me to tell whether these levels dropped or stayed the same.

Q. Doctor, you alluded to problems with study groups.

Can you tell me what those problems are?

MR. POPE: Problems with the way that Dr. Humphrey studied the groups?

MS. STEIN: Yes, that's right.

THE WITNESS: The problem that I was alluding to was the problem that I mentioned before with regard to the observation that the blood levels of PCBs are a function of a number of variables, only one of which is exposure to dietary or any other kind of PCB; another variable that is extremely important is age, it has been shown by a number of investigators that individuals over age 45 have 30 percent or more -- at least 30 percent or more PCBs in their blood than individuals below that age.

Dr. Kimbrough in one of her papers showed that.

So, Dr. Humphrey didn't take that into account. He spoke only of PCB levels as a function of dietary exposure, males having more PCBs than females, and that it is a function of age, maybe a function of weight, but that also may be a function of age; so, there are several other variables which need to be controlled if one is to make any firm statements about Dr. Humphrey's observations; so, not having control for sex or for age in his observations, then I have trouble trying to understand what he was saying.

Q. Are there any other variables that in your opinion are important that Dr. Humphrey did not control for?

A. It's possible that certain drugs may be important in this regard. For example, phenobarbital is a drug which we know stimulates the liver enzyme as we were talking about before,

which may speed up the metabolism of PCBs. Certainly we know that that happens with DDT. Whether he, Dr. Humphrey controlled for that or not, I don't know. That is another variable however.

The most important variable seems to be age, and as far as I could tell Dr. Humphrey did not control for that.

Q. Do you have an opinion as to whether adipose tissue concentration of PCBs in humans is an accurate indication of recentness of exposure to PCBs?

A. How recent would you mean? Like yesterday or last month?

Q. Well, does adipose tissue concentration of PCBs reflect the last exposure to PCBs?

A. I don't know of any evidence of that. The last exposure could have been the last meal, which wouldn't be reflected in the fact.

Q. Does adipose tissue concentration of PCBs reflect the total amount of exposure, I mean, environmental exposure, to PCBs?

MR. POPE: I object to the form of the question, and I believe the question has been asked and answered.

MS. STEIN: I believe I had asked about -- I know I asked about recency and then I asked about duration. I believe I had not previously asked about the amount in the environment.

MR. POPE: The question is, is it an accurate indication?

MS. STEIN: Yes, that is the question.

THE WITNESS: It clearly is not, if you are talking about individuals exposed to PCBs on the job.

MS. STEIN: Q. What is the basis for that opinion?

A. Because if an individual is exposed to PCBs on the job, the opportunities for exposure that would create blood and high fat levels are very good, and those would overwhelm most any environmental exposures with the exception of these catastrophic events, such as the Yusho situation.

Q. Am I correct in saying then that occupational exposure to high levels of PCBs would overwhelm, let us say ingestion through eating fish?

A. Yes.

Q. Dr. Milby, is human breast milk concentration of PCBs an accurate indication of the duration of exposure to PCBs?

A. Duration of the mother's exposure.

Q. Yes, the mother's exposure.

A. I don't know of any evidence that would answer that question.

Q. Is human breast milk concentration of PCBs an accurate indication of the recentness of exposure to PCBs by the mother?

A. I know of no evidence to answer that question.

Q. And is human breast milk concentration of PCBs an accurate indication of the total amount of environmental exposure that the mother has had with PCBs?

A. There is no evidence to answer that question.

Q. Is there any evidence of which you are aware involving transplacental passage of PCBs in humans?

A. Possibly, yes.

Q. Could you tell me what that evidence is?

A. It's generally assumed that babies born to Yusho parents were in some ways abnormal. It was originally assumed and perhaps correctly and perhaps incorrectly, that those abnormalities were a consequence of the mother's exposure to PCBs.

Since the role of dibenzofurans in the Yusho incident has been not only discovered, but better understood, I don't think that one can separate the role of PCBs versus the role of dibenzofurans in producing the abnormalities in the Yusho children.

Q. Would those effects in the children have resulted from transplacental passage, or is it possible that it would have resulted from secretion into the mother's milk and fed to the offspring?

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

THE WITNESS: The Yusho children were not breast fed.

MS. STEIN: Q. Do you have an opinion, Dr. Milby, as to whether PCB blood levels are a prerequisite to clinically observed effects of PCBs in humans?

MR. POPE: I object to the form of the question, I don't know what you mean by that.

MR. FEATHERSTONE: Same objection.

MS. STEIN: Q. Are elevated PCB blood levels in humans a necessary adjunct to clinical health effects in humans?

A. I can refer only to the study I spoke of before, the study by Ouw which seems to suggest that that indeed is the case. I am aware that other studies that have been published, studies of occupationally exposed individuals, have shown an inconsistent relationship between the PCB levels in the blood, and various other measured parameters, such as triglyceride levels, and occasionally to one or another measure of liver function. A report by Dr. Kimbrough reported an association between PCB levels in the blood and both diastolic and systolic blood pressure, although this association has never been confirmed in other studies of which there have been at least four that have looked at blood pressure and one can go on, there have been a number of associations that have been reported statistical associations between elevated PCBs and various other parameters that have been looked at.

With the exception of dermatitis, and the possible exception of triglyceride levels, there appear to be no other consistent relationships, consistent associations.

Q. I believe you just referred to a study by Dr. Kimbrough regarding an association between diastolic blood pressure and PCB blood levels. Have you reviewed that study in preparation for this deposition?

A. I read that study a lot of times before.

Q. Have you evaluated that study for what you may consider design flaws or interpretative flaws in it?

A. I am fairly familiar with that study, I have looked at it, if that is what you mean, yes.

Q. Do you agree that the conclusions in that study are

sound?

A. Well, Dr. Kimbrough is careful to point out that none of her associations were felt by her to be causal relationships, simply stastical associations, some of which she felt required additional study, for example, the blood pressure relationship, and I think that is perfectly fine, I think she's quite right. Fortunately there have been a number of studies that have examined that issue and have found no association, so I think certainly I would hope that Dr. Kimbrough would feel comfortable that that association which she found was not one of any significance.

This happens all the time, we find associations between two variables having nothing to do with causation, it's a statistical aberration, it happens all the time, and that is why epidemiology never shows causation, only association, so there is nothing wrong with finding an association and saying that attempts should be made to validate that association; and the literature is replete with that kind of thing where investigators find associations, and they suggest that these associations be looked at further; and that's fine.

Q. Does the absence of association between the PCB blood levels and for example, liver dysfunction necessarily render a study a negative study from an epidemiological standpoint?

A. I am not sure what you mean.

Q. Let's assume that you have a study where there are some people who were exposed to PCBs and show an excessive liver malfunction, but in that same study either because it

wasn't looked at or for other reasons there is not an association between PCBs and blood levels. Okay? Does that necessarily for lack of an association between PCBs -- does the lack of elevated blood levels in PCBs necessarily render let's say a positive finding -- and I am not using that in a term of art sense, negative?

MR. POPE: I object to the form of the question. If in fact one of the reasons that the study might be considered not showing an association was because it wasn't measured at all that certainly would be a very different situation from one where it was in fact measured and no association was found. You have included both of those aspects in your question, you asked him a compound question, and I don't think it's a fair question. The doctor may answer it.

MS. STEIN: All right. Let's say it wasn't looked for, PCB blood levels were not looked for.

MR. POPE: When something wasn't looked for, does that mean it was a negative study?

MS. STEIN: Yes, that's right. Let's say you are looking at liver function but you didn't look at PCB blood levels in that same study, and you did find some liver malfunction.

MR. POPE: It could be positive in one sense, and negative in another sense?

MS. STEIN: Yes, that's right.

Q. Is that necessarily negative with respect to -- does that in some way invalidate the findings regarding an excess of liver malfunction?

THE WITNESS: I am hopelessly lost.

MR. POPE: So am I.

MS. STEIN: Let me see if I can think of a better way to phrase it.

Q. Let's assume that the Ouw study, which I believe you testified indicated a correlation between PCB blood levels and clinical indication of chloracne -- is that correct?

A. Yes.

Q. Assuming you had a similar study that looked at liver function instead of looking at chloracne where one tried to make an association, and you found an excess of liver malfunction in the study group, but did not find an association of liver malfunction with PCB blood levels, does that negate the positive finding regarding liver malfunction?

MR. POPE: Do you understand that question?

THE WITNESS: I think I do. I will try to restate it however.

MS. STEIN: Sure.

THE WITNESS: If a study of the population of let us say electrical workers is done, and in that study you find an excessively high percentage of the people studied have abnormal liver function, but in that same group you also do serum PCB levels and you find no correlation one with the other?

MS. STEIN: Q. Yes, that's right.

A. Does that make that a negative study?

Q. Yes, with respect to liver function.

A. My answer would be no. It doesn't make it a negative study with respect to liver function.

Q. Does it have any effect with regard to serum levels?

MR. POPE: Does it have any effect --

MS. STEIN: Effect in the sense of making it a negative study.

MR. POPE: The fact that there was no association found between those two factors?

MS. STEIN: That's right.

THE WITNESS: It doesn't in my mind, in my opinion it doesn't negate the study, it weakens the value of the study which would be to try to relate exposure to effect, and if you have lost your measure of exposure, that is serum PCB levels. then it weakens the study because you can't relate a measure of exposure with the effect that you observed.

It doesn't absolutely negate it, it just weakens it.

MS. STEIN: Q. In the field of epidemiology, is it an accepted practice to take a literature review which interprets findings of a number of studies, and use that literature review and its conclusions regarding health effects, as a basis for one's own opinion of those studies and their findings, without one's self reviewing the studies that are the subject of the review?

MR. POPE: I object to the form of the question, no foundation.

THE WITNESS: In my opinion, the reviewer would be ill-advised to accept without review, without his own

personal review, the findings of another person who summarized the literature. I would personally go back and find the original papers, especially those which were important; if they were not very important, I wouldn't bother.

MR. FEATHERSTONE: What you were addressing your answer to was a situation in which somebody, for instance yourself, sat down and read an article written by someone else who was reviewing the studies done by third parties?

THE WITNESS: That's correct.

MS. STEIN: That wasn't the question.

MR. FEATHERSTONE: I wanted to make sure that I understood that.

MS. STEIN: At this point I will ask that this document be marked as Exhibit No. 4.

(Document, The Epidemiology of PCBs by William R. Gaffey, Monsanto Company, September 15, 1981, marked as Exhibit No. 4.)

MS. STEIN: Q. Dr. Milby, I am going to show you what has been marked as Exhibit No. 4 and I will ask you if that is the actual paper which you reviewed in preparation for your testimony in this case?

MR. POPE: Did you identify the exhibit as to what the title is?

MS. STEIN: It's a paper entitled The Epidemiology of PCBs by William R. Gaffey, Monsanto Company, September 15, 1981.

THE WITNESS: Item 8. That is the paper, Item 8 on Exhibit No. 1.

MS. STEIN: Q. Have you ever spoken to Dr. Gaffey about this paper?

A. No.

Q. Do you know Dr. Gaffey?

A. Yes, I do.

Q. Have you ever worked with him?

A. Yes.

Q. When was that?

A. I worked with Dr. Gaffey for ten years in the State Department of Public Health in California on and off in different areas, but I knew him and worked occasionally with him and I worked with him again for a year or so at the Stanford Research Institute.

Q. Doctor, I will refer you to pages 23 through 25 of Dr. Gaffey's paper and ask you which if any of the references in there you have read yourself?

A. On any occasion?

Q. On any occasion, yes. Why don't you just identify it by number as referred to in the list of references.

MR. POPE: You want him to review this list of 35 references, and tell you whether he has ever read any or all of those?

MS. STEIN: That is correct, that is the pending question. In fact, would you --

MR. POPE: I object on grounds of harrassment.

MS. STEIN: Q. Doctor, would you put a mark of some sort in the margin next to those which you have read, and for the record please identify them by number, those items that

you are checking off?

MR. POPE: Why do you want him to do both?

THE WITNESS: You want the ones that I directly have read? Some of these I have seen references to but I haven't read.

MS. STEIN: That's fine.

THE WITNESS: The following reference numbers that I have marked are articles that I have read, Nos. 4, 5, 8, 9, 10, 11, 19, 20, 21, 23, 24, 26, 29, 30, 32 and 35.

MS. STEIN: Q. On page 4 of Dr. Gaffey's paper, there is a reference to the Meigs Study,

Do you know whether the Meigs Study set for abnormal function in those persons not exhibiting chloracne?

A. No, I don't know, but had Meigs done that, the information would not be valid today because the liver function studies that were available to the clinicians at that time are no longer relevant.

Q. Would that hold true also with respect to the liver function studies that he did with regard to those that did exhibit chloracne?

A. Yes. At that time the liver studies, liver function studies, were much less sensitive than those now used. They are not invalid, I used the wrong word, but insensitive, not invalid. So I don't know whether Meigs looked at liver function, and if he did, it would be difficult to interpret it at this point.

Q. Do you know what the study size was in the Meigs Study?

A. No, I didn't check that, I haven't read Meigs, I didn't check that one.

Q. In conducting the study of humans occupationally exposed to PCBs, would it be in your opinion sound epidemiologic practice to test for liver function only with respect to those individuals in the sample population who exhibited chloracne, as opposed to sampling all of the individuals involved?

A. That is not the way I would do it, I would take liver function studies on all of them if I were going to do it on any of them.

Q. On page 5 of Dr. Gaffey's study, the first full paragraph, it begins, "Out of ten live births to women affected by Yusho," and it discusses the Yusho children, are you familiar with the work that is discussed in that paragraph?

A. This is the information that I testified to this morning.

Q. Okay. Do you agree with Dr. Gaffey's statement that "it is not atall clear that these findings" -- referring to premature eruption of teeth and unusually wide fontonelles and sagittal sutures -- "represent any more than the normal variation to be expected, since no control observations were made"?

A. The findings that Dr. Gaffey describes here, premature eruption of teeth and unusually wide fontonelles and sagittal sutures, are conditions that are not especially uncommon; so, selecting those findings, I would have to agree, limiting my comments to those findings.

I would have to agree that I would like to have control observations before I said that those were unusual.

Q. In other words, based on your experience, those rates are not higher than normal for those specific, and for the lack of a better word, let's call them symptoms?

A. I am not a pediatrician, and I don't keep track of that kind of information, but based upon my general medical knowledge, I would tend to agree with what Dr. Gaffey said.

Q. At the bottom of page 4, and carrying over to page 5, there is a discussion of the most common acute symptoms observed, and the dose-response relationship of Yusho disease in Japan. Dr. Gaffey's report in that same paragraph says, "Six years later many patients still reported such symptoms as headache, stomach pain, numbness of the extremities, joint pain, and respiratory symptoms."

MR. POPE: I will object to your characterization of Yusho as a disease.

MS. STEIN: I belive Yusho is called a disease.

MR. POPE: What is the question?

MS. STEIN: Q. Do you agree with that statement in Dr. Gaffey's study?

A. Six years later many patients still reported --

Q. That's right.

A. Let's see what the reference is. I don't recall that exact citation. This information is from the author Yurabe's report, so I can't comment on whether I agree with Dr. Gaffey or not in that matter.

Q. Assuming that that is a correct statement of Yurabe's

findings for a moment, would you attribute any significance to the fact that six years after exposure manifestations were still being seen?

A. I would consider that important, yes.

Q. In what way would that be important?

A. It would suggest to me that the individuals in question here had either received permanent injury of some kind, or that the agent producing the injury was still present, and therefore, still active.

I don't know which one would be the case.

Q. Now I will refer you to the last paragraph of page 6 of Dr. Gaffey's study, and ask you to read that.

A. Yes.

Q. Do you agree with Dr. Gaffey's, with the last sentence, regarding Yusho?

MR. POPE: Do you mean the sentence, "It is therefore doubtful whether any generalization can be made from this incident to lower level environmental or occupational exposures to PCBs"?

MS. STEIN: That's right.

Q. Do you agree with that statement, Dr. Milby?

A. Yes, I agree with that.

Q. Do you believe that Yusho, the Japanese Yusho incident, has any relevance to studies involving low environmental exposures to PCBs?

A. I don't think that one can separate with any assurance the role of contaminants such as dibenzofurans, and the effect of PCBs themselves in this clinical picture we see.

Q. I'm going to ask you to read page 10 of Dr. Gaffey's paper, the last paragraph.

A. Yes, I have read it.

Q. Do you agree with the first sentence of that paragraph, Dr. Gaffey, "In summary, body burdens of PCBs are clearly related to the level of exposure to environmental PCBs"?

A. With the exception of. If Dr. Gaffey is also including occupational exposure with the term environmental, then I would agree that the greater the environmental, including occupational exposure, the higher the lever of PCBs that are likely to be in the body. I would agree with that. The rest of this, I testified to more specifically and in general for the last two hours, I think.

Q. Okay. That goes through to the end of the paragraph?

A. Yes.

Q. I will refer you to page 11 of Dr. Gaffey's report, to the middle paragraph that begins, "Two of the studies" --

A. I have not marked this as a reference which I have read.

Q. With regard to the reference to the second study, which is, "The study of 32 workers in a capacitor plant, ten of whom were exposed regularly to PCBs. The authors state that there is no 'no evidence of physical harm resulting from working with PCBs'."

In your opinion would a study of 32 workers where ten were exposed be an adequate sample size from which to draw a conclusion regarding the health effects of exposure to PCBs?

MR. POPE: I object to the form of the question. The doctor said that he hasn't read that particular study that you are directing him to.

MS. STEIN: I understand that, but I am talking as a general principle. Is 32 an adequate sample size to draw a conclusion from.

THE WITNESS: No.

MR. POPE: Not the study proper, but rather a hypothetical study with 32 workers?

MS. STEIN: Q. In this study, is it an adequate study from which to draw a conclusion?

MR. POPE: You can't ask him that question, he hasn't read the study. If you have the study, and you want to give it to him to study and then ask him whether having read it he then has an opinion as to whether it is adequate or not, that is one thing, but to suggest that this is a quote about a study that he told you he hasn't read, and then ask him whether there is sufficient data there, is a very unfair question and I object to the question.

MS. STEIN: Q. Did you understand the question, Dr. Milby?

A. Yes, I think I understood the question.

Q. All right.

A. From reading this, these several lines here, I would think that the quote no evidence of physical harm resulting from working with PCBs unquote is a reasonable conclusion if that is what he saw in that evidence.

Now, If he were to say quote therefore it is my

opinion that there is no evidence that working with PCBs in the general would cause any problems elsewhere unquote then I would object to that statement; but if he is simply saying that he saw nothing in his 32 people, or his ten people, then I would accept that he saw nothing. In my mind he is not implying that there is no danger, he is saying that he saw none, which is okay, I would agree with that; if he saw none, he saw none.

Q. Would that be an adequate sample size?

A. He saw nothing in ten people, if he said, "I saw ten people and I saw nothing", that is a logical conclusion. But to extend that to a general statement on the absence of health effects on PCBs would not be warranted.

MR. FEATHERSTONE: What page was that?

MS. STEIN: Page 11.

Q. Dr. Milby, would you recognize, from seeing the names here, which of these are on PCBs?

A. Yes.

Q. On page 12.

A. I haven't seen that one, or that one, I assume this is the Humphrey study.

Q. Kitamura you have not seen, and Hara you have not seen?

A. These are all Japanese studies.

This one I have seen.

Q. The Michigan Department of Public Health?

A. Yes.

Q. And the Humphrey one and Inoue?

A. Yes.

Q. And Fischbein, I believe that is one that you checked?

A. Yes.

Q. And I believe you read the Baker and Maroni studies, and the Smith study?

A. Yes.

Q. In those studies that are referred to on pages 12 and 13 that you have read, do you believe that those studies had adequate sample sizes?

A. To do what?

Q. To draw a conclusion regarding the health effects that were being studied in relation to exposure to PCBs.

A. I can't answer that question in general because some studies of only two individuals could provide enough information to make very important statements. For example, if you took two patients with advanced lung cancer, and gave them both drugs and they both recovered, you could make remarkably strong statements about those two patients because patients don't recover from advanced lung cancer.

On the other hand, if you are looking for a different effect, you might take 10,000 people before you could make such a comment.

So, I'm afraid I can't answer the question in general whether the sample size was adequate. To answer a question or make a statement I would have to look at them individually.

Q. Would it depend on the purpose for which you were making the study?

A. Yes, it would depend in part on the purpose for which you are doing the study, but it would depend more on what it is that you were observing and its prominence or its frequency in a control population or in a general population.

If you are looking at just dermatitis, then you would have to make a lot more observations because dermatitis is common in the general population.

If you are looking at liver function changes, then we know that if you go on the street and pick up the first 100 people you see on the street, we know that if you did liver function studies, as many as 25 percent of those 100 individuals would have at least one abnormal test, so it depends on the frequency of observation in the general population before that would limit what you could say about a study.

If you want to talk about these studies individually, I would be glad to do that, but I can't generalize on that.

Q. Okay. Why don't we start with the Humphrey study?

MR. POPE: Let me make an objection here. If you are going to talk about the Humphrey study, why don't you talk about the Humphrey study? Why is your question framed on what Dr. Gaffey in his paper is saying about the Humphrey study? Then you are asking Dr. Milby a question about the Humphrey study as interpreted by Dr. Gaffey? Is that the methodology that you propose for these various studies? I think that is totally inappropriate. If you want to talk about a study, talk about it, but why do we have Dr. Gaffey's comments in front of us at the time you are doing it?

MS. STEIN: I am asking him about the sample sizes at this point, the adequacy of the sample size in those studies.

MR. POPE: Absolutely, but --

MS. STEIN: The basis for Dr. Gaffey's opinion, we haven't gotten to Dr. Gaffey's opinion, I am merely asking for Dr. Milby's opinion of those studies that he is familiar with, at this point.

MR. POPE: You can ask him any question you want about those studies, but I object to your handing him Dr. Gaffey's statement about what those studies said. Ask him whatever question you want but --

MS. STEIN: I am not asking about what Dr. Gaffey said about those studies, I am using the paper at this point as a reference for certain studies that purportedly deal with the epidemiology of PCBs.

MR. POPE: You are dealing secondhand when you are doing it this way, you are asking him about something else and you are handing him a third person's comment on those studies, and I think it is totally unfair to --

MS. STEIN: Do you prefer that I go through the list at the back? I was using this paper as a way of keeping them in context, rather than having Dr. Milby flipping back and forth. I would be happy to use the list.

MR. POPE: If you want to ask him about a study, why don't you hand him the study that you want to ask him the questions about?

MS. STEIN: I don't have all of them with me.

MR. POPE: Well, you can ask him what he knows about it, but I think it is totally inappropriate to give a person a third party's comment on a study and then ask him about the study itself, which is what I understand you are proposing to do.

MS. STEIN: No, that's not correct, Mr. Pope, I am asking for Dr. Milby's opinion as to the adequacy of sample size of some of the studies referred to in Dr. Gaffey's paper. I am point to it only for the purpose of having a reference point for Dr. Milby to tell me --

MR. POPE: It's a misleading reference point, that's the whole problem.

MS. STEIN: Q. Do you understand, Dr. Milby, that when I am pointing to the Michigan Department of Public Health study at this point on page 12, I am only asking for what you recall of the adequacy of the sample size of that study.

MR. POPE: Are you talking about Dr. Humphrey's study?

MS. STEIN: Yes.

THE WITNESS: Shall I comment on Dr. Humphrey's sample size in connection with which of his conclusions? Dr. Humphrey's conclusions, he made a number of them.

MR. FEATHERSTONE: Dr. Milby already testified concerning one of them at least, as I recall.

MS. STEIN: Q. Do you recall, Dr. Milby, whether the Humphrey study that you referred to earlier made any finding regarding the relationship of any Yusho symptoms through the consumption of fish with high levels of PCBs?

A. Yes.

Q. What were those conclusions that you recall?

A. Dr. Humphrey's conclusions were that there was no association between the consumption of fish with high levels of PCBs in them and any of the Yusho symptoms as cited in the IARC report; or, to restate it to be a little more clear, Dr. Humphrey said that he saw no association between any of the Yusho symptoms and eating fish with high levels of PCBs in them.

Q. As you recall Dr. Humphrey's study, do you believe that he had an adequate sample size to come to the conclusion regarding the lack of observable Yusho symptoms, and its relationship to the consumption of fish with high levels of PCBs?

MR. FEATHERSTONE: Are you attempting to impeach your own witness with studies by the federal government?

MS. STEIN: I move to strike the editorial comments.

THE WITNESS: I am trying to formulate an answer. One of the problems I had in understanding Dr. Humphrey's studies is that he was not very precise as to what it was that he did in his study, specifically with regard to the list of Yusho symptoms which he extracted from the IARC document that discussed PCBs.

Many of those symptoms were general kinds of things, with very subjective symptoms. It's extremely difficult to correlate things like that to something like dietary intake, without using a control group. And I know that Dr. Humphrey used a control group in his study in some phases, but I could

never quite tell where he was and where he wasn't, and when reading his study I could not say that I am completely satisfied that Dr. Humphrey's study design could answer very many questions at all including what the science and symptoms were of people who ate fish.

MS. STEIN: Q. Which of the symptoms that you have just been discussing would you consider to be subjective symptoms?

A. The most important Yusho symptoms, the most consistent Yusho symptoms were easy fatigue ability, headaches, those were the most common symptoms, and the most persistent symptoms of Yusho and those are the most subjective symptoms that I can think of.

The only objective sign in Yusho that I would expect to see in indivduals would be chloracne. That is a rather specific kind of skin disease that is associated with chlorinated compounds such as PCBs. Dr. Humphrey didn't see that.

Q. I believe that you testified earlier regarding the Ouw study which related to PCB blood levels and chloracne, or dermatitis.

Do you recall whether or not that study reported any correlation between PCB blood levels and any other symptoms?

A. Other symptoms?

Q. Yes.

A. I don't recall.

Q. In your opinion, was the Ouw study of a sufficient

sample size to draw an association between PCB blood levels and chloracne?

A. Would you refresh my memory on what size sample he had?

MS. STEIN: I am trying to see here what it was.

Let's mark this as Exhibit No. 5.

(Document THE TOXICOLOGY OF PCBs. AN OVERVIEW WITH EMPHASIS ON HUMAN HEALTH EFFECTS AND OCCUPATIONAL EXPOSURES, marked as Exhibit No. 5.)

MS. STEIN: Q. Dr. Milby, I'm going to show you what has been marked as Exhibit No. 5 and that was sent to us by Phelan, Pope & John, and I will ask you if that is Item 13 as designated on Milby Deposition Exhibit 1?

A. Yes, that is the article.

Q. I believe that there is a table at the end of that and --

MR. POPE: Can we indicate that this is entitled THE TOXICOLOGY OF PCBs, An Overview With Emphasis on Health Effects and Occupational Exposures, State of California, January 1981?

MS. STEIN: Sure.

MR. POPE: Thank you.

MS. STEIN: Q. There is a table in the back that refers to a number of the studies that were the subject of that paper, perhaps that table will refresh your recollection as to the study size of the Ouw group?

MR. POPE: The question is whether that refreshes your recollection.

THE WITNESS: Yes, it does.

MS. STEIN: Q. In your opinion, was the Ouw sample group of a sufficient size to draw a conclusion regarding a relationship between PCB blood levels and chloracne?

MR. POPE: Under the circumstances under which that test or that paper was done?

MS. STEIN: I am talking about that paper, yes.

THE WITNESS: Yes, in general I would say yes that the sample size was adequate to suggest that the appearance of chloracne was likely to be only after higher blood levels were attained.

MS. STEIN: Q. Do you recall what confounding variables were taken into account in that Ouw study, if any?

A. No, I don't recall that Ouw took into consideration such things as age or other aspects. He did have a control group however, and found the difference between the exposed and the controlled in connection with the dermatitis, and also saw an association as to higher levels and the prevalence of chloracne.

Q. Doctor, I believe you said that you have also reviewed the Fischbein study?

A. Yes.

Q. Is that the one involving capacitor manufacturing?

A. Yes.

Q. Do you recall what the findings of that report were?

A. They had many, many findings, but in essence the

findings were not very consistent, and not very impressive, in the sense that the capacitor workers -- in other words, that was a large group, 300 or 326, or some such number, but the findings that Dr. Fischbein and his group looked at, there was a whole host of both physical examination findings, medical history findings, and biochemical and hematological findings, then he attempted to correlate blood PCB levels with some lipid findings, and he chose to take the approach of grouping findings according to whether they were within or outside of a normal range, and he found that in each of the tests that he did, especially -- well, in each of the biochemical studies that he did, and he did the usual biochemical studies that one would expect, the enzymes and various other indicators, that some of those studies, among some of those individuals numbering up to 300 at times, that a small percentage of each of those clinical studies, in a small percentage at the time, individuals were outside of the normal range; for example, as I recall he found that perhaps 2 percent of the individuals had SGOTs which were in excess of 50, that happened to be his maximum normal, as well as ours, and he found more percentages of his study population to be in excess of some of the other categories, which is a perfectly normal finding in any group of individuals, you always find, no matter who you examine, you always find a small percentage of individuals that will fall outside of the range of clinical normals, and indeed Dr. Fischbein and his group found that, but none of these numbers were very high, none of the outlyers, if you will, were very high, the percentages were all quite low,

of the abnormal tests, almost always less than 5 percent, maybe 1 to 7 percent that were abnormal, but these were not in my opinion, are not very impressive findings, and do not suggest that he was looking at an abnormal population.

Q. Is it an accepted approach in epidemiology to group findings as being within or without normal ranges, as Dr. Fischbein did in that study?

A. It's done, but it's a very risky thing to do because what you are doing is, you are assuming that the laboratory in which you are having your tests run have as their normal range a very wide range and what you are doing is, you are ignoring the concept of using a control group, your own control group, which is a very risky thing to do, and you can be assured that you are always going to find when you use that method that you are always going to find a small percentage, 3, 4 or 5 percent of the individuals you examine are going to be outlyers, are going to lie outside the normal range. And in part, that is a consequence of the way the tests are run and the normal ranges are developed.

Q. In your opinion, does that approach that Dr. Fischbein followed have any impact on the significance of his findings?

MR. POPE: The approach that he followed?

MS. STEIN: Yes.

THE WITNESS: Yes, it does, in that he didn't find very much at all. He found what I would expect him to find in a population of well people who are not affected by the toxicants he was interested in.

MS. STEIN: Q. In that context then, can you make a definitive statement as to whether or not Dr. Fischbein's study was positive or negative?

MR. POPE: With respect to what?

MS. STEIN: With respect to those group findings.

THE WITNESS: In my opinion, Dr. Fischbein's study did not uncover any information which suggested that the population exposed to PCBs were abnormal in any significant way.

MS. STEIN: Q. Doctor, I believe you said that you had reviewed the Baker study and that is the one involving sewage sludge, is that right?

A. Yes, that is correct.

Q. Do you recall what the Baker study reported regarding exposures to PCBs?

A. Yes, the Baker study reported an association between plasma PCB levels and plasma, or serum triglyceride levels, a direct association, that is the higher the PCB levels the higher the triglyceride levels, as a general observation. That observation is made from time to time by investigators, it was made in the Yusho patients, it was made as I say by other investigators, yet other investigators haven't found that.

Dr. Kimbrough in her study with Dr. Kreiss, for example, couldn't find that, that association, and Dr. Kimbrough's comments on that in her conclusions. So, this again follows into the area of one of those associations that you find periodically but are not consistently found, and therefore are puzzling.

Q. From your recollection of the design of the Baker study, do you believe that there was adequate sample size for drawing an association between plasma serum and plasma triglyceride levels?

A. They used intervals, yes, I think that statistically the answer to your question is yes because they didn't have a statistically significant association.

Q. Doctor, I believe you have reviewed the Maroni study, is that correct?

A. Yes, there were two Maroni studies. Yes.

Q. I believe that Exhibit No. 1 indicates that you have reviewed both parts, is that correct?

A. Yes, that's right.

Q. Do you recall what -- let's take Maroni number one first, what the findings were in the first part of the Maroni study?

A. One of the studies I didn't pay much attention to because it was an idustrial hygiene study, an environmental study, Maroni number one.

The second study of Maroni was a medical study as I recall. One was medical, and the other was not. So, what would you like me to respond to?

Q. You have opened up something else, What is the difference between a study that would be an industrial hygiene study, and a medical study?

A. Well, in my way of thinking, an industrial hygiene study is one where the environmental levels are measured, the air levels are measured, perhaps wipe samples are taken and

measured, and the environment is characterized with regard to the, in this case, the amount of PCBs that are around. That is the industrial hygiene study. There is no comment as to whether or not there is an associated elevation of PCB levels, or liver function abnormalities. It is just a description of the environment.

Q. And then the Maroni study that was the medical study, what do you recall as to the findings in that regard?

A. I will have to admit that I am blank on that one, although I did read it. Do you have a specific question? Perhaps I can respond to it.

Q. Do you know what he was looking for, or what the study group was?

A. For some reason, I am blank on that. I'm sorry.

Q. Okay. I can go on to something else and we can talk about that after you have had a chance to review it.

MR. POPE: I have it.

MS. STEIN: If you have it, that will be fine.

MR. POPE: What is your question?

MS. STEIN: At this point, it is if he recalls what the findings were?

THE WITNESS: Maroni number one is environmental, and Maroni number two is health effects. Maroni showed some associations of the kinds we have been talking about all day, associations between liver function studies and elevated PCBs in the blood.

MS. STEIN: Q. Do you believe that he had an adequate sample size for his study?

A. He had an adequate sample size to examine what he was looking at, that is he simply took a sample of eight people or so and did liver function studies on them, and then ranked them according to their PCB levels, and associated PCB levels and liver function abnormalities.

Q. And that was a statistically significant association?

A. Both of those associations were significant, but viewed in the overall picture of what you find -- I haven't attempted to memorize the exact findings of all of these occupation studies, but rather to try to understand them when they are all taken together, and we discussed that earlier. Findings are not consistent, one investigator finds an association, and the next one fails to find an association. And so we don't find consistent associations, and if indeed there is a common toxic factor involved we should see the consistent differences, especially when you are talking about levels that are relatively high, such as these are.

Q. For example, the Maroni study levels were relatively high?

A. Yes, they were quite high.

Q. Do you know whether Maroni took other confounding variables into account in his study?

A. I don't know whether he did or not. He did find the association and in that case confounding variables would be of less importance as a matter of criticism.

Q. In the Baker study, do you know whether they looked for chloracne in the Baker study as well?

A. I think that is exactly what they looked for. They

found chloracne in four workers, which is not a surprising finding when you are looking at individuals exposed to PCBs, since PCBs and acne are often associated.

Q. Do you recall, was there an association between chloracne and elevated PCB blood levels in the Baker study?

A. There were only four cases. I couldn't say much about that. I don't recall. If there were only four cases it wouldn't mean much anyway but I don't recall such an association or whether he attempted to show that.

Q. In your opinion then, could one describe the Baker study as a negative study, or a positive study?

MR. POPE: With respect to what issue?

MS. STEIN: With respect to chloracne.

THE WITNESS: Inconclusive, I would say.

MS. STEIN: Q. I believe you also reviewed an article by Alexander Smith in 1981?

A. Yes.

Q. It is listed as Item No. 6 on Exhibit No. 1, is it not?

A. Yes.

Q. Do you recall what the purpose of that study was and what the investigators were looking for?

A. Well, all recent occupational health studies of PCBs were looking for the same thing, and they all looked for dermatitis, they all looked for changes in lipid metabolism, examining in that regard serum triglycerides and cholesterol levels, they all looked for liver abnormalities, and many of them looked for hematologic changes, and occasionally pulmonary

function studies are included.

And as I said, I didn't bother to memorize the study because in general they all show the same sort of general patterns, and the patterns are spotty and inconsistent with regard to exposure patterns and positive health findings. So, whether those exposure patterns are defined as serum blood levels or whether they are defined as duration or as frequency of exposure it is the absence of consistency of findings that make these studies difficult to draw conclusions from.

Q. In view of the inconsistency of the studies that you have just described, can one reach a conclusion that there is no cause for concern in terms of occupational exposure to PCBs?

A. No, one couldn't reach that conclusion. I wouldn't reach that conclusion.

Q. What are the causes for concern?

A. In my opinion, occupational exposures to PCBs are of concern because PCBs if in, again, in my opinion, clearly associated as the causal factors in chloracne. Chloracne is a serious and disfiguring dermatitis, and under occupational exposure conditions it is quite evident that there is a relationship between high exposure to PCBs and the development of this disfiguring treatment-resistant disease.

Insofar as other findings go that have been described in these various studies, and the inconsistent patterns as I said, in my opinion these studies taken as a whole do not represent a data base, if you will, that causes me much concern.

Q. By the studies as a whole that don't represent a data base that causes you much concern, are you referring to the occupational studies or any environmental studies?

A. I am referring to the occupational studies, and including in those, and I am willing to throw into that category, environmental studies in which contaminants have been involved such as Yusho and I am not willing to dismiss that as an inconsequential matter, by any means.

On the other hand, I am inclined to believe that the Humphrey study, which is an environmental study, can be comfortably tossed into the occupational health studies and insofar as the Humphrey study and his observations and conclusions, I don't feel they are the basis for much concern, either.

Q. Doctor, I believe there was a reference earlier to a Yusho outbreak in Taiwan, I believe in 1979, is that correct, discovered in 1979?

A. It was discovered at about that time, yes, that is my understanding.

Q. Have you reviewed any literature relating to that 1979 Yusho outbreak in Taiwan?

A. Yes. There was one paper that I reviewed, a recent paper I believe published in 1981 by some Taiwanese and Japanese investigators.

MS. STEIN: Why don't we mark it as Exhibit No. 6?

(Document Levels and Gas Chromatographic Patterns of Polychlorinated Biphenyls in the Blood of Patients After PCB Poisoning in Taiwan, marked as Exhibit No. 6.)

MS. STEIN: For the record, I will identify this as Levels and Gas Chromatographic Patterns of Polychlorinated Biphenyls in the Blood of Patients After PCB Poisoning in Taiwan.

(Recess.)

(Document entitled Role of Polychlorinated Dibenzofuran in Yusho (PCB Poisoning), marked as Exhibit No. 7.)

MR. POPE: For the record, we have marked as Exhibit No. 7 a document entitled Role of Polychlorinated Dibenzofuran in Yusho (PCB Poisoning), from the Archives of Environmental Health, November/December 1981.

MS. STEIN: You did a great job in identifying that, Mike.

Q. Dr. Milby, is that one of the articles you were referring to that you reviewed, concerning the Yusho incident in Taiwan?

A. Yes, I read this, and that is the subject of the article.

Q. Have you reviewed any other literature involving the 1979 Taiwan Yusho incident?

A. No other original papers; I have seen reference to it elsewhere.

Q. Do you recall whether Exhibit 7 is consistent with the paper described in the Japanese Yusho incident in terms of the symptoms that were observed?

A. Essentially, yes, that's right. The outbreaks are very similar.

Q. And did you have occasion to evaluate the study design of that paper?

A. Well, yes, I have read the paper, and I have given it some thought. One is being generous in calling it a study design. The paper reports some interesting observations but it is not however a complex scientific study.

Q. Would you agree or disagree with the results that are reported therein?

MR. POPE: The results?

MS. STEIN: The observations that are reported there. I realize you didn't see it, but do you have --

MR. FEATHERSTONE: I object on foundational grounds.

MR. POPE: Maybe you could sort of point Dr. Milby in some direction as to what you are referring to in regard to the observations that were reported.

MS. STEIN: All right.

THE WITNESS: There is an error in the summary as I recall. I think it is a translation error. It is misleading, but in any event --

MR. POPE: There is no question pending, Doctor.

MS. STEIN: Let him finish his sentence about the incorrectness.

MR. POPE: Let's proceed.

MS. STEIN: Q. I think that the incident described in Exhibit No. 7 took measurements of PCB blood levels at a time closer to the actual ingestion of the substance than did the blood tests after the Japanese Yusho incident, is that correct?

A. That is correct.

Q. Do you recall whether there were any differences in terms of PCB blood levels as a result of that time differential lapse after the ingestion of the substance?

MR. POPE: I will object to the form of the question. It's compound. Why don't you first ask him whether there is any difference in the levels and then ask him if there is any causal relationship.

MS. STEIN: Q. Is there any difference in the levels that you recall that were recorded in terms of PCBs?

A. Yes.

Q. What was that difference? I am not asking about specific parts per billion, but as a general matter.

A. Well, as you said, the levels that the authors reported in the Taiwanese Yusho patients were taken relatively very shortly after the outbreak of the epidemic, the episode, as opposed to the Japanese investigators who didn't take blood for PCB levels very close to the time of the outbreak, and as one would expect, the Taiwanese levels are higher, PCBs and dibenzofurans are higher, than the current levels of PCBs and dibenzofurans than the Yusho patients in Japan.

Q. Do you attribute any significance to that differential?

A. Yes, I attribute that difference to the duration of the time that has elapsed between the PCB episode in Japan, which has been a decade or so, and the more shorter time between the Taiwanese episode and the drawing of blood.

Q. Does that suggest anything to you in terms of health

effects?

A. It suggests to me that with time the blood levels dropped. The blood levels of PCBs can be expected to drop.

Q. Assuming exposure has stopped, is that correct?

A. Assuming exposure has stopped, yes.

Q. Can you describe for me the criteria that you believe are important in the design of a study trying to establish a risk of carcinogenicity from a substance?

A. An epidemiological study?

Q. That's correct.

A. A morbidity or mortality study?

Q. Let's take morbidity first.

A. Morbidity studies are for the most part inadequate to assess the risk of cancer as the result of exposure to toxic substances.

The reason for that is that morbidity studies are generally carried out in the workplace. All the studies that we have spoken of today, with the exception of the Humphrey study, are studies of exposures in the workplace, workplace populations, and in order for a subject to participate in such studies he or she must number one be alive in order to get to work that day to participate and number two, he or she must be in relatively ambulatory condition to get to work that day.

The people who have cancer are generally number one, not alive and number two, not particularly ambulatory sufficient to go to work, so if you do an occupational morbidity study you miss the people who are dead and who are disabled, because they are not there that day. So that morbidity studies are

not good for chronic debilitating diseases, or highly fatal diseases like cancer. So, you don't do morbidity studies to look for cancer in workplace situations.

Q. Is it possible to design a morbidity study to assess the risk of exposure to a substance that is drawn from a non-occupational setting?

A. It is possible, but it is by its very nature a very difficult thing to do because in order to do a study of cancer incidence and that is what you are looking for, cancer incidence, and not cancer death rates, if you are looking at the population such as you are describing several things have to be known. Is the population at risk to exposure to whatever it is you are interested in, whether PCBs or mercury or lead or whatever.

First of all you have to define a population that is exposed and in the occupational setting that is relatively easy because we know a segment of that work force is exposed.

To do that in a community is difficult unless everyone is exposed or unless there is a clear difference between those that are exposed and those that aren't, and that is a very difficult thing to do.

In the case of the Yusho situation, even though the exposure to PCBs and whatever else, came from ingestion of rice oil from a single company, even then the investigators couldn't clearly define the population at risk.

And secondly, after you define the population at risk you have to be able to follow that population at risk for a long time and again in the population of a community study for example

it is virtually impossible to do what we call a retrospective -- a historical prospective study, which is the usual kind of study that one does in cancer because that involves identifying the population present and exposed at some time in the past and following the mortality experience or the cancer incidence of experience of that population forward in time. That is very difficult to do in a population that is not tied together by something like occupation or working in a certain place, or something like that.

So, yes, although theoretically it is possible to use a community group for a cancer incidence study, it is very difficult to do, and generally it is not done.

Q. Doctor, can you think of any instances where it has been done?

A. Where a community study has been done to look at cancer incidence?

Q. Yes, that's right.

A. A cancer incidence study, of course, has to rely on sources other than death certificates. You can't use death certificates on a cancer incidence because some people haven't died from cancer who have it, and some don't die. So that makes it even more difficult. There have been studies looking at cancer incidence in communities, there have been studies looking at liver cancer in certain tribes in Africa who have an underlying exposure to aflotoxin. There have been studies in communities exposed to other substances, but they are not common, and not very satisfactory.

Q. Would one of the criteria that you would use in

designing a mortality study be to assess the carcinogenic potential of a toxicant?

A. Most mortality studies that are designed to look at carcinogenic potential of a single substance are occupational in nature. A population is an employed population, employed in an activity that exposes them to this compound of interest. The criteria for such a study include the ability to identify a population exposed to the compound of interest at some time in the past, generally at 20 years past, and to follow that population, to have the ability to follow that population and those who join that population and those who drop out of that population over the period of observation, and at the end of the period of occupation, that is after 20 years, to have the ability to determine the survivors, to determine the members of that population, both those who started, those who came in, those that went out, over the duration of the study period, to determine how many died, and to determine the age, time, sex, race that caused specific mortality of each individual.

Q. Age, time, sex, race --

A. That caused specific mortality for each of those individuals, and to reach an ascertation rate of at least 90 to 95 percent, that is you lose only 5 to 10 percent of your population over that period of time.

There is then the need to make some kind of an assessment of the extent of exposure of each of the individuals in the population, exposure to the toxicant interest and also to determine the duration of exposure during that, in this case, 25 years of exposure, and to determine the latency for each

individual. The latency is by definition the interval between joining the work force of interest, and the date of death, and when all those things are done and the work experience is summed then the causes of death can be compared to some control population such as the United States experience, state death certificate experience, perhaps county statistics, and after all that is done then it requires some experience and knowledge of biological plausibility to interpret the results.

Q. Doctor, can you tell me what you mean by some experience and knowledge of biological plausibility?

A. Yes. As I testified to earlier today, the issue involves, the reason for doing the study, whether you are dealing with a hypothesis generating, or an hypothesis testing analysis. Biological plausibility involves the notion of understanding the nature of the exposure and what kinds of health outcomes you observe.

For example, if you are doing a hypothesis testing study whereby you have determined or there is some suggestion that exposure to the toxicant of interest is likely to produce lung cancer, and the general route of exposure is through inhalation, which is usually the case, then you would expect certain kinds of cancer to show up, for example lung cancer. If you ended up with cancer of another site such as the kidney and that shows an excess, then the notion of biological plausibility would be that there is no particular reason why that should occur, and that would tend to limit the interpretations that you could make on that study.

On the other hand, if cancer of the lung occurred, and

that's what you are expecting because of animal studies or case reports, then that would provide you with some notion of plausibility and strengthen how you can interpret that study.

If you are doing a study that has no hypothesis, a hypothesis generating study, and you didn't have anything particularly in mind that you were expecting to come from that exposure and you found cancer of the kidney for example, the study would be strengthened if you could explain why that particular agent would be likely to cause that kind of cancer either through experience with animal data, animal data from experience reported in single case reports, or even perhaps from analogy to cancer caused by compounds of a similar chemical nature.

Q. How are single case reports used in a hypothesis generated situation where you are trying to assess risk of exposure to a particular compound?

A. Case reports that would be used would be involved in a hypothesis testing situation because a case report would give you the background and the inclination to do the study to test the hypothesis that that case report provided you. If a single case is reported of exposure to Chemical A and cancer of the brain, that would perhaps suggest to you that a more definitive study such as a mortality analysis ought to be done in workplaces where Chemical A is found, to test the notion that perhaps it causes brain cancer; so that would be a hypothesis testing study.

Q. Are they used in a hypothesis testing study? I thought I understood you to say they were used in describing

hypothesis generating studies?

A. In general a case report is usually the hypothesis to test.

Q. Let me back up for a minute. When you talked about latency a little bit earlier, I believe you defined it as the interval between joining the work force and the date of death, is that correct?

A. That is correct.

Q. Does that assume that exposure begins on the first day of entry into the work force?

A. The reason for that definition and the assumptions underlying it is that the notion of latency includes the assumption that exposure starts on the first day, yes. There are other assumptions involved of course, but yes, the answer to your question is yes.

Q. What other assumptions does that concept of latency encompass?

A. The latency notion --

MR. POPE: Are you talking about, in connection with your question, regarding studies to show incidence of cancer?

MS. STEIN: That is correct.

THE WITNESS: In a mortality analysis the notion of latency is used to test the notion that there is a long delay between exposure and development of cancer as a result of that exposure.

For example, if an individual is exposed to a suspect agent on Day 1 and develops cancer at Year 1, the

notion of latency would suggest that there is no relationship between the two, no causal relationship between the two. On the other hand, if the individual developed cancer at Year 20 after being exposed on Day 1, then the notion of latency would be fulfilled, and one would say well, perhaps there is a causal association.

MS. STEIN: Q. How long does the notion of latency assume that exposure continues before death occurs?

A. The notion of latency is not so much based on duration of exposure as it is to the notion that there needs to be a long incubation period, if you will, of the carcinogen before cancer becomes evident, and so to give an example of what I am trying to get at, is that in most epidemiological studies we say that the individual has to be employed for at least one year before he or she can enter the cohort. So that is what we assume is the minimum exposure period that would be of interest to us. Depending on what disease it is that we expect, that we may be considering, that we are faced with, the notion of latency has a different meaning. For example, we have pretty good evidence that the latency period between exposure to a leukemogen and development of leukemia, may only be a few years as opposed to exposure to a lung carcinogen like asbestos and the development of lung cancer generally is 20 plus years. This all gets into the notion of biological plausibility that I was talking about earlier.

Q. Are you aware of literature which makes a distinction between cancer initiators and cancer promoters?

A. Yes, I am generally aware of that concept.

Q. Do you agree with that concept?

A. That concept was developed in animal models, experimental animal models, and its relevance to the human situation is, insofar as I am aware of, generally unsubstantiated although it may be relevant. It would be hard to test that notion --

MR. POPE: There is no question pending at the moment, Doctor.

MS. STEIN: Q. Let me see if I understand your testimony correctly. Is it fair to state that the distinction between cancer initiators and cancer promoters is in your opinion of limited value in regard to human studies?

A. In regard to human studies?

Q. Yes.

A. Insofar as I know there has been no attempt to translate that concept from animal models to human exposure studies. It may eventually prove to be quite relevant, it is just that I know of no data where that notion has been utilized in human studies.

Q. Let me back up for a minute here. Can you tell me what your understanding is of what a cancer initiator is?

A. My understanding of a cancer initiator is that it is a substance, a chemical, or a physical agent perhaps, such as radiation would be a physical agent, which has the capacity to alter or damage DNA, and by doing so unalterably injures the genetic makeup of a cell and thereby may initiate a process which goes on to become a clinical cancer.

Q. Doctor, what is a clinical cancer?

A. A clinical cancer, by clinical cancer I mean an observable diagnosable cancer in a human being, or in an animal for that matter, an experimental animal,

Q. That means tumor, a malignant tumor?

A. A malignant tumor.

Q. Does it require metasteses, a clinical cancer?

MR. POPE: In the way he just used the term?

MS. STEIN: Yes, in the way he just used the term.

THE WITNESS: In general, if we are talking about the clinical characteristics of a cancerous process we generally expect to see a number of things one is metastatic phenomena. The second is invasiveness of tissues. The third is that the tumor we are observing, the cancerous tumor we are observing, does not regress on its own. Those characteristics are generally attributed to malignancies. That is not to say that all tumors which are considered to be malignant metastasize, a few of them don't, but most of them do.

MS. STEIN: Q. Are there specific cases of malignant tumors that metastasize and some that don't? For example, are there some that are site specific in the body, or leukemia as opposed to lung cancer?

A. I am not an oncologist, so I can't speak with great authority; but from general medical knowledge there are some malignant tumors which do not metastasize and an example of that might be the brain. Brain tumors generally do not metastasize.

Q. Can you define a cancer promoter for me?

A. A cancer promoter as I understand the term is

generally a chemical agent which does not initiate cancer, does not damage or alter DNA but modifies the environment, the body environment, in such a way that the growth of a tumorous process is enhanced or not inhibited. That implies that the body is acting under a process by which tumors if they develop are inhibited, and to remove that inhibition a promoter might either remove that inhibition or it might actually act to stimulate that cancerous process. It does not initiate the process, but it may make it, the process, grow and flourish.

Q. Among epidemiologists is the distinction between cancer promoters and cancer initiators a generally accepted premise?

MR. POPE: With respect to animal models or humans?

MS. STEIN: Animal models.

THE WITNESS: Epidemiologists don't deal with animal models, so the concept of initiators and promoters has not yet become part of mortality analyses for carcinoma.

MS. STEIN: Q. With respect to toxicologists, is the distinction between cancer initiators and cancer promoters an accepted premise?

A. Among toxicologists who are involved with experimental animals I think that may be. I don't know. I am not in that field of endeavor.

MS. STEIN: Why don't we stop now?

MR. POPE: All right, 9:00 a.m. tomorrow morning?

MS. STEIN: That's fine.

THE WITNESS: All right.

FRIDAY, MAY 28, 1982 9:00 A.M.

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EXAMINATION BY MS. STEIN (Resumed)

MS. STEIN: Q. Dr. Milby, you know of course that you are still under oath?

A. Yes.

Q. Doctor, have you ever had your deposition taken before?

A. Yes.

Q. Can you tell me in connection with what kind of matters you have had your deposition taken before?

A. Primarily in cases involving exposure to toxic substances.

Q. Do you recall the names of those cases?

A. I don't recall the names. I recall the substances, but not the names of the cases.

Q. Can you tell me the substances?

A. Yes. In one case the substance was lindane.

In another case the substance was chlordane.

And that is all I can remember. There haven't been many more times.

Q. Do you remember where the lindane case was pending?

A. In Iowa.

Q. And do you recall where the chlordane case was pending?

A. That was here in Oakland.

Q. Have you ever been qualified as an expert witness in judicial proceedings?

A. Yes.

Q. Can you tell me, do you remember the names of the cases?

A. No.

Q. Were they also involving specific substances?

A. Yes.

Q. Was one of them the lindane case that you just referred to?

A. No, that was only just a deposition.

Q. Did you testify as an expert in the chlordane case?

A. No. That again was only a deposition.

Q. Can you tell me the substances involved in the cases where you testified as an expert witness?

A. Yes. There was one case in which parathion was the substance.

Another time when malathion was the substance.

A third time when hydrogen sulfide was the substance.

Another time when carbon monoxide was the substance.

Those are the times that I can remember.

Q. Where was the parathion case?

A. In the State of New York.

Q. Do you recall about how long ago that was?

A. Perhaps four years.

Q. Do you recall where the malathion case was pending?

A. Oklahoma.

Q. Let me back up for a minute. Was the parathion case in a state court or a federal court?

A. I believe it was in a state court.

Q. How long ago did you testify in the malathion case in Oklahoma?

A. Two years ago.

Q. Do you recall whether that was in federal court or state court?

A. I believe that was also in a state court.

Q. Where was the case involving hydrogen sulfide?

A. San Francisco.

Q. How long ago did you give the testimony in that case?

A. About a year ago.

Q. Do you know whether that was in a state court or in federal court?

A. I believe that was in federal court, but I am not absolutely sure.

Q. And where was the case involving carbon monoxide?

A. That was in Sacramento.

Q. How long ago did you testify in that case?

A. I'm sorry, I misspoke. It was not a case involving carbon monoxide. It was a deposition. I did not testify, but it was in Sacramento.

Q. Have you ever given testimony before any legislative bodies?

A. Yes.

Q. Have you given any testimony before the United States Congress?

A. Yes.

Q. What did that involve?

A. In my position as Chief of the Burea of Occupational Health for the State of California, Department of Public Health, I on occasion would testify before Congressional subcommittees that were meeting in San Francisco usually on matters of occupational health legislation and things such as that.

Q. Did you ever give testimony before any of these Congressional subcommittees involving PCBs?

A. No.

Q. Have you ever given testimony before any state legislative bodies?

A. Yes.

Q. And what did that involve?

A. Again, that was in my position as an employee of the State of California, Department of Health, and it dealt with occupational health legislative matters.

Q. Did you ever give any testimony before any state legislative body that involved PCBs?

A. No.

Q. Have you ever given testimony before any federal administrative body?

A. Yes.

Q. Can you describe what that testimony was?

A. That was before an Occupational Safety and Health Administration hearing on rulemaking for -- I'm sorry, my mind is blank for a moment.

Q. Okay. Have you only given testimony on one OSHA proceeding?

A. Yes. I was testifying for OSHA at that point.

Q. Do you recall about how long ago that was?

A. About three years ago.

Q. Have you ever given testimony in any state administrative proceedings?

A. I may have in my capacity as a medical officer for the State of California over a ten-year period but nothing that comes to my mind at this point.

Q. Nothing involving PCBs in that capacity?

A. No. My mind suddenly cleared on the OSHA hearing. It was on dibromochloropropane, DBCP.

Q. Doctor, do you subscribe to any scientific journals?

A. My office subscribes to a number of scientific journals, yes.

Q. Can you tell me what they are?

A. The Journal of the American Medical Association.

Archives of Environmental Health.

The Journal of Occupational Medicine.

The Scandanavian Journal of Work Physiology.

The British Journal of Industrial Medicine.

The New England Journal of Medicine.

The Journal of the American Public Health Association.

The Western Journal of Medicine.

The American Journal of Epidemiology.

And perhaps others, but those are the ones that come to my mind.

Q. And do you regularly read these scientific journals to which your office subscribes?

A. I regularly scan the journals, and read selected articles.

Q. Does your office subscribe to Science?

A. No.

Q. Dr. Milby, is there any certification or qualification for the field of toxicology?

A. There is a certification I believe by the American Industrial Hygiene Association for Toxicology.

Q. Do you know whether there are any other certifications for toxicology?

A. Not to my knowledge.

Q. Are you certified by the American Industrial Hygiene Association for Toxicologists?

A. No.

Q. Dr. Milby, do you have any knowledge of whether PCBs adhere to dust?

MR. POPE: Adhere to what? I'm sorry, I didn't get that.

MS. STEIN: Dust.

MR. POPE: Objection to the form of the question. That is an incomplete hypothetical.

THE WITNESS: Yes, I assume that that would be the case.

MS. STEIN: Q. Do you have any knowledge of transport mechanisms of PCBs in the environment?

A. PCBs have been measured in the air and in water and in soil and in food, and in transporting from one medium to the other. That is the general extent of my knowledge on that subject.

Q. Dr. Milby, has anyone told you the estimated amounts of PCBs in the Waukegan, Illinois area?

A. In what medium?

MR. FEATHERSTONE: I object to the form of the question insofar as it seems to indicate that anyone has arrived at any single estimate of the amount of PCBs in Waukegan Harbor, including the government's own witnesses.

MR. POPE: The question was, the Waukegan area.

MR. FEATHERSTONE: I will amend my statement to include the Waukegan area.

MS. STEIN: You may answer, Doctor.

THE WITNESS: Can you be more specific? By in the Waukegan area do you mean in the air or in the water or in the soil or in the fish? I am not sure as to what you mean.

MS. STEIN: Q. I will be happy to break it down.

Has anyone given you any estimate as to the amount of PCBs in the sediments of Waukegan Harbor?

A. I believe I have seen such data, but I don't remember the exact figures.

Q. Do you recall who showed you that data?

A. I believe it was data that were contained in a report that I was given by -- the report was written by Dr. Toman. It was a modeling document.

Q. What do you recall about that Toman report?

A I recall very little about the Toman report because I did not pay a great deal of attention to it. It was a report which discussed the PCBs in the sediments of the Waukegan Harbor and their transfer to the Great Lakes, both current and historical,

together with some motion of the PCBs in the North Ditch of the OMC property and some historical estimates of the transportation of PCBs from that ditch to the lake.

I believe it only contained some estimates of PCB concentration in the sediments in the water of the harbor and of the lake and some suggestions of other sources of PCBs that end up in the lake; but the exact numbers I don't recall.

Q. Do you have any ballpark recollection regarding the numbers in the Toman report?

MR. FEATHERSTONE: Which numbers?

MS. STEIN: Let's start with the Waukegan Harbor sediments.

THE WITNESS: No.

MS. STEIN: Q. Do you have any ballpark recollection of the amount of PCBs in the sediments in the North Ditch?

A. No.

Q. Do you have any recollection of the estimates of PCBs in the water column of Waukegan Harbor?

A. No.

Q. Do you have any estimates of PCBs in the water of Lake Michigan?

MR. FEATHERSTONE: Well, I object to the question insofar as it suggests that there was any such estimate in the Toman report.

THE WITNESS: No, I don't remember those numbers.

MS. STEIN: Q. What do you recall about the numbers regarding fish in the Toman report?

A. I didn't commit those to memory, either.

Q. Did you take any notes when you read the Toman report?

A. No.

MS. STEIN: Let the record reflect that the Toman report was not identified as one of the materials submitted to Dr. Milby in connection with his testimony in this case.

MR. POPE: Nor will it form the basis of his conclusions or testimony in connection with this case.

MS. STEIN: The interrogatory asked for documents relied on or submitted to Dr. Milby.

Q. Dr. Milby, were you ever given a report by Douglas Churkhower (phonetic spelling)?

A. No, I don't believe so.

Q. Were you given any other reports regarding PCBs in Waukegan Harbor or the North Ditch?

A No.

Q. Have you read anything other than the Toman report relating to PCB concentrations in Waukegan Harbor?

A. No, I don't believe so.

Q. Have you read anything, other than the Toman report, relating to PCB concentrations in Lake Michigan?

MR. FEATHERSTONE: What in Lake Michigan? The sediments in the water, the plankton, the fish, the big fish, the little fish?

MR. POPE: Is your question in connection with this case as opposed to his scientific reading?

MS. STEIN: No, it is not so limited.

MR. POPE: All right, so the question is, has he ever

read anything about PCB concentrations in Lake Michigan?

MS. STEIN: That's right.

THE WITNESS: Yes, I am sure I have, I have read such information periodically, but the nature of that information is such that I don't recall the numbers, and I am not really sure where I read that but from time to time in my readings I come across statements about Lake Michigan PCB levels, and I could guess from my memory what levels were in the lake from what I have read but it would only be a guess, and I don't pay any attention to that.

MS. STEIN: Q. Doctor, in your capacity as a consultant for the utility company in this area, regarding PCBs, have you ever confirmed whether any of the patients discussed with you by the other physicians had in fact been exposed to PCBs?

MR. FEATHERSTONE: Objection, asked and answered yesterday.

MR. POPE: By confirmation, you mean beyond the medical history that the patients gave to either Dr. Milby or to the other physicians?

MS. STEIN: That's right.

THE WITNESS: Some of these events have been reported in newspaper articles which I have read after I had discussed that case with the physician; but beyond that sort of confirmation, if you will, no I have not attempted to confirm any of the reports that I have had.

MS. STEIN: Q. Do you have any knowledge regarding whether the PCBs in Waukegan Harbor, in the North Ditch,

contained any amounts of dibenzofurans?

A. I have never seen any reports on that, so I have no knowledge of that.

Q. Do you have an opinion as to whether the PCBs in the sediments of Waukegan Harbor and the North Ditch constitute a risk to human health?

A. As I testified to earlier, I don't know what those levels specifically are; I have however from the Toman report which I did read some time ago, received some idea of the magnitude of those sediments, and at that time I was not especially impressed with concern for public health because of the PCBs in the sediments in that area or in the water, and I can state at this point that I am still not particularly concerned about that as a public health matter.

MR. FEATHERSTONE: If the answer is finished, may I hear the question and the answer read back?

(Record read as requested.)

MS. STEIN: Let me see if I understand that.

Q. When you say that you are not particularly concerned about that as a public health matter, are you referring to the existence of PCBs in the sediments of Waukegan Harbor and in the North Ditch?

MR. FEATHERSTONE: That was not the question.

MS. STEIN: I want to make sure that is what he says, that he doesn't believe -- you are referring specifically to those levels, and are you saying -- my question specifically was whether or not those residues in the sediments pose a risk to human health. You said you were not particularly

concerned about that as a public health matter. May I equate your statement that you are not particularly concerned about that as a public health matter, as a statement of your opinion that those PCBs in Waukegan Harbor in the North Ditch do not constitute a risk to human health?

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

THE WITNESS: Perhaps I could restate what my testimony was meant to be.

MS. STEIN: Certainly.

THE WITNESS: I don't consider the sediments, the PCB levels in the sediments of Waukegan Harbor to be a significant public health problem.

MS. STEIN: Q. Can you tell me what you mean by a significant public health problem?

MR. FEATHERSTONE: I object to the form of the question, he said it's not a significant public health problem. You mean, what does he mean by that?

MS. STEIN: Sure.

THE WITNESS: By that I mean, it's my opinion that the existence of those PCB residues in the sediments are not currently a threat to public health, nor are likely to be a threat to public health in the future if they remain where they are.

MS. STEIN: Q. And does that opinion have as one of its underlying assumptions that there are no dibenzofurans in the PCBs in Waukegan Harbor in the North Ditch?

MR. POPE: I object to the form of the question. When you say no dibenzofurans, do you mean no measurable levels,

no significant levels, or do you mean absolutely zero?

MS. STEIN: I mean absolutely zero.

MR. POPE: How is anybody going to know the answer to that question?

MS. STEIN: When Dr. Milby responded to one question yesterday he said assuming there were no dibenzofurans. Okay? Whatever he meant by that is what I am meaning here.

MR. POPE: Proceed.

THE WITNESS: My statement pertained only to PCBs without regard or assumption that anything else was around such as dibenzofurans or any other toxic substances, so when I said that I don't consider those residues in sediments to be a threat to human health, I was talking about PCBs.

MS. STEIN: Q. Do you know whether in fact American commercially prepared mixtures of PCBs are totally free of dibenzofurans?

MR. FEATHERSTONE: Objection, foundation.

THE WITNESS: We talked about that previously and at that time it was my testimony that I recall that I had read in one or more places where American PCBs had in some cases been found with small concentrations of dibenzofurans in them.

That statement came from I believe Dr. Kimbrough's book which I cited at that time and I believe I also have read, although I cannot give you a citation, that there have been situations where American PCBs have been found to be free of dibenzofurans, but I can't cite that. It is my understanding that American PCBs are very low in dibenzofurans or perhaps free of dibenzofurans.

MS. STEIN: Q. By free, do you mean not detected, or dibenzofurans are absent totally?

A. Not detected.

Q. Do you know whether the PCBs in Waukegan Harbor in North Ditch contained any dibenzofurans?

MR. FEATHERSTONE: I object to the question as having been asked and answered. I object for lack of foundation. And I also would say that your Complaint nowhere speaks at all about dibenzofurans. The people that you put to the task of trying to find dibenzofurans up there have utterly failed, there is no evidence of any dibenzofurans in Waukegan Harbor and if you are trying to convert this case into a dibenzofurans case we are going to have a big, long battle before the judge on that.

THE WITNESS: I have no knowledge of the presence or absence of dibenzofurans in Waukegan Harbor.

MR. POPE: Let me add one thing to Mr. Featherstone's outburst.

MR. FEATHERSTONE: It was not an outburst, it was a statement.

MR. POPE: If the government has evidence of the presence of dibenzofurans in the area around my client's plant, we not only have an obligation to find that out as part of the lawsuit, of course you have a continuing obligation to provide such information, but beyond the lawsuit as well, we would like to know that fact if you have any such information. It may well be that your questions to Dr. Milby are hypothetical rather than based on any particular facts, but if there are any facts I

would like to make a request right now that we be provided with whatever information there is on that.

MR. FEATHERSTONE: Monsanto makes the same request, but Monsanto also assumes that it has been required under the requests that were filed when the lawsuit was started, unless of course the government is lying in the woods.

MS. STEIN: Are you finished?

MR. FEATHERSTONE: It depends on what your next question is.

MS. STEIN: Q. Dr. Milby, from your familiarity with the literature regarding PCBs, are there any contaminants other than dibenzofurans that are present in PCBs?

MR. POPE: I object to the form of the question. You haven't identified whether you are talking about mixtures that were made available commercially in the United States or elsewhere, and Dr. Milby testified yesterday that there is a distinction between the two types or groups; and secondly I am not sure whether the question is contaminants in the PCBs or rather in the fluid, the mixture that is actually being sold.

I object to the form of the question.

MS. STEIN: I will be happy to clarify the question and rephrase it.

Q. Based on your knowledge of the literature and your experience do you know whether there are any contaminants other than dibenzofurans that are present in American commercially prepared mixtures of PCBs as sold?

A. There are two major classes of contaminants found in PCB fluids of which I have read.

First are the polychlorinated quater phenyls.

The second class of compounds are collectively described as dibenzofurans. This is essentially a collective term for a host of compounds, the most important of which and the one I referred to during my testimony is specifically 2, 4, 7, 8, tetachlorodibenzofuran.

MR. FEATHERSTONE: Doctor, was that statement or that answer directed to American made PCBs, which is what I believe the question addressed?

THE WITNESS: No, I misunderstood the question.

That answer refers to PCBs generally described in the literature but specifically in those compounds which have been discovered in Japanese and Taiwanese PCBs.

I have not seen information which specifically describes those contaminants in American PCBs other than the very short statement which is contained in Dr. Kimbrough's book on the occurrence of small concentrations of dibenzofurans in American PCB mixtures.

MS. STEIN: Q. Does that book refer specifically to the 2, 4, 7, 8 tetrachlorodibenzufuran as occurring in American commerical mixtures of PCBs as sold?

MR. FEATHERSTONE: May I hear the question back?

(Record read as requested.)

THE WITNESS: It is my recollection that the author of the chapter to which I refer in Dr. Kimbrough's book spoke only of polychlorinated dibenzofurans, and I don't recall that that was discussed in more detail.

MS. STEIN: Q. Doctor, based on your experience and

your knowledge of the literature involving PCBs, are you aware of any reports of 2, 4, 7, 8 tetrachlorodibenzofurans in environmental residues of American commercial mixtures of PCBs?

A. No, I am not.

Q. Are you aware of any reports of any of the other dibenzofurans being present in environmental residues of American commercial mixtures of PCBs?

A. No, I am not.

Q. Dr. Milby, do you know which Aroclors were components of the hydraulic fluid used at the Outboard Marine facility in Waukegan, Illinois?

MR. FEATHERSTONE: I object to the form of the question, it misstates the record. Listen to your question.

MS. STEIN: I will rephrase the question.

Q. Doctor, do you know which Aroclors were components of the materials sold by Monsanto to Outboard Marine for use at the Johnson Motors Waukegan facility?

A. That information has been provided to me, and I seem to recall that it was a 54 percent chlorine compound; however, because all PCB mixtures are indeed just that, mixtures, the issue of which of the Aroclors is present in sufficient percentage to lend its name to that mixture is as far as I can tell from reading the available scientific literature on human exposures and the effects of those exposures, has no particular meaning. I am cognizant of the fact that in animals you can show some difference in the toxicology of these mixtures and we discussed that yesterday in my testimony that there are some

differences reported in terms of both acute and perhaps even chronic toxicity, but insofar as humans go and the information on the effects of human exposures, I can think of no time when the nature of the Aroclor was shown to be of any consequence.

MS. STEIN: May I hear the answer read back?

(Record read as requested.)

MS. STEIN: Q. Dr. Milby, let me ask you for your definition of Aroclor?

A. I used the term Aroclor in that testimony to mean the percent of chlorine and perhaps I used it incorrectly.

Q. Are you familiar with the numerical designations of American -- well, of the Aroclors?

MR. FEATHERSTONE: I object to the question as being incomprehensible.

MS. STEIN: Well if Dr. Milby doesn't understand it I'm sure he will tell us.

MR. FEATHERSTONE: I'm entitled to understand what the question is intended to elicit.

THE WITNESS: I am aware of in general the meaning of the nomenclature. I am aware that the nomenclature often includes the percent of chlorine and that most of the PCB mixtures that I have read about have either 42, 48, 54, or 60 percent chlorine in them. There may be other PCB compounds, but those are the ones that I recall reading about in the preponderance of my reading.

MS. STEIN: Q. Is that then referred to as Aroclor 1242, 1248, 1254 and 1260?

A. I believe that is the case, yes.

Q. Let me back up a moment to your testimony yesterday when you talked about higher chlorinated and lower chlorinated compounds. Is there a different identifying point between the two in terms of the number of chlorine atoms in the phenyls?

MR. POPE: I would object to the question because it fails to take into account the physical fact that these are mixtures and therefore when you are talking about lower chlorinated and higher chlorinated you are talking about the Aroclors which are the combination of a whole bunch of --

MS. STEIN: I am trying to get his understanding, and then --

MR. POPE: I understand what you are trying to do, but I don't think it is fair to ask a question that kind of implies something different from what we all know to be the physical facts.

MS. STEIN: Well, wait until you see the way my question goes before --

MR. POPE: Well, I object to the question as presently formulated.

MS. STEIN: Okay. I was not talking now about Aroclors in my question to Dr. Milby, I was talking in terms of his testimony yesterday regarding lower chlorinated and higher chlorinated, and if in his testimony he was referring to a commercial mixture as opposed to the number of chlorine atoms in the biphenyl, that is exactly the distinction I am trying to find out right now.

MR. POPE: Do we have a question outstanding? Do you understand what Ms. Stein is asking?

THE WITNESS: I think I understand. I have never considered there to be a distinct, sharp dividing point but in general the lower chlorinated compounds in the papers that I have read refer to the 42 and 48 percent chlorinated biphenyl, as opposed to the 54 and 60 percent which are the higher chlorinated compounds.

MS. STEIN: Q. Do you know whether the lower chlorinated compounds, in this case Aroclor 1242, contains any molecules of the tetrachlorobiphenyl, and higher chlorination?

A. Other than being aware that they are all mixtures, I don't specifically know about that.

Q. Do you know whether Aroclor 1248 has any PCBs that are tetrachlorobiphenyls or higher chlorinated molecules?

A. No.

Q. In assessing the risk to human health of exposure to PCBs, do you assume that the PCBs contain a given percent of chlorination?

MR. FEATHERSTONE: May I hear the question?

(Record read as requested.)

MR. POPE: I object to the form of the question. Are you talking about part of a whole group? He already testified two or three times that we are talking about mixtures. Is that what you are talking about, a mixture of PCBs?

MS. STEIN: Maybe I can make you understand. The difference between percent of chlorination and degree of chlorination, and they are not the same thing. Degree of chlorination, when talking about a specific molecule is one thing; percentage of chlorination of a mixture is another.

MR. POPE: I believe it is your obligation to ask a fairly intelligible question so that the witness can give a straightforward answer.

MS. STEIN: I have repeatedly invited Dr. Milby in instances where he may not understand my question, to ask me to clarify it.

MR. POPE: The witness may well understand what you are attempting to do, and Dr. Milby is a very nice man and he is struggling to answer the question, not the one you are asking, but the one that you are grasping for and I believe it is a lawyer's obligation to ask a straightforward question, and that is all I would like you to do, ask whatever question you want but give him a straightforward question.

MS. STEIN: I have repeatedly invited Dr. Milby, if he doesn't understand, to --

MR. POPE: It's not his job to --

MS. STEIN: I'm sorry that you don't agree, but I have been doing my best and if he doesn't understand, I am sure he will ask for clarification. And I don't agree that he has been struggling to answer and I don't agree with your characterization that I am grasping for a question. If he doesn't understand he is perfectly free to ask me to clarify the question and I will do my best, or make every effort to do so. I am not in any way attempting to mislead him or to ask unclear questions. He is certainly an intelligent and capable man, and he will ask me for clarification if the circumstances warrant it.

MR. POPE: I will agree that you are not intentionally

trying to mislead him, but you are --

MS. STEIN: I am not intentionally trying to mislead him.

MR. POPE: You certainly can mislead a witness with a question that is too vague or contains premises that are not true.

MS. STEIN: If in any way my questions contain those flaws I would be happy to have Dr. Milby point them out and I will correct them.

Shall we go back to the question that is pending?

MR. FEATHERSTONE: Why not state another question? We have had about two pages of colloquy.

MS. STEIN: I know, but I would like to go back to the question.

(Thereupon, the pending question was read the reporter as follows:

"Q. In assessing the risk to human health exposure to PCBs do you assume that the PCBs contain a given percent of chlorination?")

THE WITNESS: I would like to try to clarify my testimony in this matter.

As a physician, and not an experimental toxicologist, most of my concern deals with reports of PCB exposures in humans, although I am conversant with much of the animal literature, at least the assumptions that come from those reports.

Insofar as I am aware, there is little or no information which would suggest that the percent of

chlorination makes a significant difference in the way the human responds to the PCB mixture, and in general while many authors provide information on the nature of the PCBs, the percent of chlorine in the PCBs that they are reporting, the differences between those reports, despite the fact that some report on PCBs with 54 percent chlorine, others with 48 percent, and some with 60 percent, those differences have never been analyzed in terms of human response.

So to answer your question specifically, when I read a report of PCB exposures, I really am not overly concerned about the particular mixture which is being described.

MR. FEATHERSTONE: Doctor, just so that I understand, you are speaking from the standpoint of human health assessment?

THE WITNESS: Yes, human health assessment.

MR. FEATHERSTONE: Thank you.

MS. STEIN: Q. Are you aware of any reports in the literature, first on human health effects that discuss differences between say trichlorabiphenyls and lower degree of chlorination, as opposed to tetrachlorobiphenyls and higher chlorinated molecules?

A. Other than reports that discuss dermatitis which have been over the past several decades that such reports have occasionally occurred, no, I am not familiar with that distinction.

Q. With regard to animal studies involving PCBs, have there been any reports in the literature that draw a distinction between trichlorabiphenyls and lower degree of chlorination of

the molecules, as opposed to tetrachlorobiphenyls and higher degree of chlorination of the molecules?

A. I don't know.

Q. Dr. Milby, do you know whether PCBs interact with sunlight in the environment?

MR. FEATHERSTONE: I object to the question as being indefinite.

MS. STEIN: Have a chemical reaction in the presence of sunlight.

THE WITNESS: I believe they do, but the nature and extent of that reaction is something that I am not familiar with.

MS. STEIN: Q. Is that discussed in literature that you are familiar with, that chemical reaction in the presence of sunlight?

A. I believe it's discussed in a body of literature that I don't read very much, that is the chemistry of PCBs.

Q. Do you know whether these reported chemical reactions of PCBs in the presence of sunlight have any effect on the toxicity of PCBs?

MR. FEATHERSTONE: Objection, lack of foundation.

THE WITNESS: To my knowledge, there have been no reports involving human subjects which show that the effect of sunlight on PCBs is of significant importance.

MS. STEIN: Q. Do you know whether there have been any reports regarding animal studies on that subject?

A. No.

Q. Dr. Milby, do you have an opinion regarding the

appropriateness of the F.D.A. five part per million tolerance level in fish?

MR. FEATHERSTONE: I object to the question as vague and indefinite.

MS. STEIN: Let me back up.

Q. Are you familiar, Dr. Milby, with the F.D.A. regulations relating to PCB concentrations in fish?

A. Yes.

Q. Do you know what that level is?

A. Yes.

Q. What is it?

A. Five parts per million.

MR. POPE: Are you talking about the edible fish?

MS. STEIN: Yes.

Q. Do you have an opinion as to whether or not you think that that level, that limitation, is appropriate?

A. I have no opinion on that.

Q. Yesterday you indicated that you had read Dr. Humphrey's deposition. Is that correct?

A. That's correct.

Q. What do you recall from Dr. Humphrey's deposition?

MR. POPE: As distinguished from his report?

MS. STEIN: That is correct.

THE WITNESS: My major recollection of Dr. Humphrey's deposition is that when questioned Dr. Humphrey gave his opinion that the amount of PCBs that he observed in the blood of the subjects of his study, in his opinion could not be related to any illness of any kind, whether short-term or

long-term, and that he also could not relate levels of PCBs in fish, as described in his report, to any human illnesses, whether long-term or short-term.

That is my major recollection of Dr. Humphrey's rather lengthy deposition.

MS. STEIN: Q. Does your review of Dr. Humphrey's deposition form a basis for your opinion regarding the human health risks of PCBs?

A. No.

Q. I believe you testified that you have also reviewed Dr. Ringer's deposition. Is that correct?

A. Yes.

Q. What do you recall of Dr. Ringer's deposition?

A. I recall very little about Dr. Ringer's deposition because it had to do with PCBs in the feed of mink, I believe, and I didn't study that much in detail, I recall reading the document and that is all I can comment on.

Q. What were the reasons that you didn't study it in much detail?

A. Because Dr. Ringer was describing a situation that I didn't feel had a whole lot of relevance to human health effects, namely the feeding of feed-containing PCBs, to mink.

Q. What was the basis for your belief that the situation described by Dr. Ringer didn't have much relevance to human health effects?

A. Well, the whole issue of mouse to man is a difficult one to understand and going one further step, from mink to man, makes it even more difficult, and there is a great deal of

information in experimental animals through which there is a lot more understanding of the relationship of the metabolism and that sort of thing, between experimental animals to man than there is from mink to man, and I simply didn't feel that Dr. Ringer's information was the kind of thing that I could relate to my own interest in this problem.

MS. STEIN: May I have the answer read back?

(Record read as requested.)

MS. STEIN: Q. Let me ask you, Dr. Milby, and correct me if I am mischaracterizing your testimony, are you saying that there is literature demonstrating that there are certain animals whose metabolisms have relevance to man, and certain animals whose metabolisms do not, and that mink fall into the latter category?

A. My testimony was that I know nothing about mink and their metabolism, and so to translate Dr. Ringer's information into something that I could use was not possible for me.

Q. Do you know something about rodent metabolisms?

A. I know enough about rodent metabolisms that I am very careful when extrapolating from rodent information to human experience, and specifically when we are discussing problems such as those that were discussed by Dr. Ringer that have to do with reproductive effects, and since there is information in other species as well as in men, as well as in humans, concerning their reproductive consequences of PCB exposure, I felt that Dr. Ringer's information was not useful to me.

MR. FEATHERSTONE: May I have the last 12 words or

so of that answer?

(Record read as requested.)

THE WITNESS: There is something I meant to say, as I believe is reflected in the court reporter's reading, that there is information on the health consequences of PCBs in other species, I didn't say whether that was positive or negative information.

MS. STEIN: Q. What is it in your knowledge of the metabolism of rodents that causes you to use caution in trying to extrapolate findings involving rodents to humans?

MR. POPE: I object to the form of the question, no foundation. He didn't say that there was something about the metabolism of rodents that caused him to use caution.

Go ahead and answer the question as best you can, Doctor.

THE WITNESS: In general, information on the toxic response to essentially any toxicants in rodents is information which can only be translated to man with great uncertainty is the generally accepted rule I think among toxicologists and people who deal with that kind of information.

MS. STEIN: Q. What are the reasons for that uncertainty?

A. Man and rodents differ in a lot of ways.

Q. Can you specify what they are?

MR. POPE: Objection. Liz, are you asking him to tell you the way in which a man and a woman and rodents, differ? Is that your question?

MR. FEATHERSTONE: Explain that in 20 words or less.

THE WITNESS: There is a wide species variation in all sorts of toxic responses, and that wide variation is recognized as being present, and that is why one only translates responses in rodents to potential responses in humans with great care. Specifically I am not prepared to enumerate all the enzyme systems and that sort of thing. That is beyond my capability.

MS. STEIN: Q. Dr. Milby, are you aware of any scientific work that is being done regarding the hypothesis that PCBs exhibit a structure activity relationship?

A. No.

Q. Dr. Milby, on Exhibit 1 that was identified yesterday, one of the first items on Exhibit 1 refers to Dr. Kimbrough's work.

Are you familiar with her rat studies?

A. In general I am, yes.

Q. Are you familiar with her rat study involving Sherman strain female rats and the occurrence of liver cancer?

A. Are you talking about her 1975 report?

Q. That's right.

A. I am familiar with that, yes.

Q. Have you reviewed that report recently?

A. I have reviewed the report in the last month or so.

Q. Do you have any disagreement with Dr. Kimbrough's conclusions in that article?

MR. POPE: I object to the form of the question. We don't have that article in front of us and --

MS. STEIN: Let me ask you this.

Q. What do you recall to be Dr. Kimbrough's conclusions in that study?

A. Dr. Kimbrough's conclusions were that she observed an excess number of hepatocellular carcinomas in animals fed PCBs at the level of 100 parts per million in their diet for 21 months. The PCB species that she fed was 60 percent chlorinated compounds to an equal number of male and female rats, I believe, and her conclusion was that under the experimental conditions that she set up that PCBs were associated with an excess of hepatocellular cancers.

My opinion with regard to her interpretation is that I am not fully satisfied that her observation is the last word on this matter because other investigators have not been able to confirm her observations in other studies, nor that she in one of her earlier studies, in 1973, in which she had fed female rats at 500 parts per million for six months of 54 percent chlorinated compounds, observed them for ten months and found no excess in hepatocellular carcinoma, and other studies which failed to support Dr. Kimbrough's observations and interpretations include a study reported out by the National Cancer Institute in 1973 which fed rats with 54 percent chlorinated compounds, and did not find an increase in the number of hepatocellular carcinomas, as well as reports by Calandra, in 1975, who was reporting on work, I believe, done by Gordon and Richter, in which the investigators fed 48, 54, and 60 percent chlorinated compounds to rats for 20 or 21 months, I think 21 months, and failed to observe hepatocellular carcinomas, although their doses, their feeding, was the same

dose as in Dr. Kimbrough's study of 100 parts per million, which she determined that she had found in excess.

So, in summary Dr. Kimbrough's single study reported in 1975 has not been substantiated by other studies by responsible and competent investigators, including the National Cancer Institute.

Therefore, as a physician who reads these studies and tries to understand their importance to human health, I am not prepared to accept Dr. Kimbrough's observations at this time.

Q. Doctor, do you believe that there is any basis to investigate further the potential carcinogenic effects of PCBs in rat studies?

A. Frankly, I don't know what else can be done. N.C.I. has carried out an intensive study and has published their results of that study, and in my experience N.C.I. doesn't do that, doesn't report out studies that they have done unless they are convinced that that study design is proper and that their observations and interpretations are widely accepted by their various panels of experts, so I tend to feel that I put a great deal of faith of N.C.I.'s work, in this particular case particularly.

Q. Are you prepared to say at this time that American commercial mixtures of PCBs, as sold, are not potential human carcinogens?

A. I am prepared to say that assuming that these various studies were done using American PCBs, and I might add that insofar as I am aware no analyses for contaminants were

done, at least they were not reported in any of these studies that I recall, certainly not in the Kimbrough study, and assuming that, as I said, that these were representative samples of American PCBs, then I believe that the preponderance of evidence is that American PCBs are not carcinogenic in rats when fed under the conditions of these experiments.

Q. Doctor, my question was whether you are prepared to opine that American commercial mixtures of PCBs, as sold are not potential human carcinogens.

A. It is my opinion that there is no convincing evidence, whether we are talking about the rat studies that we just spoke of, or other studies of workers and others exposed to PCBs, that there is no convincing evidence that PCBs are carcinogens, notwithstanding any reference to contaminants, I'm talking strictly about PCBs.

Q. Doctor, I am trying to find out whether or not American commercial mixtures of PCBs have been demonstrated to be human carcinogens. Do you have an opinion as to whether or not American commercial mixtures of PCBs are not potential human carcinogens?

MR. POPE: I object to the form of the question, asked and answered, and secondly you have no definition of what you mean by potential human carcinogens. If Dr. Milby's answer has not satisfied your first question, you must have some different meaning of the term than he does, and that I do.

MR. FEATHERSTONE: I would also object to the form of the question, also as being indefinite with respect to what the parameters are.

MS. STEIN: Q. Dr. Milby, do you understand what I am asking?

A. I think I understand what you are asking.

Q. All right.

A. And as I thought I testified a moment ago, it is my opinion that there is no evidence to substantiate the notion that American PCBs are carcinogens either in animals or in humans.

Q. Is it your opinion that environmental residues of American commercial mixtures of PCBs are not potential human carcinogens?

A. Insofar as I am not aware that there have been any reports that environmental residues of American PCBs contain contaminants such as dibenzofurans, then it is my opinion that environmental residues of PCBs, American PCBs, are not carcinogenic.

Q. Based on your knowledge and experience, do you have an opinion as to whether American commercial PCB mixtures as sold have potential for human mutagenicity?

MR. POPE: I object to the form of the question, no foundation as to what you mean by potential.

MS. STEIN: Q. Doctor, do you understand the question?

A. Yes, I do, I have an opinion. PCBs are not mutagenic in the standard in vitro tests such as the Ames test and this is true with the possible exception of the mono-chlorinated compounds; and secondly, in animal studies that have been designed to examine the matter of mutagenesis of

PCBs, have not been shown to be mutagens; thirdly, in observations in humans I know of no studies which suggest that PCBs are mutagenic in humans.

Q. Then is it your opinion that PCBs are not potential mutagens for humans?

A. That is my opinion, yes.

Q. And does that opinion assume that the PCBs are free of any contaminants?

A. That opinion assumes that. If it were shown that they contain contaminants I would have to rethink that question.

Q. Dr. Milby, do you have an opinion as to whether the environmental residues -- let me ask you this first, did your previous answer relate not only to American commercial mixtures of PCBs as sold, but also to environmental residues of American commercial PCB mixtures?

MR. FEATHERSTONE: Objection, it has been asked and answered, you asked him directly if he knows of any evidence that there are any contaminants in environmental residues in PCB mixtures and he answered that in the negative.

MS. STEIN: That was a different question, Mr. Featherstone.

MR. FEATHERSTONE: I object on the ground that it has been asked and answered, and it is not a different question.

MS. STEIN: Q. My previous question, do you understand it?

A. Yes. It is my opinion that environmental residues of American PCBs are not mutagenic.

Q. And is that opinion based on the information that

you described in your answer to the previous question regarding potential mutagenicity of American commercial PCB mixtures as sold?

A. Yes.

Q. Dr. Milby, do you have an opinion as to whether American commercial PCB mixtures as sold have any human teratogenic potential?

MR. POPE: I object to the form of the question, and lack of foundation, and vague.

THE WITNESS: Yes.

MS. STEIN: Q. What is your opinion?

A. My opinion is that American PCBs are not teratogenic.

Q. And would you give the same answer with respect to environmental residues of American PCBs?

A. Yes.

MR. FEATHERSTONE: Objection, vague.

THE WITNESS: Yes.

MS. STEIN: Q. Can you give me the basis for your opinion to the two preceding questions?

A. In animal studies which I have read PCBs lacking contaminants have not been shown to be teratogenic.

Also, I know of no evidence based on human observations that would suggest that PCBs are teratogenic in humans, and that includes the observations made in the Yusho incident.

Q. Dr. Milby, do you have an opinion as to whether American commercial PCBs as sold have any potential human fetotoxic effects?

MR. FEATHERSTONE: Object to the question as being vague and indefinite.

MS. STEIN: Q. Do you understand the question, Dr. Milby?

MR. FEATHERSTONE: That is not the point.

THE WITNESS: Yes. I believe I understand the question. Assuming that studies in experimental animals have utilized PCBs which are representative of American PCBs and -- I'm sorry, assuming that the PCBs used in experimental animal studies which I am aware are representative of American PCBs, it is my opinion that American PCBs would be fetotoxic, only under conditions of very heavy exposure, exposures well in excess of any that I have ever encountered, as described in environmental levels such as in fish, sediments, water, or air.

The Yusho situation did describe fetotoxic effects among some of the babies born of Yusho mothers, and insofar as the literature describes, these effects were transient, and the contribution to those fetotoxic effects of contaminants such as dibenzofurans, has not been fully described, but in my opinion are likely to be substantial.

MS. STEIN: Q. And is your answer the same regarding potential fetotoxic effects of environmental residues of American commercial mixtures of PCB?

MR. POPE: I object to the form of the question, he just said that there is a substantial difference in this area, in the method of exposure.

MR. FEATHERSTONE: I also object to the form of the question.

MS. STEIN: I object to Mr. Pope's characterization of the witness's testimony.

MR. FEATHERSTONE: Ms. Stein, it's not your position to object to objections, either you ask for the answer or you can restate the question.

MS. STEIN: Q. Doctor, do you understand what I am asking?

A. Yes, I believe I understand what you are asking.

It was my intention to testify to the previous question that insofar as I was aware there have been no circumstances of environmental contamination in this country that has involved levels of PCB exposure sufficient to produce fetotoxicity; however, in experimental animals fed very high doses of PCBs there is some suggestion that those high doses can produce fetotoxicity.

I also testified, I believe, that in the Yusho incident fetotoxicity was observed but this fetotoxicity was transient, and may have been due to the presence of dibenzofurans rather than PCBs.

(Pages 181 through 184 of this transcript will be filed separately under seal of confidentiality pursuant to protective order.)

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF ILLINOIS

EASTERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, vs. OUTBOARD MARINE CORPORATION, Defendant, Third-Party Plaintiff, and Cross-Claim Defendant, and MONSANTO COMPANY, Defendant, Third-Party Defendant, and Cross-Claim Plaintiff.	)	No. 78 C 1004

Excerpt from the
DEPOSITION OF THOMAS H. MILBY, M.D., MPH

May 27-28, 1982

(Pages 181-184)

Reported by:
ROBERT A. FORTINI
C.S.R. 146

PHONE
982-6008

ROBERT A. FORTINI, C.S.R.
DEPOSITION REPORTER & NOTARY
110 SUTTER STREET
SAN FRANCISCO, CA. 94104

MS. STEIN: Q. Dr. Milby, are you familiar with the work being done by Greta Fine and her associates?

A. I have read a report which as I recall was a preliminary report from Dr. Fine and her group in Michigan.

Q. What do you recall of that report?

A. I recall that -- preliminarily, it was a preliminary report and --

MR. FEATHERSTONE: Let me interrupt here and I apologize Doctor.

Is the government now taking the position that this is no longer confidential? The last time we got into this the government insisted that it be under confidential transcript.

MS. STEIN: Well, it was provided to Dr. Milby, it's indicated on this exhibit that --

MR. FEATHERSTONE: I understand it is indicated there but the question, is this under confidential transcript? And if it is not, why not? We went through this in the Swain deposition. Questions regarding the Greta Fine study were required by the government to be asked under confidential transcript, and sealed with the court, not available for distribution. Have you changed that position? Because you have not asked that his testimony in answer to your questions be under seal. My question simply is, are you going to put this under seal, or not?

MS. STEIN: I don't know right now, Bruce.

MR. POPE: Let me ask this and may we go off the record for a moment? If it is off the record I would have no objection but --

MS. STEIN: Let me think about it for a second.

MR. POPE: Let's take a break.

(Recess.)

MS. STEIN: All right, on the record.

The last two questions which related to the Greta Fine work in Michigan are under seal, and any questions and answers pertaining to her work in Michigan will be under seal and we will proceed on that basis until we notify the court reporter otherwise, that the transcript will be under seal.

MR. POPE: Pursuant to the judge's protective order that was entered into.

MS. STEIN: That's right.

Let's go back to what the pending question was. I don't remember what it was.

(Thereupon, the record was read as follows:

"Q. Dr. Milby, are you familiar with the work being done by Greta Fine and her associates?

"A. I have read a report which as I recall was a preliminary report from Dr. Fine and her group in Michigan.

"Q. What do you recall of that report?

"A. I recall that -- preliminarily it was a preliminary report and --")

MS. STEIN: Q. Dr. Milby, do you recall we were just beginning to discuss the Fine report?

A. I have read at least one of the Fine reports and also

a grant proposal, and based on those data and those reports I considered, as did the authors, the information to be extremely preliminary, it was presented in a preliminary fashion, it was incomplete in terms of the precise description of the way the information was gathered, and because it was not meant to be a final report, therefore the importance to which I could place on those reports is minimal, since information of that kind is likely to be changed and modified and so it was my impression that the information was so preliminary that it was not worth a detailed study and therefore other than to read it and attempt to understand the general idea, I did not in any way attempt to analyze it or form a concrete opinion on the Fine work.

Q. What is your recollection of what these preliminary findings were?

MR. FEATHERSTONE: I object to the question and also I object to the relevancy of the question, particularly in light of the government's continued insistence that preliminary data is not at all relevant to this litigation.

THE WITNESS: It was my impression that the authors were interested in examining neonatal behavior patterns in relationship to PCB levels in I believe cord blood, and perhaps relating those to other variables; but the general idea was to examine neonatal behavior as it relates to PCBs in the tissues, and no conclusions were drawn.

MS. STEIN: Q. Doctor, when you say neonatal behavior, could you define specifically what you mean by that?

A. Yes. Neonatal is the period shortly after birth,

and investigators were interested in certain behavioral patterns of these very young infants, and they carried on a series of behavioral studies, which were very complex, and they reached no definite conclusions.

Q. And does the definition of neonatal behavior exclude physical manifestations?

A. No, they looked at physical manifestations, they looked at weight, they looked at maturity, they looked at other measures of thriving, and that sort of thing.

MS. STEIN: I won't be asking any more questions about that so we can go back to the opened transcript.

MR. FEATHERSTONE: Doctor, do you understand that you can no longer refer to the Fine study in your answers?

THE WITNESS: I now understand that.

(Refer back to page 185 of the open transcript.)

MS. STEIN: Q. Dr. Milby, are you familiar with the study, Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls, by David P. Brown and Mark Jones?

A. Yes.

Q. Do you agree with this statement, and I am reading from page 127 of the article, it was in the Archives of Environmental Health, Volume 36 -- well, strike that and let me ask you, do you recall what their findings were?

A. Yes.

Q. What were they?

A. The study they carried out was a mortality analysis of I believe electrical workers, it was a cohort study with some 40,000 person-years, the number of individuals observed was around 2500, and they as I recall examined something like 163 deaths.

They found three cases of liver cancer in those deaths, and four cases of rectal cancer. There was an excess overall mortality from malignancies which was, I don't recall whether it was significant or borderline significant, it wasn't a great excess, the liver cancers that they found were in excess, but were not significantly so nor were the rectal cancers.

The authors were unable to relate any of these observations to either duration or latency.

Q. In your opinion do you believe the Brown and Jones study suggests anything with regard to the carcinogenic potential of occupational exposure to PCBs?

A. Yes.

Q. What does that report suggest to you?

A. It suggests to me that within the limitations of the study that the authors were unable to relate exposure to PCBs and excess mortality in any category. This was especially convincing because first of all they found no single cancer in excess, significantly in excess, and they could relate none of the cancers to duration of exposure, or, of equal importance, to latency.

Therefore, despite the fact that the number of person-years was relatively small, the period of observation of some 20 or 25 years was substantial and adequate in my opinion, and nothing was found.

The point is that the study was based on available data, it was well done, properly carried out, and was unable to find little or nothing in the way of excess, significantly excess tumors.

Q. In your opinion is the Brown and Jones study a negative study with regard to carcinogenic potential of exposures to PCBs?

MR. POPE: I object, we had a lot of testimony yesterday but I don't think we ever reached any agreement as to what those terms mean.

MS. STEIN: Q. Would you define for me what in your opinion is a negative study, Doctor, and then the next question is whether or not in your opinion the Brown and Jones work is a negative study with regard to the carcinogenic potential of exposures to PCBs?

MR. FEATHERSTONE: I will object to the question as compound.

THE WITNESS: I will attempt to answer it as best I can.

To begin with, as I testified to earlier, it is very difficult to clearly define what one means by a negative study because each study must be taken on its own merits.

The Brown and Jones study was properly designed and carried out. It suffered from the fact that the number of individuals that Brown and Jones could collect into a cohort was relatively small, some 2500 or so. The number of person-years that they were able to observe was also relatively small, some 39 or 40,000 person-years. The number of deaths that they were able to observe, 162 or 163 or something like that, was also relatively small; nonetheless, the study was carried out on a population that had been exposed to PCBs for a long time, 20 or 25 years, and they found very little in the way of excess and significant excess of malignancies, specifically they found no excess, no significant excess in deaths from cancer of the liver, which has been an open question in my testimony to some extent, and so while I would not go so far as to call the Brown and Jones study a negative study, I would call it a study which was properly devised and carried out, but it suffered from the fact that the population available for study was not very large.

MS. STEIN: Q. Do you recall whether there was -- I'm sorry, you say there was no excess of liver cancer in the Brown-Jones study?

A. No significant excess as I recall. They saw three, and expected 1.07, and if it was significant it was only borderline.

Q. Do you recall whether they had any findings regarding cirrhosis of the liver?

MR. POPE: Counsel, you have the report in front of you.

MS. STEIN: I will be happy to show it to you but let's mark it first as an exhibit, and for the record let me identify it.

This is the Brown-Jones Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls, and that will be marked as Exhibit No. 8.

(Document, Brown-Jones Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls, marked as Exhibit No. 8.)

THE WITNESS: "In one of the plants the observed mortality due to cirrhosis of the liver was also elevated."

MS. STEIN: Q. Doctor, does that suggest anything to you with respect to a potential human health impact due to exposure to PCBs?

A. I am looking at the document to see whether it was a significant elevation.

According to Table 6 in this document, while they found an elevation in the observed deaths from cirrhosis of the liver, that excess was not significant statistically; therefore it would be my opinion that that finding was of marginal importance.

Q. Doctor, I'm going to read to you a statement from page 127 of the Brown and Jones report and then I will ask you whether you agree or disagree with this statement, and then I'll be happy to show you this and you can put it into context if that is required.

"However, the excess in liver cancer is noteworthy because it is consistent with the toxicology data observed in laboratory animals exposed to PCBs, where effects have been noted in the liver. The slight increase in deaths due to cirrhosis of the liver in the Plant 2 cohort is also consistent with the notion that PCBs have a toxic effect on the liver."

MR. POPE: What is your question? Is it whether he agrees with all of --

MS. STEIN: If he agrees with the two sentences that I just read, and take your time to review the article, Doctor.

THE WITNESS: Well, the first sentence, "However, the excess in liver cancer is noteworthy because it is consistent with the toxicology data observed in laboratory animals," it has been my testimony that the only laboratory study of note which reported an excess of cancer of the liver in rats was the Kimbrough study of 1975, and I have testified as to my opinion on that study, and other studies; so that this sentence may be the opinion of the authors, but in my opinion the non-significant excess of liver cancer described by Brown

and Jones is of marginal significance, and I have the same opinion with regard to the observation of a non-significant excess of cirrhosis of the liver in a single plant, and it is my opinion that there is every likelihood that that is a statistical artifact as opposed to being a suggestion of causal relationship.

MS. STEIN: I see that it is 11:30.

Do you want to go on or --

MR. POPE: Shall we break?

MS. STEIN: We can. There are other documents that I would have started with.

MR. POPE: Do you want to indicate for the record that Dr. Milby has been unable to reschedule his patients and other work for this afternoon, and consequently the government will submit a proposed date when it is convenient to return, and we will talk to Dr. Milby and try to set up a time to conclude the deposition?

MS. STEIN: All right. Thank you very much, Doctor.

(The deposition of Dr. Thomas H. Milby will be resumed on a date to be agreed upon by the parties.)

THOMAS H. MILBY, M.D., MPH

STATE OF CALIFORNIA)
: ss.
)

I, the undersigned, a Notary Public of the State of California, hereby certify that the witness in the foregoing deposition was by me duly sworn to testify the truth, the whole truth, and nothing but the truth in the within-entitled cause; that said deposition was taken at the time and place therein stated; that the testimony of said witness was reported by me, a Certified Shorthand Reporter, and was thereafter transcribed under my direction into typewriting; and that the witness was given an opportunity to read and, if necessary, correct said deposition and to subscribe the same.

I further certify that I am not of counsel or attorney for either or any of the parties in the foregoing deposition and caption named, or in any way interested in the outcome of the cause named in said caption.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my seal this _____ day of _____, 1982.

_____
NOTARY PUBLIC, State of California

My Commission expires:

51 cont'd

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF ILLINOIS

EASTERN DISTRICT

UNITED STATES OF AMERICA,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	No. 78 C 1004
	)	
OUTBOARD MARINE CORPORATION,	)	
	)	
Defendant, Third-Party Plaintiff and Cross-Claim Defendant,	)	
	)	
and	)	
	)	
MONSANTO COMPANY,	)	
	)	
Defendant, Third-Party Defendant and Cross-Claim Plaintiff.	)	
	)	

DEPOSITION OF THOMAS H. MILBY, M.D., MPH

Wednesday, August 4, 1982

VOLUME II

(pages 191 to 230)

10-4-82 pp 43

Reported by:
ROBERT A. FORTINI
C.S.R. 146

ROBERT A. FORTINI, C.S.R.
DEPOSITION REPORTER & NOTARY
110 SUTTER STREET
SAN FRANCISCO, CA. 94104
PHONE
982-6008

I N D E X

BE IT REMEMBERED that, pursuant to Continuance from May 28, 1982, and on Wednesday, the 4th day of August, 1982, commencing at the hour of 10:00 A.M. thereof, at One Embarcadero Center, San Francisco, California, before me, ROBERT A. FORTINI, a Notary Public in and for the City and County of San Francisco, State of California, there personally appeared

THOMAS H. MILBY, M.D., MPH,

called as a witness herein, and who having been previously sworn was thereupon examined and interrogated as hereinafter set forth.

--oOo--

ELIZABETH STEIN, Attorney-at-Law, U.S. Department of Justice, Land and Natural Resources Division, Tenth and Pennsylvania Avenue, N.W., Washington, D.C. 20530, appeared as counsel on behalf of the plaintiff.

MICHAEL A. POPE, Esq., representing the Law Offices of PHELAN, POPE & JOHN, 30 North LaSalle Street, Chicago, Illinois 60602, and RICHARD J. KISSEL, Esq., representing the Law Offices of MARTIN, CRAIG, CHESTER & SONNENSCHEIN, 115 South LaSalle Street, Chicago, Illinois 60603, appeared as counsel on behalf of the defendant Outboard Marine Corporation.

BRUCE A. FEATHERSTONE, Esq., representing the Law Offices of KIRKLAND & ELLIS, 200 East Randolph Drive, Chicago, Illinois 60601, appeared as counsel on behalf of the defendant Monsanto Company.

EXAMINATION BY MS. STEIN (Resumed)

MS. STEIN: Q. Dr. Milby, you understand that you are still under oath from the 27th and 28th of May?

A. I do.

Q. In the earlier phase of this deposition you gave testimony where you said, on page 54 of the transcript, lines 10 through 15, "it's my opinion that PCBs are a minimal health problem, that their health significance is considerably overemphasized, that their acute toxicity is not especially important from a health standpoint, and that their implications in connection with long-term chronic health effects are also minimal."

Would you like me to show you that page?

MR. POPE: What is your question?

MS. STEIN: What I would like is clarification of the last phrase which is, "and that their implications in connection with long-term chronic health effects are also minimal," and specifically what I am getting at is, do you mean that the long-term effects are minimal, or do you mean that long-term exposure to PCBs poses minimal risks?

THE WITNESS: Will you state that again please?

MS. STEIN: I would like the reporter to read it back.

(Record read as requested.)

MR. FEATHERSTONE: I will object, compound.

MS. STEIN: You may answer the latter.

Q. I would like to draw your attention now to what is known as the Japanese Yusho incident. Do you recall we discussed that in your earlier deposition testimony?

A. Some aspects of it, yes.

Q. Do you recall, was chloracne one of the observed manifestations in the Yusho incident?

A. Yes.

Q. Was that seen in most of the patients, all of the patients, do you recall the prevalence of chloracne?

A. As I recall that was seen in more than 50 percent.

Q. And by chloracne, we are talking about eruption as opposed to swelling and edema?

A. Chloracne is a very specific term for acne which is seen upon exposure to chlorinated, certain chlorinated compounds. Essentially it's a very severe form of acne that is refractory to treatment, and I am not sure whether the Japanese investigators used the term chloracne in their earlier reports, but subsequently they have and indeed that is what it is, chloracne.

Q. Earlier, we had talked about exposure. Do you recall your testimony regarding route of exposure?

A. Yes.

Q. What I would like to know is does route of exposure to PCBs affect the type of biological response?

A. What do you mean by type?

Q. Okay. Why not get rid of the word type, does it affect the biological response?

A. Yes.

Q. Could you give me examples?

A. In my earlier testimony I indicated that the route of entry was not a particularly important determinant of the

nature of the response, of the biologic response; on the other hand, the route of entry has implications in terms of the rapidity with which the response occurs, but in general the actual end response of the chloracne or other responses are not very much affected by the route of entry and PCBs can enter through the skin, through the intact skin, and they may be inhaled through the lungs, and absorbed through the lung, and they may be ingested and absorbed through the G.I. tract. But, as a practical matter, the end response is pretty much the same no matter which route of entry is involved.

Q. Dr. Milby, have you spent any time preparing for your testimony today?

A. Yes.

Q. In addition to that which you had mentioned in the earlier phase of this deposition?

A. Yes.

Q. Can you tell me how much time you spent since the last phase of your deposition?

A. In the last two months since the last deposition I have spent I suppose in the neighborhood of 20 hours.

Q. What did this 20 hours consist of?

A. It consisted of reading my deposition when I received it, it consisted of reexamining some of the publications and reports which I had read before, and it consisted I believe of reading one or two new publications on PCBs.

Q. Did you have any further conversations with any of the attorneys for Outboard Marine?

A. I had a couple of phone calls inquiring about whether

or not I had received the deposition, and we didn't talk about anything substantive in most cases, except that the deposition copy was to be made available to me, and last night I spoke to Mr. Pope and Mr. Kissel for an hour or so about my deposition.

Q. About how much time did you take reading your deposition?

A. Several hours.

Q. You said you had gone back and reexamined some publications that had been discussed in the first phase of this deposition. Which publications were those?

A. I don't remember, I scanned most of the publications that I had testified about last time.

Q. Did you draw any different conclusions than that to which you testified in the first phase of your deposition, after the reexamination?

A. No.

Q. How long did you take to reexamine these publications that you testified to in the first phase of your deposition?

A. Fifteen, sixteen, or twenty hours, or so.

Q. You stated that you had looked at one or two new publications. What were those?

A. There was a publication by Dr. Fischbein in the Archives of Environmental Health, I believe, that discussed the dermatologic aspects of PCB exposures.

That is the only one I can recall to mind, there may be another, but it doesn't come to my mind at this point.

Q. And that was a recent issue of the Archives of

Environmental Health?

A. It was recent, yes, it was recent because I generally get that publication and I would have seen it earlier had it been before this year, perhaps it was a couple of months ago, that journal takes several weeks to get to my desk, but yes, it was a recent article.

Q. So, we are talking about 1982?

A. Yes.

Q. In your earlier testimony I believe that you said that epidemiology shows association, but it doesn't show causation. Do you recall tnat?

A. Yes.

Q. Could you explain that for me, please?

A. That is a very academic definition of epidemiology. In fact, epidemiology is considered by a majority of scientists, both in government and elsewhere, to be as I understand their position, to be the highest form of proof of a causal relationship, even more powerful than animal studies.

Now, by its very nature epidemiology shows associatic and the strength of that association, and if the association is very strong and it is consistent among other epidemiological studies, it's tantamount to proof in many ways. For example, cigarette smoking and lung cancer is generally accepted as a causal relationship and that was first and foremost shown by epidemiological techniques and yet that is accepted as a causal relationship while indeed epidemiology has shown a close association consistently and frequently between cigarette smoking and excess mortality from lung cancer, so it's academic

to say that epidemiology doesn't show causation because in the real world in many cases the very close and consistent association shown by epidemiology is accepted as a causation.

Q. In your earlier testimony you referred to lower chlorinated PCBs. Were you talking there about Arochlors designationsor were you talking to PCB homologs, for example dichlorobiphenyls or trichlorobiphenyls as opposed to tetrachlorobiphenyls?

MR. POPE: Object to the form of the question, the term was used several different places in several different contexts, sometimes by the witness, sometimes by the questioner, and I object to the question, what did you mean by this term, in the general context of a deposition of two days.

MS. STEIN: You may answer.

THE WITNESS: I'm afraid I can't be specific because during the ten hours or so of deposition we did talk about the subject in a number of contexts. I thought it was my testimony that, I intended it to be my testimony, that while Arochlors are generally described by a percent chlorine, 1242, 1254, 1260, 1016, each is a mixture of many homologs. It is generally the case that the higher chlorinated mixtures, 1254, 1260, even 1248 and 1242, are made up largely of homologs of the higher chlorinated homologs, so that the tetra-chlorobiphenyls, on up, are the homologs that comprise the higher chlorinated mixtures; so, there is a general relationship between the higher homolcgs and, the higher chlorinated homologs, and the higher chlorinated mixtures; but each one is a mixture and there is a difference in definition.

MS. STEIN: Q. Let me ask you this then, when you referred to lower chlorinated biphenyls in your previous deposition testimony, were you in fact using lower chlorinated biphenyls differently at different points in that deposition?

A. I may have, yes.

MR. POPE: The same objection. That is an impossible question to ask a witness at this stage, and I object to the form of the question.

MS. STEIN: Q. Dr. Milby, I am going to refer to page 85 of your previous deposition testimony, starting at line 4 and I will read this answer -- let me back up and read to you the question as well as the answer -- the question begins on line 26 of page 84 and the question is:

"Q. And I believe you said that as a result a toxicologist would predict that the lower chlorinated may be or would be more likely to be more carcinogenic. Could you tell me the basis for that statement?

"A. The basis for that statement is that the lower chlorinated compounds are more readily metabolized and the step through which they are metabolized produces an intermediate called arene oxide which is likely to be a carcinogen, so by that rather relatively simply assumption, that is the basis for my statement and for the general understanding in that regard."

Do you recall that testimony?

A. Yes.

Q. With regard to that question and that answer, were you referring when you said lower chlorinated compounds, to homologs, or were you referring to Arochlor designations?

MR. POPE: Are you talking about what a toxicologist would predict? Is that part of the question?

MS. STEIN: I'm talking about his answer on page 85.

MR. POPE: The question was about the question and the answer. He was giving you what a toxicologist would predict in connection with the question that you asked. Right?

MS. STEIN: Fine.

THE WITNESS: Before specifically answering what you are saying, I do want to emphasize that I was talking about toxicological theory, which has not in any way been shown to be true, and I was talking about the lower chlorinated homologs.

MS. STEIN: As a preface to that last answer you said that the toxicological theory has not been shown to be true. What is the basis for that statement?

THE WITNESS: The basis for that statement is that that is the state of the art as I understand it, having read a substantial amount of literature on that subject.

MS. STEIN: Q. Is what you are saying, that the toxicological theory that you are describing in this testimony on page 85 has not been borne out by actual studies?

A. Not to my knowledge.

Q. And is that because there have been no studies, or because there have been studies that have not in fact demonstrate

the theory?

A. I don't know.

Q. In terms of that same answer that you were giving, "the lower chlorinated compounds are more readily metabolized and the step through which they are metabolized produces an intermediate called arene oxide which is likely to be a carcinogen," can you tell me what the basis for that statement is?

MR. POPE: Which one?

MS. STEIN: What I just read.

MR. POPE: I object to the form of the question, it's a compound question.

MR. FEATHERSTONE: I will object, asked and answered, as shown by the transcript itself.

MS. STEIN: Doctor, you may answer.

THE WITNESS: I am not specifically clear on what answer you would like to have.

May I have the question again?

MS. STEIN: Certainly.

(Record read as requested.)

MR. POPE: This is in the context of your question as to what a toxicologist will predict?

MS. STEIN: Yes.

THE WITNESS: I will try, but I am not quite sure that I quite understand.

MS. STEIN: Q. Would you like me to show you the page?

A. I can hear what you are saying. The basis for the

answer, I am not sure, I have read that in my readings, what is the basis for my making that statement.

Q. Let me see if I can clarify this. Have you seen literature that specifically discusses arene oxide as a possible carcinogen?

A. Well, clearly that is where I obtained the information to give you the answer that I gave you. Yes, I have seen that statement made in the literature, that arene oxide may be a cocarcinogen under some circumstances. Yes, I have seen that.

Q. Is there a difference between a carcinogen and a cocarcinogen?

A. Yes, there is a difference, and my memory is not quite clear as to whether I read that arene oxide is a carcinogen or a cocarcinogen, because I don't remember which I read.

Q. Then, what is a carcinogen as you understand it?

A. As I said in my testimony several months ago, a carcinogen is an agent which damages DNA and produces irreparable change in the cell, in DNA.

Q. Are you talking now about a cancer initiator?

A. Yes.

Q. What about cancer promoter, are you saying that is not a carcinogen?

A. Cancer promoter can be classified, is sometimes classified, as a carcinogen. There is this theoretical difference between two classes of agents which are considered to be carcinogens, one is an initiator and one is a promoter, and their mechanisms of actions to produce cancer is considered

to be different.

Q. What is a cocarcinogen?

A. A cocarcinogen is an agent which requires some other agent to act in conjunction with that agent to produce cancer.

Q. Do you know whether, or have you read in the literature that higher chlorinated PCBs metabolize and produce arene oxide?

MR. FEATHERSTONE: Objection, compound.

MS. STEIN: Q. Do you understand the question?

A. Yes. Well, in the first place, when you are talking about metabolism of the chlorinated biphenyl homologs, there is no crisp difference from one to the other of which I am aware in terms of whether they metabolize readily. In general, the higher chlorinated homologs are metabolized much more slowly than the lower chlorinated homologs, and it is my understanding from reading the literature on PCBs that this is in general the case, but to put a number as to which one is more readily, one homolog is metabolized than another, I can't do that, but in general that statement appears to be the case, and it has been borne out by a number of investigators.

Q. Doctor, maybe my question wasn't clear. What I am trying to get at is, are the metabolites, including arene oxide, of lower chlorinated bipheyls, and we will talk now about the homologs, the same metabolites that one sees with regard to metabolism of higher chlorinated homologs of chlorinated bipnenyls?

MR. FEATHERSTONE: Objection as to foundation, and I also object as misleading the witness. He testified as to

toxicological theory, not as to toxicological fact.

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

THE WITNESS: To begin with, I can't answer the question specifically, I don't know whether there has been evidence that shows, evidence that exists, that metabolites of the lower homologs are different than the metabolites of the higher homologs. I would think they would be different, by the very nature of the molecules. One has more chlorine in it than the other, so the metabolites one knows when the molecules split would be likely to be different depending on which homologs you are talking about.

MS. STEIN: Q. Do you recall Dr. Renata Kimbrough's studies involving female Sherman strain rats fed Arochlor 1260?

A. Yes.

Q. Now, let's assume for the purpose of this question that you accept the findings in that study involving hepatocellular carcinoma in female Sherman strain rats fed Arochlor 1260, would you expect based on the toxicological theory that you discussed on pages 84 and 85 in your earlier deposition testimony that Arochlor 1242 and 1248 would be more likely to produce hepatocellular carcinoma than 1260 female Sherman strain rats.

MR. POPE: I object to the form of the question as to foundation, as to what the findings were in Dr. Kimbrough's work, and secondly you are not clear at all in your question as to whether you are asking him to hypothesize based on what a toxicologist would expect if that toxicologist adopted the

theory that you asked him about at page 85 of his first deposition, or are you asking him his opinion as to whether in fact that isn't true and therefore the conclusion you suggested is his opinion or somebody else's opinion.

MR. FEATHERSTONE: Object as to foundation, and I object on the ground that the question calls for speculation, and I also object to the question as a misstatement of in fact what Dr. Kimbrough reported.

MS. STEIN: Did you understand the question, Dr. Milby?

MR. POPE: Just answer a question if you understand it. If not, give it back to her, tell her that you don't understand it.

THE WITNESS: It would be helpful to me if you could have the question read again.

MS. STEIN: I will be happy to do that.

Would you do so, Mr. Fortini?

(Record read as requested.)

THE WITNESS: Experimental evidence indicates that the 1242 and 1248 compounds do not produce hepatocellular carcinoma in rats. As to the theory, I would be stretching my understanding of the theory to suggest that when the authors were talking about lower chlorinated homologs that they were talking about 1242 and 1248, perhaps you are talking about 1216 and mixtures with the very low chlorinated homologs, and so I cannot answer that, it's beyond the realm of my knowledge.

MS. STEIN: Q. Since your last deposition have you read or reread any depositions other than your own?

A. No.

Q. Have you had any conversations or contact with Dr. William Gaffey about PCBs since you have been retained by OMC as an expert witness in this case?

A. No.

Q. Did you have any conversations or contact with Dr. Gaffey about PCBs before you were retained by OMC within a year of the date that you were retained by OMC?

A. No.

Q. Do you know Morris Cranmer?

A. I know the name, I don't know him personally.

Q. Have you ever had any conversations or contact with Dr. Cranmer about PCBs?

A. No.

Q. Do you know Edward Smuckler?

A. I only know him by name.

Q. Have you had any conversations or contact with Edward Smuckler regarding PCBs?

A. No.

Q. Have you had any conversations or contact with Dr. Smuckler concerning Renata Kimbrough's rodent study slides?

A. No.

Q. Do you know Dr. Vasolinovich?

A. I don't think so.

Q. Have you sent any written reports to counsel for Outboard Marine regarding your testimony in this case?

A. No.

Q. In your earlier testimony you testified that as of that

point in time you had spent about 10 to 15 hours preparing for your deposition, as opposed to about 100 hours of preparation for your testimony in the case. You also mentioned that you had gone, out of that 100 hours or so, that you had gone to Waukegan and visited the facility.

What were the other things that you did during that 100 or so hours in preparing for your testimony in this case?

MR. POPE: I will object to the form of the question, it has been asked and answered.

THE WITNESS: That time was spent over the period of a number of months, and it was spent reading various publications and reports and depositions, as I testified earlier. Essentially, that is it.

MS. STEIN: Q. If you were designing a morbidity study to test the hypothesis that long term, low level exposure to PCBs from other than a work place standpoint causes cancer, what are the design factors that you would consider for that study?

A. To begin with, I must say that to answer your question fully would take a long, long time.

I do, in my professional work, occasionally design studies somewhat similar to that, and it takes me weeks to do it, and hundreds of pages to describe it, and I will try to distill that if I can.

In the first place, I am not sure that I would select a morbidity study approach, and perhaps I would choose a mortality study approach, but if I were to select a morbidity study approach I would probably attempt, depending on where I

happened to be at the time, and what resources I happened to have available, I would probably attempt to utilize the resources of a tumor registry, a community tumor registry, and utilizing the tumor registry I would then attempt to define a population base which if I chose to follow this population base prospectively into time I would follow this population prospective through the tumor registry.

The biggest problem, or a major problem in such an endeavor would be to define a population because when you are talking about community studies, defining a population, especially if you are attempting to define a population as of some period past, some period of time ago, five years ago, ten years ago, that is a very difficult thing to do in a community study, as opposed to an occupational study, so I would, to try to answer your question, one, I would define a cohort sometime in the past in the community which would be very difficult to do; I would follow the experience of that population in the tumor registry which would give me only cancers, so if we are talking about other disease end points, morbidity from other diseases, that is a different problem, and one that would be extremely difficult to do.

Q. Now, for the purposes of this question, we will limit it to the testing, the hypothesis of PCBs causing cancer.

A. Okay. The earlier question didn't say anything about PCBs. Is the question testing the hypothesis that PCBs are associated with cancer?

Q. Yes, from exposures other than in an occupational context.

A. Then I will have to start over again because that is an element that I wasn't including.

If I were interested in PCBs then I would have to define a population in the community, a cohort in the community, that had a definable exposure to PCBs, definable in terms either of PCB exposure, nonoccupational PCB exposure, such as using sewage sludge in gardens, or eating substantial amounts of fish from waters known to contain PCBs, living perhaps downwind from a plant that was emitting PCBs, some kind of exposure pattern that would lead me to believe that this exposure to PCBs was greater than background population not so exposed to fish or to sludge or to the plant emitting PCBs.

Then I would, after defining those two populations, I would follow them forward in time and follow their experience forward in time, experience in terms of whether or not they developed tumors which would be registered in the tumor registry, and after some suitable period of time which would permit me to accrue enough numbers, a large enough sample of tumors, then I would compare the two populations.

There are a myriad of confounding variables that have to be considered that I haven't even mentioned, but that is the general sort of approach I would take.

Q. Okay. Let's break some of these down for a minute then. We talked briefly about confounding variables and some of them were age, sex, social class, smoking, nonsmoking, alcohol consumption, and so forth, those would be things that you would take into account also?

A. Yes.

Q. And would you look for site-specific cancers?

A. I would look for cancers of all kinds.

Q. When you talked about a suitable period of time, what do you think would be a suitable period of time for conducting a morbidity study of the sort we have just been discussing? In other words, enough time to get a sufficient data base to draw associations, if any?

MR. POPE: I object to the form of the question. I think it's too vague.

THE WITNESS: The problem is not so much getting a large enough data base, the problem is defining a cohort that has a period of exposure which is sufficiently far in the past that if indeed the exposure of interest were to produce cancer, that it would begin to develop. Obviously, you wouldn't take a population that had only been exposed for two years because it is well known that cancer requires a latency period of anywhere from 15 to 20 or 30 or more years, so the biggest problem would be trying to define a cohort that had been exposed over a long enough period of time so that you would have a reasonable expectation that cancer would develop if it was going to. That would be a major problem, defining crisply such a population and following it through time.

Q. If you were designing a mortality study to test the hypothesis that long-term, low-level exposure to PCBs causes cancer, and we are talking now about environmental exposures other than in the work place, what would be the design factors that you would consider?

MR. POPE: If you accept the same preface he gave to

your other question, that it may well take two weeks to answer all of them, if you would take into account the same preface he gave to his last long answer that to do such a study right would take perhaps weeks or months, to list all of the design considerations, you are not asking him to do that, but rather some of the more important considerations that he would take into account as he sits here today.

MS. STEIN: I believe that there was some modification to that qualification when I restated the question. I thought I had said in my first question to which Dr. Milby was responding, that I was limiting this design of morbidity study to PCBs. Perhaps I didn't state it, but that is what I meant, and when I rephrased it I believe Dr. Milby then said, "Well, I will have to start over," so I am accepting whatever it was that was in response to the second question.

Okay?

MR. POPE: I object to the form of the question. If you are asking for each and every design consideration in order to do such a study, then he is unable to provide you with an answer today. You are asking for a professional opinion without giving him an opportunity to consider all the considerations. If what you are saying is simply, and it's a fair question, give us some of the major considerations as you sit here today that you would take into account, then I would have no objection.

MS. STEIN: I understand Dr. Milby to testify that these things are not something that, that is often a lengthy process, and I am not asking for that, I am asking within the

confines of this deposition and this question what the factors are and I realize what he tells me may not be totally exhaustive Okay? I think that meets the substance of your objection very well.

MR. POPE: My objection stands. Go ahead.

THE WITNESS: With regard to mortality studies first of all I must say that I would not choose a population exposed through environmental, general environmental mechanisms to examine this hypothesis, I would choose an occupationally exposed population and --

MS. STEIN: Before we go any further, I would like to have you tell me why.

THE WITNESS: Because in occupationally-exposed populations, you are much more likely to be able to define the cohort, the historical cohort, because records are available at the plant site from the employer of a population, a cohort, if you will, sometime in the distant past. In a community study that information is rarely if ever available. So, in the community study it's practically impossible to define a cohort in a satisfactor way from the past.

MS. STEIN: Q. Okay. Given that your testimony regarding the difficulty of designing a cohort for such a mortality study, then let's go on to the other factors that you would consider.

MR. POPE: If he was going to be doing such a study.

MS. STEIN: That's right, yes.

THE WITNESS: I can't emphasize strongly enough that I would never do it that way. So, what would I consider in a

study that I would never do?

MR. POPE: If you can't answer the question, then don't answer the question.

MR. FEATHERSTONE: It's calling for utter speculation at this point. Do you really want this, Elizabeth?

MS. STEIN: You may finish your answer, Doctor.

THE WITNESS: Assuming I could define a cohort, a general population made up of individuals in the general population 20 years or so prior to the time I decided to embark on this study, if I could do that, then my considerations would involve the need of ascertainment of death, that is how many of this population that I defined 20 years ago for example, how many have died and --

MS. STEIN: We are talking now about cancer?

THE WITNESS: That's right.

MR. FEATHERSTONE: Are you talking about a cross-sectional study, Doctor?

THE WITNESS: No, I am talking about a historical prospective study because a cross-sectional study is of no value in this exercise that were are doing because you can't define a cohort, so you can't do it, a cross-sectional study would not be the approach I would take. I would require a historical prospective study and a historical prospective study demands that a cohort be defined from sometime in the past, generally at least 20 years ago, so I am making that assumption that I can define such a cohort in the environment, in the community, I should say. Then I would simply ascertain the number of the people who died, and I would do that, in part at

least, by using Social Security numbers which I would have obtained from my cohort if I could, and I would send those Social Security numbers to the Social Security Administration and ask them to tell me which ones are alive and which ones are dead, which they would by whether or not they are paying into the system. Those that are not paying, then I would assume for the moment that those people were individuals that I would have to follow up. Those who were paying into the system I would ignore because for my purposes they would be defined as alive.

This creates all sorts of problems because we have children in the population that may not be working, we have women in the population that may not be working, and these are all problems that are involved in a community study that are not involved in an occupational study.

In any event, I would go through the exercise of determining who was alive and who was dead. For those that died I would have obtained the death certificates from the state that they died in, and I would determine that by the last address that they paid Social Security benefitis from, so if they were paid from Maine I would write to the Maine Department of Public Health and ask for the death certificate, and they would send it to me and after I had all these death certificates in one stack, representing all those individuals who I had to assume were dead, because I couldn't determine that they were alive, and this would be a small portion by the way probably because a lot of people would have escaped my examination because of the nature of the cohort, then I would

simply analyze those death certificates, using standardized mortality ratio statistics, and determine as best I could what the mortality experience was for cancer.

You understand that there are all sorts of variables, such as age adjustments, and a whole series of other things, and the study would not be satisfactory, I am sure, because so many would be lost to follow up in a study of a community cohort.

MS. STEIN: Q. Would there be any way to try to try to control, this is a mortality study I realize, but is there any way to analyze possible confounding variables that might have occurred?

A. You can --

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

THE WITNESS: You can control for some confounding variables such as age, sex, and race, but you can't control such a study as I described such as smoking, alcohol intake, dietary habits, and a variety of other things, because your cohort as you defined it was 20 years in the past, and they are not around to ask those questions of.

MS. STEIN: Q. Dr. Milby, in your earlier deposition testimony we had some discussion about morbidity and mortality studies and in response to this question:

"Q. What are the different kinds of studies that epidemiologists do?"

you said, and this is at page 40: "Epidemiologists primarily are involved in two kinds of studies, morbidity and mortality.

"A study of morbidity uses as an endpoint any measure of health that is appropriate, which may include sickness," -- and then this says over sickness, and I think you meant overt sickness, "which may include subclinical disease, which may include nothing more than psychological function, or it may include even less and it may include nothing more than the storage of a compound in the body".

If we were designing a morbidity study using storage of PCBs in the body as an endpoint, and we are talking now about environmental exposures to PCBs other than in a work place, how would you design that study?

MR. FEATHERSTONE: Objection, the question calls for speculation, and I also object as to relevance.

THE WITNESS: You mean, which endpoint would I use or --

MS. STEIN: I am giving as a given endpoint, storage of PCBs in the body, and we would be designing a morbidity study looking at that as an endpoint.

THE WITNESS: What would be the hypothesis of the study?

MR. POPE: The question is incomplete.

MS. STEIN: Whether or not you could predict in the future sometime some kind of -- I think if you are talking about storage of PCBs as an endpoint, isn't that -- well, let me ask you, is there a problem with that as an endpoint?

MR. POPE: I object to the form of the question. Is there a problem with what? It doesn't make any sense.

MS. STEIN: I am taking his testimony and he is

talking about the kinds of morbidity studies.

All right. We were talking about using something as an endpoint in a morbidity study. What hypothesis would you be testing if you were using storage of a compound in the body as an endpoint?

MR. POPE: I object to the form of the question, it lacks foundation.

MS. STEIN: I am trying to get at what he meant in his earlier testimony so that I can proceed to some other question.

MR. POPE: That is a laudible end, Ms. Stein, but perhaps you can ask a question that makes some sense and he will try and answer it, and also you might try to comply with the rules of evidence regarding the form of the question and then maybe we can get along here in the deposition.

MS. STEIN: Doctor, do you understand the question?

MR. POPE: Are you lost as to what the question is? The problem is, it's only a part question.

MS. STEIN: Tell me what else you need, then.

MR. POPE: To do what? The question has to stand for something, Liz. I object to the form of the question.

MS. STEIN: All right.

Q. Let me show you page 40 of your previous deposition testimony, referring to lines, I believe it's 9 through 14 of that page, page 40, can you explain what you meant there?

A. Sure. An endpoint as I am attempting to describe it in this testimony on page 40, is the outcome that you are

examining in connection with some kind of effect.

For example, if you're interested in examining let's say the body burden of PCBs in cancer patients to see whether cancer patients have more PCBs in their body than people who don't have cancer, you can do that.

If you are looking at a body burden of PCBs as a liver function to see whether there is a correlation, you can do that.

So, when you ask about body burden and how you use it, you will have to tell me what it is you are looking for, if you are trying to correlate liver function studies or cancer or high blood pressure, or chloracne, that kind of thing.

Now, what I meant here was --

MR. POPE: And by here, you are referring to --

THE WITNESS: Page 40 in the last deposition.

You asked what different kinds of studies epidemiologists do, and in morbidity studies I was testifying that there are a number of endpoints that are used, one of which is body burden.

If you are asking about the suitability --

MR. POPE: No, let her ask the questions.

MS. STEIN: Q. If you were designing a study, a morbidity study, to test the hypothesis that people who eat fish containing PCBs have or will have higher body burdens of PCBs, how would you design that study?

A. First of all I would need to identify the population who consumed fish that I would have some reason to believe have PCB levels that are higher than background from elsewhere,

so-called high exposure population, if you will. This might be a population of fishermen, people who consume fish, so first of all I would identify such a population and that population would have to be of some reasonable sample size, and I don't know exactly what that would be, and it would have to be, in that population there would have to be an age distribution that reasonably characterized the general population, so I need some infants and I need some children and I need some people in all age groups that generally reflected the make-up of the general population.

I would have to, if I wished to pursue this issue in more detail, I might wish to have a sex breakdown so that I had people in each sex, males and females, and I might even wish to test the hypothesis of race and I might need different races, and I would then choose a control population, an unexposed population that was matched as closely to my exposed population of fish eaters in every way I could think of, age, sex, race, geographical locations, occupation and perhaps other things. Things like smoking and nutrition would be difficult to control for, those are biases that you probably can't control.

Then I would determine which indicator of body burden I would like to use. This would take some thought, and I don't think there is any specific answer to that question.

Now, based on what we know about the pharmacokinetics of PCBs in humans, I would prefer to use adipose, fat tissue, as my indicator of body burden because of blood which is much easier to obtain of course, I have never seen anyone show what

the relationship between blood levels of PCBs was and fat levels of PCBs might be.

That is known in general, but not specific enough so that I could use it for my tissue of interest, and so therefore I would use fat tissue, adipose tissue, subcutaneous adipose tissue, as an indicator of body burden, and I would carry out my study and see whether or not people who consumed more fish -- and I might indeed in the population that consumed fish, I might categorize them as people who ate a lot of fish, and people who ate fish but not a whole lot of fish, I might do that, and then I would correlate that, compare that, with body burden.

Q. How long would you run such a study? What would the duration of the study be, do you have any idea in terms of the amount of time that you would need to reach any conclusions?

A. If my hypothesis was that people who consume fish with PCBs in them have higher fat levels than people who don't consume fish, then I could just do a cross-sectional study and do it one time and do it in one fell swoop, just go out and identify the population, collect the proper information, on the demographics of the situation, of the consumption patterns, and that sort of thing, and then take the fat samples and analyze them, and if my hypothesis is so simple that I just want to know if people who eat more fish have higher levels than people who eat no fish, that is all you would need.

Q. Doctor, earlier this morning I referred you to page 54 of your deposition, lines 10 to 15, and with respect to the last phrase, "and that tneir implications in connection with

long-term chronic health effects are also minimal," and you said that by that you meant that long-term exposure to PCBs poses minimal risks.

I would like to know whether you are aware of any studies that disagree with your opinion that long-term exposure to PCBs poses minimal risks.

A. In humans?

Q. We are talking about human health effects.

A. How would define for me so I can answer your question, how would you define minimal effects versus something else?

Q. However you were defining it in your answer, which I will be happy to provide for you. Here you are. Why don't you state that for the record so that we have a common understanding of what that answer meant?

A. From my earlier deposition I stated, on page 54, line 10 through line 15:

> "It's my opinion that PCBs are a minimal health problem, that their health significance is considerably overemphasized, that their acute toxicity is not especially important from a health standpoint, and that their implications in connection with long-term chronic health effects are also minimal."

Long-term exposure to PCBs are known to cause dermatitis in the work place. Insofar as long-term exposure in nonoccupational situations, I know of no studies which indicate that there any health-related effects from such exposures, such

as fish eaters or people who are exposed in some other environmental way, and this includes sludge users, so I don't know of any environmental effects, effects of people exposed in the course of their environment, that are very important, and in terms of occupational exposure the only consistent health effects that have been reported to my knowledge, the only one is dermatitis.

Q. Let me see if I understand your answer or if I am mischaracterizing it.

MR. FEATHERSTONE: We will object.

MS. STEIN. There is no doubt about that.

Q. Doctor, are you saying by minimal, since dermatitis appears to be the only one that is consistently found, that is what you mean by minimal?

A. Yes.

MR. FEATHERSTONE: I object to the question insofar as it attempts to characterize Dr. Milby's testimony as stating that chloracne or dermatitis is consistently found. In fact, he testified that in environmental effects studies it was not found.

(Recess.)

MS. STEIN: Q. Dr. Milby, in connection with your opinion regarding the health effects of exposures, of environmental exposures, to PCBs, can you tell me whether you have assumed that all isomers of PCBs exhibit the same degree of toxicity?

A. You mean, all homologs versus all mixtures?

Q. Isomers as opposed to homologs.

MR. POPE: Object to the question, lack of foundation

MS. STEIN: Q. Do you understand the distinction I am talking about?

A. Are you talking about mixtures? Or are you talking about molecules?

Q. I am going to be talking about molecules.

A. All right.

Q. There would be a class of PCBs that would be, say the whole class of dichlorobiphenyls, two chlorines, those are what I am using as homologs. Now, within that class of homologs there are isomers, different isomers, depending on where the chlorine is placed on the biphenyl. So, for homologs I am using di, tri, tetra, penta, and whatever, and isomers relates to specific placement on the biphenyl. Okay?

A. Yes, all right.

Q. All right. So I am asking now whether you assumed that all isomers of PCBs exhibit the same degree of toxicity. Would you assume that with regard to your opinion on the health risks representative by environmental exposures to PCBs?

MR. FEATHERSTONE: Object to the form of the question.

THE WITNESS: Specifically no, I did not assume that.

MS. STEIN: Q. Did you make any assumption at all concerning specific isomers?

A. No.

Q. Did you make any assumption regarding the homologs of PCBs in reaching your opinion, for example did you assume that all homologs of PCBs exhibit the same degree of toxicity?

MR. FEATHERSTONE: Objection, compound.

THE WITNESS: To begin with, we are talking about environmental effects, and in my answer I am excluding the Yusho when talking about long-term effects. In my testimony of long-term effects and their being none from environmental exposure, I was not including Yusho. And if we wish to discuss Yusho, that is a separate case. I am talking about people who eat fish and who are exposed in other ways and not so dramatic as the Yusho events.

Now, with regard to homologs I know of no data that suggests that environmental exposure to PCBs, long-term environmental exposure, other than Yusho, produces any effects, any health consequences, important health consequences, from environmental exposures. I haven't assumed anything about homologs in that connection. It doesn't seem to fit in my mind.

MS. STEIN: Q. Did you make any assumption with regard to whether you were talking about a commercial mixture of PCBs, or environmentally weathered samples of PCBs?

MR. POPE: Object to the form of the question, lack of foundation.

MR. FEATHERSTONE: May I have the question read back?

(Record read as requested.)

THE WITNESS: Insofar as I am aware, there are no reports of environmental exposure to either the commercial compounds or the weathered compounds which suggest that they create any human health effects, with the exception of the two Yusho incidents.

Q. Does your opinion regarding the health effects of PCBs, or lack thereof, resulting from the environmental exposures to PCBs, assume that there would be no accidental high exposures?

MR. FEATHERSTONE: Objection, vague and indefinite.

THE WITNESS: I don't understand what you mean by accidental high exposures.

MS. STEIN: Q. Let's assume you are talking about low-level, long-term environmental exposures, and I am trying to get at whether or not your opinion takes into account the possibility that somebody may unbeknownst to him or her come across a patch of ground where there is oil on the ground, what appears to be oil on the ground, and they stand over it and breathe it for a long time, or it's a child who eats it. Okay?

MR. POPE: You are talking about long-term exposure?

MS. STEIN: His opinion was on long-term exposure. I am talking about some kind of incident that may not be over a protracted period of time, but where there is high exposure to PCBs.

MR. POPE: I will object to the form of the question.

MR. FEATHERSTONE: I object to it as being vague and indefinite. He asked what you meant by exposure, and you haven't given him a definition of that.

MS. STEIN: Q. Did you understand the question, Dr. Milby?

A. I'm sorry, I'm afraid not enough so that I can give an answer to it.

Q. As an example of a high exposure, I am talking about

a Yusho-type incident, or somebody coming in contact with spilt transformer fluids containing PCBs.

MR. POPE: I object to the form of the question. Those two are hardly an example that have anything in common with each other. I think it's a very confusing question.

MR. FEATHERSTONE: I renew my objection, vague and indefinite, it still says nothing about the degree of exposure.

MS. STEIN: Q. Did you understand the question, Dr. Milby?

A. I would like to have the question itself reread, and then I will try to answer it with those examples of high exposure in mind.

Q. What I am getting at is this, you had given an opinion, your opinion, regarding the health effects of long-term, low-level environmental exposure to PCBs, and I am trying to find out whether your opinion takes into account the possibility of high exposures such as Yusho or such as exposure to PCB transformer fluids. Okay?

MR. POPE: The question is, does his opinion take those two examples into account?

MS. STEIN: No, examples of that type into account.

MR. POPE: I object to the form of the question, there is no type that can possibly be defined to fit those two examples.

MS. STEIN: Q. Do you understand the question, Dr. Milby?

A. As I testified earlier, my opinion does not include

such incidents as Yusho. When I testified that long-term, low-level effects are not of much consequence I don't include Yusho.

Q. The reason I was trying to stay away from Yusho is that there has been discussion and testimony, including in your deposition, implicating polychlorinated dibenzofurans, and I am trying to get away from whatever the confounding effect, if any there is, of that, so I am talking about exposure to a massive dose of PCBs without the confounding effects of any possible impurities that might affect the opinion.

MR. POPE: Do you have a question?

MS. STEIN: Q. What I am trying to get at is whether your opinion regarding PCBs takes into account high exposures of the nature of Yusho without what some have described as the complications of polychlorinated dibenzofurans and polychlorinated quater phenyls.

MR. FEATHERSTONE: I object to the question as being vague and indefinite because the Yusho exposure did include things other than PCBs, and when you say the nature of Yusho you haven't clarified it at all.

MS. STEIN: Q. Do you understand the question, Dr. Milby?

A. I'm sorry, I'm lost. What is it that you are asking me? If you are asking me -- well, I'm sorry, could we nave that part of it reread?

Q. What I am trying to get at is, you have given your opinion regarding the health effects of PCBs, exposure to PCBs, --

A. Long-term, low-level, and of course, that excludes intermittent high-level exposures.

MS. STEIN: All right. That is exactly what I was getting at. Thank you.

Q. And what if anything does your opinion assume, again with regard to long-term, low-level environmental exposures, what if anything does your opinion assume regarding the presence or absence of impurities in the PCBs?

MR. FEATHERSTONE: Objection, asked and answered.

THE WITNESS: My opinion assumes that impurities exist at most in trace amounts, and no greater than trace amounts.

MS. STEIN: Q. And those impurities would be polychlorinated dibenzofurans, that would be one?

A. Yes, that's right.

Q. And polychlorinated quater phenyls would be another?

A. Yes.

Q. And let me ask you then, does your opinion regarding the health effects of long-term, low-level exposure to PCBs contemplate that there is no potential risk to human health from long-term, low-level exposures to PCBs?

A. In my opinion there is no important significant risk to exposure to long-term low levels of PCBs in the environment.

Q. We are talking now about projecting into the future?

A. Projecting into the future, yes.

Q. As an epidemiologist, do you believe that there is any cause for concern from a human health standpoint over

environmental exposures to PCBs, such that further study is appropriate?

A. Yes, I believe further study is appropriate.

Q. Are there specific areas that you think should be further studied?

A. In my opinion, and based on my experience, the level of concern in the general population, in individuals that I have come in contact with, my patients who have been exposed to PCBs for example, that the level of concern is great, and that additional studies properly designed studies ought to be done to allay those concerns, so that the risk if any to PCBs in the general population can be better defined.

I think the evidence now is convincing to me that there is not much hazard. Unfortunately, others don't necessarily agree with me, and I would like to see more research done specifically to clarify the issues to the point where the health officials and others could, with enough confidence, persuade or describe to their patients and to the general community that the problems are not very important, so in that sense I would like to see more research done.

MS. STEIN: I have no further questions.

MR. FEATHERSTONE: Mr. Pope, will Dr. Milby give testimony at trial regarding any of the issues raised by the lawsuit between OMC and Monsanto?

MR. POPE: None of the issues that relate solely to the third-party claim. Obviously, there is some overlapping of factual matter, as Ms. Stein has asked the questions of definitic of Dr. Milby. We have not asked him to conduct any studies with

respect to Monsanto's actions, and he has advised me that he has no opinions with respect to Monsanto, either in the testing area or any other areas relating to your client.

MR. FEATHERSTONE: Based on that representation, Monsanto has no questions of Dr. Milby.

MR. POPE: I have no questions.

MS. STEIN: Thank you very much, Doctor.

MR. POPE: Signature is reserved.

THOMAS H. MILBY, M.D., MPH

EXHIBITS

U.S.A.

12

OUTBOARD, A

5/27/82

5/28/82

U.S. Department of Justice

United States Attorney
Northern District of Illinois

United States Courthouse
Chicago, Illinois 60604

JTH:cd
#78,0475

May 19, 1982

HAND DELIVERY

Roseann Oliver, Esquire
Phelan, Pope and John
30 North LaSalle Street
Chicago, Illinois 60602

Re: United States v. Outboard Marine Corporation and Monsanto Company
No. 78 C 1004 - (USDC ND IL ED)

Dear Roseann:

This is to confirm our telephone conversation of May 18, 1982 concerning the information reviewed by Dr. Milby for his testimony.

The following items have been sent to Dr. Milby for his review:

1. All of Dr. Kimbrough's rat studies, together with the various articles discussed in her deposition, including the Selikoff works on the decrease in vital lung capacity and Dr. Kimbrough's work in Triana, Alabama regarding the association of high blood pressure with PCB exposure.

2. The report by Dr. Humphrey which was an exhibit in his deposition.

3. The Greta Fine infant study produced under protective order during the Swain deposition.

4. The 2/19/82 Drill, Friess, Hays & Loomis study.

5. Two CMA reports dated 11/19/81 and 1/19/82 concerning health effects of PCB's.

6. The Alexander Smith article dated 11/81, concerning Metabolic and Health Consequences of PCB's discussed in Dr. Kimbrough's deposition.

7. The 8/81 article by J.F. Brown entitled Human Health Effects of Electrical Grade PCB's.

Exhibit # 1
witness D. Milby
5/27/82
Reporter

8. Dr. Gaffey's 9/18/81 article entitled the Epidemiology of PCB's.

9. A report dated 10/81 from George Levinscus produced by Monsanto.

10. An article dated 4/81 by David Brown entitled Mortality and Industrial Hygiene of workers exposed to PCB's.

11. Articles recently published concerning Yusho.

12. An article by Kashimoto concerning the role of Dibenzofurans in Yusho.

13. An article entitled Toxicology of PCB's, an overview with emphasis in human health effects, by the state of California, 1/81.

14. Comments submitted by the CMA to USEPA in response to two advance notices of rulemaking on PCB's.

15. Process notes by Dr. Puffer.

16. An aritcle dated 2/79 by Kodama on the transfer of PCB's to infants from mothers.

17. An article dated 2/4/80 by Edward Baker, Jr. on the metabolic consequences of PCB's in sewer sludge.

18. Occupational Exposure in Electrical Workers, Part I and Part II by Maroni, 3/7/80.

19. PCB contamination in mothers' milk in Michigan, by Thomas Wichizer, 4/20/80.

20. Levels and GCM of PCB's in blood of patients after PCB poisoning in Taiwan.

In addition, you stated that Dr. Milby has not reviewed any of the depositions already taken in this case.

As we anticipate having difficulty obtaining copies of some of the above items we ask that you produce copies of items 11, 12, 13, 15, 20 as soon as possible, but no later than Friday, May 21, 1982.

Very truly yours,

DAN K. WEBB
United States Attorney

BY: _____
JAMES T. HYNES
Assistant United States Attorney

cc: Bruce Featherstone
(Hand delivery)

Kaye Jacobs - H/D cc

THOMAS H. MILBY, M.D., M.P.H.
President

Environmental Health Associates, Inc.
2150 Shattuck Ave., Berkeley, CA 94704

Curriculum Vitae

Professional Background

1977 - Present	President Senior Occupational Physician Environmental Health Associates, Inc. Berkeley, California
1973 - Present	Private Practice Occupational and Environmental Medicine, Toxicology, Epidemiology
1975 - 1977	Senior Medical Scientist/Consultant Stanford Research Institute, Palo Alto, California
1971 - Present	Adjunct Associate Professor of Occupational Medicine University of California Berkeley, California
1966 - 1973	Chief Bureau of Occupational Health and Environmental Epidemiology California Department of Public Health and Project Director California Community Study on Pesticides
1962 - 1966	Head Epidemiology Unit Bureau of Occupational Health California Department of Public Health
1959 - 1962	Medical Officer Clinical Studies Unit Division of Occupational Health U.S. Public Health Service Cincinnati, Ohio

Education

1953	B.S. Purdue University
1957	M.D. University of Cincinnati

Exhibit #2
Dr. Milby.
5/27/82
R.A. Sorter

1958	Internship, Ohio State University Hospital
1965	M.S., Industrial Hygiene, University of Cincinnati
1966	M.P.H., University of California

Professional Affiliations

Fellow, American Academy of Occupational Medicine
Fellow, American Occupational Medical Association
Member, New York Academy of Sciences

Medical Licensure & Board Certification

Licensed to practice medicine-Ohio, 1957
Licensed to practice medicine-California, 1959
Certified in Occupational Medicine by
American Board of Preventive Medicine, 1966

Other Professional Activities

Adjunct Associate Professor of Occupational Health, University of California, Berkeley, California
Department Editor, Clinical Case Reports, Journal of Occupational Medicine
Member, Secretary of Health, Education, and Welfare's Commission of Pesticides and Their Relationship to Environmental Health
Member, Study Section, Environmental Control Administration Department of Health, Education, and Welfare
Special Consultant, World Health Organization, India (DDT Epidemiology)
Special Consultant, U.S. Food and Drug Administration, Japan (Polychlorinated Biphenyls)
Editorial Board, Western Journal of Medicine
Chairman, Task Group on Occupational Exposure to Pesticides, Federal Working Group on Pesticide Management.
Member, Subcommittee on Hydrogen Sulfide, National Research Council, National Academy of Sciences
Technical Advisor/Editor. Environmental Health Criteria. Hydrogen Sulfide. World Health Organization, Geneva, Switzerland.

Publications

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IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

UNITED STATES OF AMERICA,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	
	)	Consolidated Cases
OUTBOARD MARINE CORPORATION,	)	
and MONSANTO,	)	78 C 1004
	)	78 C 3187
Defendants.	)	

NOTICE

TO: See Attached Rider

PLEASE TAKE NOTICE that I have this date filed with the Clerk of the United States District Court for the Northern District of Illinois, Eastern Division, Defendant Outboard Marine Corporation's Partial Response to Plaintiff's Interrogatory Regarding Expert Witnesses.

Dated at Chicago, Illinois, this 17th day of May, 1982.

Phelan, Pope & John, Ltd.
Attorneys for Defendant
Outboard Marine Corporation

OF COUNSEL:

PHELAN, POPE & JOHN, LTD.
30 North LaSalle Street
Chicago, IL 60602
312/621-0700

MARTIN, CRAIG, CHESTER & SONNENSCHEIN
115 South LaSalle Street
Chicago, Illinois 60603
312/368-9700

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, vs. OUTBOARD MARINE CORPORATION, Defendant, Third-Party Plaintiff, and Cross-Claim Defendant, and MONSANTO COMPANY, Defendant, Third-Party Defendant, and Cross Claim Plaintiff.	No. 78 C 1004

DEFENDANT OUTBOARD MARINE CORPORATION'S
PARTIAL RESPONSE TO PLAINTIFF'S INTERROGATORY
REGARDING EXPERT WITNESSES

Defendant OUTBOARD MARINE CORPORATION, by its attorneys, hereby responds to the plaintiff's interrogatory regarding expert witnesses as follows:

INTERROGATORY

With respect to each of the following:

a) Clarence Klassen
b) Allison Brigham
c) David Belluck
d) William Schwartz
e) Dr. Thomas Milby
f) Dr. James W. Patterson
g) Designated representative of Peterson & Company
h) The three representatives of Versar, Inc.

Exhibit #3 Milby D.D. 6/27/82 R.C. Stein

whom Outboard Marine Corporation has identified as expert witnesses that Outboard Marine intends to call at trial to give opinion testimony and as to

a) Raymond P. Schiwall
b) Robert Holstine
c) Roger Crawford

whom Outboard Marine Corporation has identified as witnesses that it may call at trial as occurrence witnesses with expert credentials and through whom Outboard Marine Corporation may seek to introduce opinion testimony at trial, please state:

(a) each and every field in which he or she is to be offered as expert;

(b) a summary of his or her qualifications within the field in which he or she is expected to testify;

(c) the substance of the facts to which he or she is expected to testify;

(d) the substance of the opinions to which he or she is expected to testify and a summary of the grounds for each opinion;

(e) identify by title, date and address all written reports or analyses rendered by such expert relating or pertaining to any testimony he or she is expected to give;

(f) identify and list all documents reviewed by or submitted to such expert; and

(g) identify and list all documents relating to the terms and conditions of such expert's employment by any person associated with or employed by Outboard Marine Corporation or any counsel on behalf of Outboard Marine Corporation.

RESPONSE:

With respect to Dr. Thomas H. Milby:

a) Dr. Milby will be presented as an expert in the field of occupational and environmental medicine.

b) A copy of his curriculum vitae is attached.

c) Dr. Milby will testify concerning published literature relating to the effects of PCBs on human health, and the risks to human health presented by PCBs.

d) Dr. Milby's opinions will be based upon his experience, personal knowledge, and the published literature in the field.

e) Dr. Milby has prepared no written reports relating to his testimony on this case.

f) Dr. Milby has reviewed much of the published literature in the field of PCBs and human health. The relevant articles have previously been the subject of deposition testimony in this case.

g) Dr. Milby has been retained as an expert consultant by counsel on behalf of Outboard Marine Corporation for purposes of providing expert testimony in this case. No contracts or documents relating to the terms and conditions of his employment exist.

Attorneys for Outboard
Marine Corporation

Of Counsel:

PHELAN, POPE & JOHN, LTD.
30 North LaSalle Street
Chicago, IL 60602
312/621-0700

MARTIN, CRAIG, CHESTER & SONNENSCHEIN
115 South LaSalle Street
Chicago, IL 60603
312/368-9700

STATE OF ILLINOIS)
) SS.
COUNTY OF COOK)

Frank Bochte, being first duly sworn, on oath deposes and says that he served the above and foregoing Notice by hand delivering a copy of same to the persons to whom said Notice is directed on the 17th day of May, 1982.

Frank Bochte.

SUBSCRIBED AND SWORN to before me this 17th day of May, 1982.

Notary Public

James H. Schink, Esq.
Kirkland & Ellis
200 East Randolph Drive
Chicago, Illinois 60601

Department of Justice
Washington, D.C. 20530
ATTN: Elizabeth Stein, Attorney
Pollution Control Section
Land & Natural Resources Division

M. Kaye Jacobs, Esq.
Enforcement Division - Water
U.S. Environmental Protection Agency
230 South Dearborn Street
Chicago, Illinois 60604

James T. Hynes, Esq.
Assistant United States Attorney
219 South Dearborn Street
Chicago, Illinois 60604

John Van Vranken, Esq.
Assistant Attorney General
Environmental Control Division
188 West Randolph Street
Suite 2315
Chicago, Illinois 60601

The Epidemiology of PCBs

by William R. Gaffey

Monsanto Company

September 15, 1981

I. Summary

Twenty four published and unpublished reports covering 21 epidemiologic studies of human exposure to PCBs were reviewed and evaluated. The studies showed that high occupational exposures to PCBs have resulted in chloracne and dermatitis. Alterations in liver and fat metabolism were found in most studies that examined these functions, but there was no clinical illness associated with these alterations or with level and duration of exposure to PCBs. Studies of mortality rates in exposed populations have shown no pattern of cancer deaths related to PCB exposure.

Exhibit 4 of
Dr. Milby
5/27/82

II. Introduction

This is a review and evaluation of the epidemiologic evidence concerning the health effects of exposure to PCBs, particularly at levels that do not cause acute toxic effects. A study is considered "epidemiologic evidence" if it measures, directly or indirectly, the differences in the risk of ill health among populations with different exposures to PCBs.

In the past several decades there have been many clinical studies of the effects of heavy exposures to PCBs (e.g. Von Wedel et al [1], Schwartz [2]). Such studies are extremely useful in identifying the kinds of effects that should be investigated. However, they do not address the question of the risk of incurring such effects, and are therefore not included in this review.

The studies reviewed here fall into three categories. First, there are studies of accidental heavy exposures and the resulting acute and chronic effects. In each case the study was prompted by an outbreak of illness or the occurrence of a death in an exposed population, after which the population was studied.

Second, there are studies of the relationship between exposure to PCBs and the resulting body burden of PCBs in serum or adipose tissue. Strictly speaking these are not epidemiologic studies since they do not deal with health effects. However, if a relationship between level of exposure and body burden cannot be verified, the interpretation of epidemiologic studies becomes difficult if not impossible.

The third category is studies that were done because the populations in question were known or suspected to be exposed to PCBs, rather than because some untoward health outcome had been observed first.

Many published reports combine some or all of these types of investigations. In the sections that follow, we consider first the studies of accidental overexposure, second the studies of PCB exposure versus body burden, and third the epidemiologic studies of exposed populations. In the latter section the discussion will be organized with respect to the health effects that were investigated. These are (a) dermatologic symptoms, (b) biochemical alterations, (c) other symptoms and illnesses, (d) carcinogenicity.

III. Accidental Heavy Exposures

Two epidemiologic studies of accidental exposure have been reported. The first, by Meigs et al [3] in 1954, described an outbreak of chloracne in a plant in which a process change had introduced an unspecified PCB compound into the work environment. Breathing zone levels of PCB were stated to be 0.1 mg/cum. Seven of 14 exposed workers developed chloracne, but liver function tests were normal in six of these, with some borderline abnormalities in the seventh. The chloracne disappeared after treatment, and the single borderline liver function abnormality improved, but did not disappear after 13 months. Improved process control prevented any recurrence.

Although the estimated PCB level must be accepted with reservation because of the state of the art at that time, it is clear that the chloracne resulted from the PCB exposure. Given the lack of controls and the small rate of abnormal liver function, it is unlikely that the PCB exposure had any connection with the liver function findings.

The second incident is the now famous Yusho incident in 1968 which has been documented in many reports (Kuratsune et al [4], Urabe et al [5]), in which some thousand Japanese became ill after eating cooking oil which had been contaminated with Kanechlor 400, a PCB compound of Japanese manufacture.

The most common acute symptoms observed were hyperpigmentation and acne-like lesions, discharge from the eyes, central nervous system symptoms, and vomiting and diarrhea. There was a

dose-response relationship between the amount of oil ingested and the proportion of persons reporting symptoms. Three years later about half the patients had improved, but still had symptoms. Six years later many patients still reported such symptoms as headache, stomach pain, numbness of the extremities, joint pain and respiratory symptoms [5].

Out of ten live births to women affected by Yusho, nine showed hyperpigmentation and most had increased eye discharges. These symptoms later disappeared. Although there have been reports of premature eruption of teeth (two children out of a series of 13) and unusually wide fontanelles and sagittal sutures (three out of 13) it is not at all clear that these findings represent any more than the normal variation to be expected, since no control observations were made (Funatsu et al [6]).

In general, laboratory tests of the Yusho victims showed elevated serum triglyceride levels, low serum chlolesterol in serious cases, and elevated SGOT and SGPT levels in serious cases (Higuchi [7]).

As of the end of 1977, 51 deaths among Yusho patients had been identified [5]. The percentage of cancer deaths (35.4) exceeded that of the prefecture in which the deaths occurred (21.1). However, the figures do not appear to be very useful for several reasons. First, after the original incident, the criteria for diagnosis of Yusho had been changed, so that it is impossible to determine the denominator which produced this number. The completeness of ascertainment of the deaths is unknown. In addition, no adjustment for age appeared to have been made in the

above comparison. Finally, the average elapsed time from exposure to death was less than ten years, and cannot be calculated precisely because the dates of death are not provided. This may well be too short a period for cancers resulting from the exposure to show up.

Although the Yusho incident represented a massive ingestion of PCBs, recent reanalysis of the cooking oil and of the estimated intake by the patients shows that the exposure to polychlorinated dibenzofurans (PCDFs) and polychlorinated quater-phenyls (PCQs) was about equal to the exposure to PCBs, and current determinations of PCQs in blood and other tissues of Yusho patients have shown levels similar to that of PCBs [8]. It is therefore doubtful whether any generalization can be made from this incident to lower level environmental or occupational exposures to PCBs.

IV. Environmental Levels and Body Burdens

Two studies of the relationship between ingestion of PCBs and blood levels of PCBs have been reported (Michigan Dept. of Public Health [9] and Kreiss et al [10]). In each case the study was concerned with ingestion of fish known to contain relatively high levels of PCBs. In the first, an association was found between blood PCBs and exposure level as estimated by the amount of Lake Michigan sport fish consumed. In the second the relationship between blood PCBs and a complex of factors was examined in a population in an area with high levels of environmental contamination. Age, sex and fish consumption, in that order of importance, were associated with blood levels of PCBs. To the extent that fish consumption measures ingestion of PCBs, these studies confirm that blood PCBs are a function of ingestion of PCBs as well as of age and sex. Other associated variables were examined in [10] but will be discussed in the following section.

A number of studies of blood PCBs and exposure to atmospheric PCBs have been made, most of them in conjunction with studies of health effects. The portions of the studies relevant to this section are reviewed here.

There are three types of studies. The first compares groups which have had different exposure levels as estimated from process considerations or environmental measurements. For convenience such a study design will be called Type A. The second, which we will designate Type B, measures the change over time in a single group after PCBs have been removed from the environment (or after

the group has left the environment). The third, Type C, compares groups that have had different durations of exposure. Often the same report will contain more than one type of study. For example, an exposed group may be compared with an unexposed group (Type A) and within the exposed group long term exposed workers may be compared with short term workers (Type C).

The measure of body burden has in most cases been a single number representing, depending on the study, blood PCBs, plasma PCBs, serum PCBs (all of which are called "blood" PCBs in this review), or level of PCBs in adipose tissue. Analytic methods have varied over time and among investigators. More recently measures of body burden have sought to determine separately the levels of higher chlorinated biphenyls (5 or more chlorine atoms per molecule) and lower chlorinated biphenyls.

Table 1 lists the studies considered in this section, with the type of design and whether or not separate determinations of higher and lower chlorinated biphenyls were made. All of the studies except Baker et al are occupational.

All of the Type A studies agree in showing a higher body burden of PCBs in populations with higher environmental exposure, except for one anomaly in Baker et al. There, persons exposed to sludge containing PCBs had slightly lower blood levels than the controls, on the average. However, the sludge exposed persons and the controls were not matched for age, which Kreiss et al showed to be the most important factor associated with blood PCB level. It therefore appears unequivocal that higher exposure to PCBs means a higher body burden, all other things being equal.

The Type B studies appear at first glance to be more equivocal (Table 2). Two studies show a decrease when exposure ceased or decreased and two do not. However, the studies showing no decrease remeasured their study groups within a month or two after exposure changed. The ones showing a decrease remeasured after three months and one year.

The fact that Ouw et al found no decrease after two months while Kitamura et al found over a 50 percent decrease after three months gives rise to some uneasiness. However, in the former study exposure was decreased but still present, while in the latter study PCB use had ceased. Ouw et al also suggest that after exposures in their study plant had decreased, workers did not wear gloves as recommended, so that the blood PCB levels may have resulted from skin contact.

Table 3 shows the findings for the Type C studies other than Maroni et al and Smith et al that is, for those that compared duration of exposure with a single measurement of blood PCB level. The results are not consistent. The study of Baumgarner et al found very low levels (average 4 ppb) in exposed workers, which may have accounted for their failure to find a relationship with duration. On the other hand the exposed workers in Hasegawa et al had an average level of 370 ppb and still showed no relationship with duration.

The studies of Maroni et al and Smith et al suggest a possible explanation. Maroni et al made separate comparisons of high chlorinated PCBs and low chlorinated PCBs between workers with present and past exposures. They found differences in the

low chlorinated PCBs but not in the high chlorinated compounds. Even though their analysis did not adjust for age, it suggests that the relationship between blood PCB levels and duration and recency of exposure may be a function of the level of chlorination of the PCBs. Smith et al however, in an elaborate analysis of high and low chlorinated blood PCBs versus present and past exposure, found no "evidence either to support or refute different accumulation kinetics in humans for the lower and higher chlorinated biphenyls". Nevertheless, they found a significant correlation between current personal air PCB levels and low chlorinated blood PCBs, but no significant correlation with high chlorinated blood PCBs.

In summary, body burdens of PCBs are clearly related to the level of exposure to environmental PCBs. Observations of a decrease in the burden of PCBs after exposure is eliminated or decreased are not consistent. The lack of consistency may be due to the short periods of observation of some of the studies, or possibly to differences in the average chlorination of the PCBs involved. Studies of the relationship of PCB burden to duration of exposure again are not consistent. There is a suggestion that this may be due to the confounding effects of age and sex, or to differences in the metabolism of high and low chlorinated PCBs, with the higher PCBs being more likely to accumulate in adipose tissue.

V. Epidemiologic Studies of PCBs and Health

Excluding mortality studies, there are 17 epidemiologic studies of health effects related to PCB exposure. The accident report of Meigs et al is included since it did not differ in design from many of the studies that were not motivated by accident reports.

These studies are listed in Table 4 with a summary of the findings by major category. Five of the reports are in Japanese [13,14,15,16,18]. The details of those studies are taken from the NIOSH criteria document for PCBs [34].

Two of the studies, Kappanen and Kolhol and South Carolina Department of Health and Environmental Control are not specific as to health effects. The first of these is a comparison of groups with different work exposures and different blood PCB levels (74-1900 ppb in the 12 persons with the greatest exposure) in which the authors simply state that all persons studied were in good health. The second is a study of 32 workers in a capacitor plant, 10 of whom were exposed regularly to PCBs. The authors state that there is "no evidence of physical harm resulting from working with PCBs".

The remaining 15 studies in Table 4 are reviewed below with respect to their findings in each major category of health effects. The studies are considered in the order of their publication.

Dermatologic effects. There are 11 studies of dermatologic effects associated with PCB exposure. The first is Meigs et al

described in Section II above, who found that 7 of 14 exposed workers got chloracne where the PCB concentration in their breathing zones averaged 0.1 mg/cum. Hasegawa et al reported an unstated number of cases of hyperpigmentation of the hands, and acne-like lesions of the jaw, back and thighs in exposed workers. The average blood PCBs in the workers was 370 ppb. However, the authors state that skin complaints were unrelated to blood PCB levels and appeared to be due to skin contact. Kitamura et al reported a range of skin disorders in 10 of 13 exposed workers with an average blood level of 820 ppb. The disorders occurred on parts of the body not normally in direct contact with PCBs. Hara et al reported that about 45 percent of 118 capacitor workers complained of blackheads and other acne-like symptoms while working with PCBs. The complaints were not related to blood levels of PCBs, and virtually disappeared within a year after exposure had ceased.

Inoue et al reported one case of chloracne in an exposed worker whose blood PCBs were in the 190-210 ppb range, but no symptoms in the rest of a small work force whose blood PCBs ranged from 130 to 520 ppb. The Michigan Department of Public Health reported no relationship of any Yusho symptoms to consumption of fish with high levels of PCBs. Ouw et al reported 14 cases of dermatitis, eye irritation or burning sensations on the skin out of 34 exposed workers, where air levels of PCBs ranged from 0.32 to 2.22 mg/cum. The complaints appeared to occur more often in those with higher blood PCB levels. Fischbein et al reported that about 50 percent of 326 capacitor manufacturing workers reported a

history of dermatological symptoms, the most common symptom being a rash. Those with symptoms had higher blood levels of high chlorinated PCBs. Baker et al reported no chloracne in 18 exposed workers (average blood PCBs 75.1 ppb) or 19 members of their families (average blood PCBs 33.6 ppb). Maroni et al reported 10 cases of dermatitis (5 diagnosed as active or past chloracne) out of 80 exposed workers. The average blood PCB level in the study was 342 ppb. Smith et al found no chloracne in a study population of 324 exposed workers in capacitor manufacturing and transformer repair, whose average blood PCBs ranged from 38 to 546 ppb. However, there was a significant association of skin rash or dermatitis with blood levels of high chlorinated PCBs.

Interpretation of this mass of data is complicated by the difficulty of diagnosing chloracne, the uncertainties of blood PCB determinations, and the changing technology for making such determinations. Nevertheless, the data suggest strongly that when PCB blood levels exceed about 150-200 ppb chloracne can occur. However, most studies have shown that the occurrence of chloracne is not further associated with blood PCB levels. This suggests that (a) personal idiosyncratic factors may be involved and/or (b) that the high blood levels are an indicator of the existence of environmental contamination which actually produces chloracne by skin contact.

The reports of dermatitis other than chloracne suffer from an additional complication. According to the National Health Survey, about one-third of all Americans of working age have at least one current skin condition serious enough to warrant evaluation by a

physician [25]. Clearly, substantially more than one-third must have either a current condition or a history of such a condition in the past. The prevalence figures reported by Maroni et al and Fischbein et al are therefore not in themselves remarkable, but the agreement of Fischbein et al and Smith et al on the relationship between dermatitis and high chlorinated blood PCBs suggests that this association may be real.

Liver Function. Nine studies examined liver function. Meigs et al found one borderline abnormal liver function in 14 exposed workers. Hasegawa et al found mild disturbances in exposed workers (increased SGOT, SGPT, SAP, decreased serum cholinesterase) which they did not consider to be clinically significant. Ouw et al, Kitamura et al, Fischbein et al and Baker et al (a non-occupational study) found no abnormalities associated with exposure, except that Ouw et al found a high BSP retention in 4 out of 7 workers with blood levels above 500 ppb.

Maroni et al found 16 out of 80 workers with abnormalities in GGT, OCT and transaminases. Their blood PCB levels were higher than those in the workers with normal liver function. Kreiss et al (non-occupational study) found no relation between liver function and blood PCBs when age and alcohol consumption were taken into account. Smith et al found elevated SGOT and GGT levels in persons with higher blood PCB levels.

In summary, 5 studies of the 9 found some mild liver function abnormalities, none of which were associated with any measurable adverse health effects. The two non-occupational studies, Baker et al and Kreiss et al, found no abnormalities associated with

blood PCB level. Fischbein et al, in their study of capacitor manufacturing workers, noted that "there was a paucity of abnormal results in the biochemical studies".

Fat Metabolism. Six studies considered fat metabolism. One, Bumgarner et al, found no relationship between blood cholesterol and blood PCBs. One of the remaining 5, Hasegawa et al, found a decrease in cholesterol, glycerides, phospholipids and beta-lipoprotein in exposed workers. Of the remaining 4, Hara et al, Baker et al (non-occupational study), and Smith et al found increased triglyeride levels with increased blood PCBs. Kreiss et al found no association of triglycerides and blood PCBs when cholesterol level was taken into account. Smith et al and Kreiss et al also present contradictory findings with respect to HDL cholesterol levels; the former found an inverse relationship of HDL to blood PCBs; the latter found no relationship, but found a positive association between total cholesterol and blood PCBs.

Most studies, including one non-occupational study (Baker et al) have associated increased tryglycerides with PCB exposure. The data on cholesterol are not consistent; an increase, a decrease and no change were found (one study each). HDL cholesterol either decreased or was unchanged (one study each). Even if PCB exposure has some effect on fat metabolism, it appears to be without any apparent clinical significance.

Blood and Blood Pressure. There are five studies of blood chemistry; Bumgarner et al, Kitamura et al, Fischbein et al, Baker et al, and Maroni et al. None of them report any relationship of blood chemistry to PCB levels.

Bumgarner et al and Kreiss et al measured blood pressure in exposed persons. Bumgarner et al found no association with PCBs, but Kreiss et al found a statistically significant association between diastolic blood pressure and blood PCBs. Since there was no control group and since Kreiss et al are the only investigators to report this finding, its significance is not clear at this time.

Symptoms, Illness and Other Conditions. Six studies investigated reported symptoms in persons exposed to PCBs. Two of them reported allegedly increased symptoms of various kinds. Fischbein et al reported a history of gastrointestinal symptoms in 18 percent of 326 capacitor manufacturing workers, a prevalence of from 3.0 to 15.2 percent of various musculoskeletal symptoms, and a prevalence of from 4.8 to 27.8 of various neurological symptoms. These were, however, unrelated to duration of employment or to level of blood PCBs. Maroni et al reported 8 cases of gastrointestinal complaints in 80 exposed workers, with no indication of whether there was a relationship to duration of employment. They also reported two bleeding haemangiomas and one case of chronic myelocytic leukemia. These findings do not appear to have any significance, since they apparently are unrelated to the circumstances of exposure, and since the following 4 studies reported no symptoms related to PCBs.

The Michigan Department of Public Health compared a group of persons who consumed sport fish contaminated with PCBs to a group of unexposed controls. The incidence of 18 conditions, many of them the ones reported for Yusho disease, was measured in the two

groups. There were no health conditions that could be correlated with blood PCB levels or fish consumption. Baker et al reported that none of the following conditions were associated with blood PCB levels in a community study; fever, weight loss, anorexia, fatigue, headache, eye irritation, cough, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, arthralgia, and persistent skin rash. The community study of Kreiss et al reported the same thing for prevalence of illness or weight loss in the preceding year, use of medication, use of medical care, history of heart disease, and percentage of pregnancies ending in miscarriage, stillbirth or infant death. Finally, Smith et al reported an increased prevalence of general malaise and possibly altered peripheral sensation with increased blood PCB levels among occupationally exposed workers, but found no clinical abnormalities on physical examination.

The weight of evidence, as Smith et al conclude, is that no studies to date "have shown that occupational exposure to PCBs is associated with any adverse health outcome, to be distinguished from demonstrable subclinical biochemical alterations".

Two studies considered other conditions in persons exposed to PCBs. Warshaw et al reported decreased vital capacity in capacitor manufacturing workers. However, the pulmonary function values in the study population, most of whom were current or ex-smokers, were evaluated in comparison with a standard population of non-smokers, so that the effect of smoking as a confounder was not allowed for.

Alvares et al reported that in 5 workers occupationally exposed to PCBs, the rate of drug metabolism was significantly higher than in a group of controls matched for age, sex, and smoking and drinking habits.

There appear to be no significant clinical effects associated with the occupational or environmental exposures studied in these reports.

Carcinogenicity. It is generally agreed that epidemiologic evidence for carcinogenicity should fulfill certain requirements in order to be acceptable. These requirements deal with the study design, the logic of the observed pattern, and the repeatibility of the results. Table 5 lists these requirements as given by Doll [28].

There are four studies directed solely or primarily to the question of the carcinogenicity of PCBs. Table 6 lists the studies and their findings. They are reviewed here keeping in mind Doll's requirements.

The most obvious feature of Table 6 is that no study agrees with any other. That is, the requirement of repeatibility is not met.

The first study, by Bahn et al, observed three melanomas in a group of 92 research and development and refinery workers. These workers had an unknown exposure to other possible carcinogens, so that there could have been confounding. In any case the study was withdrawn for revision in the definition of the exposed population, and has not yet been released [34].

Zack and Musch studied 89 workers exposed for at least six months between 1945 and 1965 inclusive. There were no deaths from cancer of the liver or cirrhosis. The excess in respiratory cancer was based on four deaths and was not statistically significant. As with Bahn et al there was confounding because of other chemical exposure at the plant and, in this case, possibly cigarette smoking.

Brown and Jones studied 2,567 workers in a capacitor plant. About half the cohort had a latency period of 20 years or more. Although there was an excess of liver cancer deaths, it was inversely related to duration and latency of exposure, which does not support an occupational explanation. There was also an excess of rectal cancer. However, the two plants studied are located in an area whose mortality from rectal cancer is greater than the U.S. average [35]. Since U.S. population rates were used as a basis for comparison, the rectal cancer excess is at least partly an artifact.

Bertazzi et al studied 1,310 workers with at least six months employment in capacitor manufacturing between 1946 and 1970. Although excess digestive cancer was observed, there were no liver cancer deaths. The total number of deaths was small (27) and the excess cancer observed was based on two or three deaths for each of the two major sites involved. There is no indication of the duration or latency of exposure for the cancer deaths. The authors state that there were no other major exposures at the plant, and propose to continue the study with a larger cohort. In spite of the statistical significance of the excesses from all

cancers, this study must be considered a preliminary report, particularly since it shares with the other studies a failure to agree on any particular pattern of mortality.

The existing mortality studies of occupational exposure do not show the agreement that would lead one to infer an excess risk of cancer. Much of the conflicting findings can be attributed to the possible effect of confounding exposures, and to the "noise level" of sporadic excesses which would be expected in the absence of any occupational hazard.

VI. Summary and Conclusions

The epidemiologic studies of exposure to PCBs show that the body burden in exposed persons, whether the exposure is by ingestion, inhalation or skin contact, is related to the environmental levels and distribution of PCB. The relation of body burden to duration of exposure is less clear, and appears to differ depending on the degree of chlorination of the PCBs. Nevertheless, the evidence is clear that higher exposures mean higher blood PCB levels, and that persons with occupational exposures have blood PCB levels that may be an order of magnitude greater than that of environmentally (that is, non-occupationally) exposed persons.

Occupational exposure to PCBs at high levels has been associated with the occurrence of chloracne, but the relationship is not straightforward, suggesting that the actual risk of chloracne is also a function of individual susceptibility and personal work habits, as well as possible exposure to other contaminants.

Dermatologic problems other than chloracne are associated with occupational exposure, and may be related to exposure to high chlorinated PCBs.

Alterations of liver function and fat metabolism associated with PCB exposure have been observed in several studies, but are characterized by investigators as mild and of no clinical significance.

The one fact on which all occupational studies of health effects agree is that there has been no clinical illness associated with PCB exposure other than dermatitis. Studies of non-occupationally exposed populations have found neither dermatitis nor other clinical evidence of exposure-related effects, with the exception of a single study which suggests that diastolic blood pressure may be related to blood level of PCBs.

Mortality studies concerned primarily with cancer present problems of interpretation due to the small sample size of some of the studies, and to the confounding effect of other exposures. However, they do exhibit a pattern, which is that none of the studies agree on the cancer sites at which an excess mortality was found, and the excesses that were found are in general not statistically significant. One must conclude that the findings of the mortality studies reflect a sporadic pattern of excess mortality at different sites which is not consistent with a carcinogenic effect of PCBS. In addition, where an examination of duration and latency of exposure was possible, no association with these variables was found [32].

Taken as a whole, the epidemiologic studies find that high occupational exposures to PCBs may cause dermatitis of various kinds, but that there are no other clinically observable effects, including the occurrence of cancer.

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Table 1

Studies of Environmental Levels and Body Burden of PCBs by Type of Body Burden Measure

Study	Study Type*	High & Low Chlorinated PCBs	Adipose PCBs
Baker, E et al [11]	A	No	No
Bumgarner, JE et al [12]	C	No	No
Hara, I et al [13,14]	B,C	No	No
Hasegawa, H et al [15]	A,B,C	No	No
Inoue, Y et al [16]	A,C	No	No
Karppanen, E, Kolho, L [17]	A	No	Yes
Kitamura, M et al [18]	B	No	No
Maroni, M et al [19]	A,C	Yes	No
Ouw, HK et al [20]	A,B	Yes	No
Smith, AB et al [21]	A,C	Yes	No

* A = comparisons of groups with different exposure levels
  B = evaluation of results of decreasing or removing exposure
  C = comparisons of groups with different durations of exposure.

Table 2

Studies of Blood PCB Levels Before and After Exposure Levels Changed, and Interval from Exposure Change to Remeasurement

Study	Exposure Change	Interval to Remeasurement	Decrease in Blood PCB Level
Hara et al [13,14]	Ceased	1 year	~75%
Hasegawa et al [15]	Ceased	1 month	None
Kitamura et al [18]	Ceased	3 months	>50%
Ouw et al [20]	Decreased	2 months	None

Table 3

Studies of PCB Levels by Duration of Exposure

Study	Relationship of Blood PCB to		
	Duration of Exposure	Age	Race
Bumgarner et al [12]	No	No	No
Hara et al [13,14]	Yes		
Hasegawa et al [15]	No		
Inoue et al [16]	Yes		

Table 4

PCB Epidemiology Studies (other than mortality) and Summary of Findings*

	Dermatologic Findings	Physiological Parameters	Symptoms and Illness	Other
Alvares et al [27]		Y		
Baker et al [11]	N	Y	N	
Bumgarner et al [12]		N		
Fischbein et al [23]	Y	Y	Y	
Hara et al [13,14]	Y	Y		
Hasegawa et al [15]	Y	Y		
Inoue et al [16]	Y			
Karppanen, Kolho [17]				N
Kitamura et al [18]	Y	N		
Kreiss et al [10]		Y	N	N
Maroni et al [24]	Y	Y	Y	
Meigs et al [3]	Y	Y		
Michigan Dept of Public Health [9]	N		N	
Ouw et al [20]	Y	N		
Smith et al [21]	N	Y	Y	
South Carolina Dept. of Health and Environmental Control [22]				N
Warshaw et al [26]		Y		Y

* Y = Findings associated with exposure
N = No findings associated with exposure
No entry = No data presented

Table 5

REQUIREMENTS FOR ESTABLISHING CARCINOGENICITY FROM EPIDEMIOLOGICAL EVIDENCE

- Positive associations in groups of individuals with known exposure (case-control or cohort studies).
- That are not explained by bias in recording or detection.
- That are not explained by confounding.
- That are not explained by chance.
- That vary appropriately with dose.
- That vary appropriately with period of exposure.
- That are observed repeatedly in different circumstances.

Table 6

Inconsistencies in Studies of Cancer in PCB Exposed Populations, with Findings

Study	No. Studied	Findings
Bahn et al [29,30]	92	Melanoma**
Zack, Musch [31]	89	Lung
Brown, Jones [32]	2,567	Liver Rectum
Bertazzi et al [33]	1,310	Digestive* Lymphatic and hematopoietic

* Significant at 5 percent level

** Significant at 1 percent level

THE TOXICOLOGY OF PCB'S

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Prepared by the

Hazard Evaluation System

Epidemiological Studies Section
State of California
Department of Health Services/Department of Industrial Relations
2151 Berkeley Way
Berkeley, California 94704
(415) 540-2115

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THE TOXICOLOGY OF PCB'S

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I. INTRODUCTION

As a consequence of the EPA ban on further manufacture of PCB's* in 1977, occupational exposures to these compounds have been drastically reduced. However, significant exposures may remain for particular occupational groups. Utility workers, for example, may experience sporadic but potentially massive exposures when cleaning up spills, or when servicing and dismantling transformers and capacitors that still contain PCB fluid. Electricians, appliance service workers and firefighters also may have continued occupational exposure. NIOSH estimates that 12,000 workers have potential exposure as a result of current uses of PCB's (NIOSH, 1977). Despite the vast scientific literature on the toxicology of PCB'S, the human health effects likely to result from such exposure remain ill-defined.

The Hazard Evaluation System has reviewed the literature on PCB toxicology in response to inquiries about worker health. Requests for information have come from unions and workers who handle PCB fluids in clean-up of spills, in maintenance work, and in transportation, storage and disposal of used equipment. Toxicology information has also been requested by medical professionals evaluating the clinical significance of PCB exposures, and public health officials who are attempting to set standards for occupational and environmental exposures. Our primary goal has been to review the data relevant to the human health effects of PCB's especially those resulting from occupational exposures. Since the published epidemiologic evidence is limited we have utilized animal toxicology studies where appropriate in anticipating potential biologic effects in humans. We have not attempted to summarize the extensive literature on PCB toxicology, but the reader is referred to a number of recent reviews (DHEW, 1978; IARC, 1978; Fishbein, 1974; Kimbrough, 1974; EPA, 1977; Nelson, 1972; NIOSH,

1977).

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* PCBs: Polychlorinated Biphenyls

II. GENERAL BACKGROUND INFORMATION

In all animal species that have been studied PCB's have a very low acute toxicity. They are readily absorbed across biological membranes, poorly metabolized and only very slowly eliminated. Because PCB's persist in the environment and accumulate in living tissue, they are concentrated ("biomagnified") in the food chain in a similar manner to other organochlorine compounds like DDT. Concern about exposure to PCB's has, therefore, focused on their resistance to biodegradation with the consequent potential for long-term or delayed health effects.

A number of published reports have established "background" levels of PCB's in the blood and tissues of human populations with no previous history of exposure. Surveys in various geographical areas have found detectable residues in blood, fat and mothers' milk. Measurable levels of PCB's are typically found in greater than 50% of subjects tested with maximum blood levels generally less than 20 ppb (Finklea, 1972). The levels reported from adipose tissue are typically somewhat higher, in the range of 1-2 ppm (Kutz, 1975). Residues of PCB's in human milk have ranged from 40-100 ppb in whole milk (New York State Health Council, 1977).

Two facts complicate the documentation of the human and animal toxicology of PCB's:

1. Commercial products are rarely single agents, but rather are complex mixtures of chlorinated biphenyls with different numbers and arrangements of attached chlorine atoms (see Figure I). The metabolism and toxicology of PCB's seem to vary with the percent of chlorination and with the isomeric structure of the PCB molecule.

2. All commercial products are potentially contaminated with chlorinated naphthalenes and polychlorinated dibenzofurans (PCDF's). The degree of this contamination varies with different commercial mixtures (see Figure III).

Contamination by dibenzofurans (PCDF's) is of particular concern because of the structural similarity of these compounds to the highly toxic dibenzodioxins (see Figure II). The pattern of observed effects in animals exposed to PCDF's closely resembles that seen following exposure to 2,3,7,8 tetrachlorodibenzodioxin (TCDD). In comparative animal studies the toxicity of PCDF's is much greater than the PCB's, particularly in the thymus, skin (acne), liver and hematopoetic system (Oishi et al., 1978; Moore et al., 1979). In addition, PCDF's are 1000 times more potent than PCB's as enzyme inducers (see Section VI).

Uncertainties in the analytic methods used for detection of PCB's must be considered when reviewing the published data on PCB toxicology. Monitoring PCB's in environmental or biological samples by gas-liquid chromatography/mass spectrometry (GC/MS) is made difficult by the presence of other chlorinated hydrocarbons (e.g., pesticides) which are commonly present at similar concentrations (Stalling et al., 1979). Because of the difficulties in the interpretation of GC/MS spectra, the PCB levels reported from different laboratories may show considerable variation.

III. PHARMACOKINETICS

Absorption

There is relatively little information on the rate or degree of absorption of PCB's by any route for any species of animal. Since similar systemic toxicity has been observed in rodents after dermal, oral and inhalational adminstration of comparable doses, it is likely that PCB's are easily absorbed by all routes. The few quantitative measurements of relative absorption rates indicate that most, if not all, PCB's which contain six or fewer chlorine atoms are efficiently absorbed from the GI tract (Albro and Fishbein, 1972; Van Miller et al., 1975).

Distribution, Accumulation (Mammals)

As with other heavily chlorinated chemicals the major storage tissue for PCB's is body fat. The concentration in adipose tissue is 10-1000 times that found in other tissues, both following single oral doses (Grant et al., 1971) and after chronic administration. (Curley et al., 1971) The lowest concentrations are found in whole blood and plasma where levels are usually several fold lower than in other tissues examined. This preferential distribution of PCB's into fat has been well documented after i.v. dosing in the rat (Lutz et al., 1977). Results are consistent with the high distribution coefficient of PCB's in fat and low perfusion of adipose tissue compared to skin, liver, muscle and blood (Anderson et al., 1977).

Two important pharmacokinetic questions cannot now be resolved on the basis of available data:

1. Does the concentration of PCB's reach steady state with constant exposure? and

2. Will mobilization of adipose tissue after starvation or illness lead to a transient increase in PCB concentrations in blood and other tissues ?

Like most heavily chlorinated hydrocarbons the half-life of PCB's in animal tissue is quite long. In a chronic feeding study with Aroclor 1245 at 100 ppm in the diet of rats, a steady build-up of PCB's occurred in all tissues analyzed without a plateau level even after 240 days of treatment. By comparison, in a similar rat dietary study using DDT, plateaus in fat were attained after 90-140 days (Curley et al., 1971). In dairy cows a steady state was reached in 40-60 days (Fries, 1972), probably due to mobilization into fat micelles and secretion into milk. Thus, PCBs are unlikely to reach steady state levels in non-lactating animals; and fat mobilization or lactation may be expected to result in release of stored PCBs.

Transplacental Exposure, Secretion in Milk

Transplacental exposure of PCB's has been documented in mammals. Term fetuses taken from rats exposed to 10 mg/kg/day during days 7-15 gestation contained 0.63 ppm PCB, or about 1/60 the maternal dose. When the dose to the mother was increased five fold, the concentration in the fetuses increased two fold (Curley et al., 1973). The hyperpigmented babies observed in the Yusho incident (see Section VII) represent additional circumstantial evidence of transplacental passage of PCB's.

Secretion of PCB's into milk has also been observed. In mice, little passage of PCB's occurred across the placenta once PCB's had been sequestered into maternal adipose tissue, but they were readily transferred to suckling offspring through the milk (Vodicnik and Lech, 1980). These observations suggest that secretion of PCB's into milk may be quantitatively much more important as a source of exposure in newborns than is

transplacental passage. This has recently been documented in a prospective study of Japenese mothers and their infants. (Hirokadzu and Ota, 1980)

Metabolism

PCB's are metabolized primarily by hydroxylation and conjugation with glucuronic acid. The primary site of biotransformation is assumed to be the liver, although no data is available currently on the possible role of peripheral metabolism, e.g., skin.

Many experimental feeding studies in both mammals and birds have shown an inverse relationship between percent chlorination and rates of metabolism. Less chlorinated PCB's are more readily metabolized than are more chlorinated ones, the rate of metabolism and excretion decreasing sharply as the number of chlorine atoms increases above five (EPA, 1977). The metabolism of the higher chlorinated biphenyls is also dependent on the position of chlorine atom substitution. The presence of two adjacent, unsubstituted carbon atoms is needed for the rapid enzymatic hydroxylation reaction (Jensen and Sundstrom, 1974). Since the more highly chlorinated biphenyls have a very much slower metabolic rate and longer half-life, they are more generally found as residues in human and animal tissues. This relationship alters with PCB's above 54% chlorination, presumably as a result of lower absorption from the gastrointestinal tract.

Arene oxide intermediates have been described in a major pathway of the metabolic transformation of PCB's by hepatic mixed function oxidases (Safe et al., 1975; Gardner et al., 1973). These intermediates are of particular concern since they are capable of direct interaction with DNA and may be the active form of carcinogenic polyacyclic hydrocarbons. (Jerina and Daly, 1974) The PCB molecules which are more readily metabolized and excreted also are more likely to form these arene oxides. It does not necessarily follow, however, that those compounds which persist in tissue and are more

likely to be measured in population sampling are less important in terms of their carcinogenic potential.

From the limited data available, it appears that significant differences exist between non-human primates and rodents in the metabolism and pharmacokinetics of PCB's. The marked variation observed in PCB toxicity between rodents and primates may be explained by such differences. Primates appear to be more susceptible to the toxic effects of PCB's than are rats or mice (see Section IV and Figure IV). When single doses of radiolabeled PCB were administered by gastric intubation to infant monkeys, the metabolites measured in urine, tissue (liver) and serum included hydroxylation products derived from arene oxide intermediates (Allen et al., 1976); while in the rat, direct hydroxylation is the rule (Hsu et al., 1975).

There is virtually no pharmacokinetic data in humans. A few generalizations can be made, however, based on studies reporting PCB blood levels: The higher the exposure levels, the higher blood concentration of PCB's (Hara et al., 1975; Inoue et al., 1975; Karppanen and Lolho, 1973; Baker et al., 1980); and the higher the environmental concentration and/or the longer the period of exposure, the longer the blood levels of PCB's remain elevated (Hara et al., 1975; Baker et al., 1980). However, there are a few reports which are inconsistent with this latter trend (Bumgarrer et al., 1975; Hasegawa et al., 1972; Kitamura et al., 1973). PCB levels have also been correlated with race and geographic residence (NIOSH, 1977) and with age and dietary intake of fish (Kimbrough, 1980)

Comments

Certain generalizations can be made from the limited pharmacokinetic data that is available:

1. Absorption occurs by all routes (skin, GI, inhalation).

2. Distribution is primarily into fat.

3. Metabolism and excretion are dependent on specific molecular structure, varying inversely with percent chlorination.

4. Excretion is in general quite slow so that bio-accumulation occurs even at low exposure levels.

5. Transplacental transfer occurs but may be quantitatively less significant than secretion into milk,

6. Arene oxide metabolites are found in the metabolic transformation of PCBs. There compounds are highly reactive and may represent the active carcinogens. (see Section V)

7. The relationship between percent chlorination and potency as carcinogen has not been established.

8. There are essentially no pharmacokinetic data in humans; it is not known, for example, if intermittent high doses are more or less hazardous than low level chronic exposures to the same total dose.

IV. ANIMAL TOXICOLOGY

Acute Toxicity

When given as a single dose, the acute oral LD_{50} of PCB's in rats, rabbits and mice ranges from 1-10 grams/kg of body weight. According to the American Industrial Hygiene Association classification system for acute toxicity, PCB's are classified as "slightly toxic" (0.5 - 5 g/kg), or "practically non-toxic" (5-15 g/kg). There is some evidence that young animals are more sensitive than adults, and that females are more susceptible than males to the acute effects of PCB's (Kimbrough et al., 1978). In rodents, the acute oral toxicity appears to decrease with increasing chlorine content of the administered PCB's. This may be secondary to decreased absorption of the higher chlorinated compounds or to the differences in metabolic transformation previously discussed.

Although few clinical signs of toxicity have been reported in experimental animals, pathologic findings are extensively documented. CNS depression (decreased pain response and diminished exploratory behavior), anorexia and oliguria followed by ataxia, coma and death have been observed in rats following acute administration of large doses of PCB's (Brackner et al., 1973). Consistent pathologic findings associated with death in rats, rabbits and guinea pigs include liver damage with fatty infiltration, centrolobular atrophy, and in some cases necrosis. Pathologic changes in other organs in these species are not often described, except for chloracne-like lesions which occur at the site of skin or intradermal application.

Comments

The low order of acute toxicity in experimental animals is consistent with the lack

of acute effects observed in workers exposed to PCB's. Reported symptoms after occupational exposures include mild irritation of the skin and eyes at levels above 0.1 mg/m^3 with unbearable irritation occurring above 10 mg/m^3 (ACGIH, 1976). Systemic symptoms of nausea and headache have been reported but may be secondary to the solvents (such as trichlorobenzene) in the PCB mixtures.

Sub-acute and Chronic Toxicity

In contrast to the low order of acute toxicity, effects from chronic exposures to relatively low doses of PCBs have been consistently observed and are of far greater concern. These sub-acute effects show appreciable variation among species, but liver damage is again the prominent finding.

The major changes in rats fed Aroclor 1248, 1254, and 1262 at 100 ppm in their diet for six weeks included liver hypertrophy, marked fatty infiltration and degeneration of parenchymal cells. As in acute toxicity studies PCB mixtures with lower chlorine content were more toxic (Allen and Abrahamson, 1973). In 8-12 month feeding studies increased serum lipids and focal areas of liver damage were observed (Allen et al., 1976; Kimbrough et al., 1972).

Non-human primates are more sensitive than rodents to the toxic effects of PCB's (see Table I and Figure IV). Adult female monkeys exposed to dietary levels of 2.5 ppm for 12 months (=0.08 mg/kg/day) developed facial edema, alopecia, acne, gastritis with ulceration, anemia, hypoproteinemia and bone marrow hypoplasia. At 100 ppm (=10 mg/kg/day) there was considerably more evidence of tissue damage than in rats, including marked hepatic hypertrophy with ultrastructural abnormalities (Allen, 1975). Based on extrapolation from the Yusho data, PCB's may cause symptoms to humans at levels (0.2 mg/kg/day) which are comparable to the lowest doses which produce effects in non-human primates (see Table I).

Most of the animal data are derived from feeding or oral intubation studies. There are relatively few reports of dermal or inhalation experiments. Inhalation studies again revealed liver damage to be the prominent finding in rodents. For summary of inhalation data see the NIOSH criteria document, page 125 (NIOSH, 1977). Dermal toxicity studies in rabbits have produced skin lesions at the site of application as well as systemic effects including liver and kidney damage, thymic atrophy, lymphopenia and increased fecal porphyrins (Vos and Beems, 1971).

Comments

Liver damage, documented histologically, is the consistent finding among various laboratory animals exposed to low chronic levels of PCB's. It has not been observed in the limited surveys of exposed workers. This may be an artifact, however, of the relative insensitivity of the standard liver function tests (such as serum levels of SGOT, SGPT) as compared to biopsy and histologic analysis.

Reproductive Effects

Adverse reproductive effects of PCB's have been noted in many mammalian and avian species. The pattern of reproductive effects include alterations in estrus cycles, failure of implantation, increased frequency of spontaneous abortions, low birth weight offspring and decreased post-natal survival. No specific teratogenic effects of PCB's have been observed in a variety of avian species. Transplacental effects, however, have been documented in both animals and humans (see Section VII).

PCB's given to mice for 10 weeks at dosage of 1.0 mg/kg/day lengthened the estrus cycle by more than two days and decreased the number of successfully implanted ova (Orberg and Kihlstrom, 1973). Similarly, mice that received PCB's as sucklings in a

long-term transgenerational study showed subsequent alterations in estrus cycles, decrease in implantations, and when mated to each other (F1 studies), reduced number of offspring per litter (Kihlstrom et al., 1975).

In rats, studies suggest that reproductive effects of PCB's decrease as chlorination increases. No reproductive effects have been found with Aroclor 1260 (60 percent chlorination) at 1, 10, 100 ppm, but significant effects have been noted with Aroclor 1242 and 1254 (42 and 54 percent chlorination, respectively) at doses of 20 and 100 ppm. Aroclor 1260 began to exert toxic effects at doses of 500 ppm. Rats chronically fed from 20 to 100 ppm Aroclor 1242 and 1254 had reduced numbers of offspring. Surviving newborns showed increased mortality, with only 30 percent surviving to weaning. Five ppm of either Aroclor 1242 or 1254 produced no effects over two generations. Thus, the minimum effective doses ranged from 20 ppm for the lower chlorination mixtures to 100-500 ppm of the more highly chlorinated compounds. (Keplinger et al., 1971; Linder, et al., 1974)

Evidence of adverse reproductive effects is also available for non-human primates. Rhesus monkeys fed 2.5 and 5.0 ppm Aroclor 1248 for 18 months in the diet showed changes in menstrual cycles in addition to other systemic signs of toxicity. Evidence was also obtained for frequent resorptions and spontaneous abortions following breeding to normal males. In all, six infants were carried successfully to term out of 14 pregnancies. The offspring were of low birth weight and by two months began to show evidence of PCB toxicity, presumably from PCB's in the maternal milk; only three infants survived to six months. Behavioral tests in the three surviving animals showed marked deficits in several learning tasks, with increasing errors correlated with increasing body burdens of PCB's (Allen and Barsotti, 1976; Bowman et al., 1978; Barsotti et al., 1976).

The effect of PCB's on the male reproductive system is not known. There is one report of four male Rhesus monkeys exposed to 5.0 ppm Aroclor 1248 in the diet for 18 months. After 12 months, one of four animals developed clinical signs of PCB intoxication, showed marked sperm count depression and was functionally sterile. A testicular biopsy revealed an absence of spermatogonia. A second biopsy one year after exposure showed complete recovery (Allen et al., 1979). PCB's are negative in the mouse sperm morphology assay (Heddle and Bruce, 1977).

Comments

PCB's show significant effects on reproductive competence in a variety of species. These effects increase in intensity with increasing dosage and decrease with increasing chlorination of the PCB isomers. PCB's do not appear to be mammalian teratogens. A reasonable explanation for most of the reproductive effects of PCB's could be based on their estrogenic activity (see below).

PCB's have been detected in human semen (Dougherty et al., 1980), but there have been no studies of semen quality in relation to PCB exposure in humans. The effects of PCBs on the male reproductive system in animals or humans has not been adequately studied. The only other evidence to date on reproductive toxicity in humans come from the Yusho incident and is summarized in Section VII.

Other

1. Immunosuppressive Effects

   A number of reports implicate PCB's as immunosuppressants (Fishbein, 1974). Lymphoid atrophy has been observed in rabbits, chickens and guinea pigs. Suppression of humoral immune responses to several antigens was observed in rabbits and guinea pigs, and decreased cell-mediated immune response

followed PCB exposure in guinea pigs. A decreased tolerance to hepatitis virus was seen in ducklings without apparent intoxication. In monkeys exposed transplacentally and through contaminated milk, the lymph nodules of the spleen were extremely small and without germinal centers (Allen and Barsotti, 1976); morphologic changes were indicative of reduced immunologic competence.

2. Endocrine Effects

Subcutaneous administration of Aroclor compounds with lower chlorination produced an estrogenic effect on the rat uterus which was not shown with Aroclors of higher chlorination (Bitman and Ceal, 1970). Female primates fed Aroclor 1248 for six months showed an increase in concentration of urinary ketosteroids and a prolongation of their menstrual cycles with increased bleeding (Barsotti et al., 1976). Antiandrogenic effects have been described in birds although the mechanism is not clear. It may be secondary to an increased rate of androgen metabolism in the liver by induction of microsomal enzymes (see Section VI), or by virtue of PCB's exerting estrogenic effects.

Comments

The effect of PCB exposure on immune and endocrine system function has not been carefully studied in humans, so the relevance of these animal observations to human health remains unknown. There is one cross-sectional study of occupational exposure to PCB's which will include analysis of serum hormone levels and urinary metabolites, but results have not yet been published (Selikoff et al., in progress).

V. CARCINOGENICITY/MUTAGENICITY

Carcinogenicity

Several PCB mixtures are clearly carcinogenic in rodent bioassays, producing liver tumors (hepatocellular carcinomas). Kanechlor 500 and Aroclor 1254 are carcinogenic in male mice (Ito et al., 1973; Kimbrough and Linder, 1974); and Aroclor 1260 is carcinogenic in separate studies in two strains of female rats (Kimbrough et al., 1975; Norback et al., 1980). In addition, a purified component of a PCB mixture, 2,4,5,2',4',5'-hexachlorobiphenyl, has recently been found to be carcinogenic in female rats, causing hepatocellular carcinomas (Norback et al., 1980).

Because high doses of PCB's are known to cause extensive injury to liver tissue it is important to consider the dose levels at which liver carcinomas were produced in the rodent bioassays. In two studies in rats, significant increases in hepatocellular carcinomas were present at doses which did not produce gross histologic changes. Hepatocytes were somewhat enlarged (probably due to microsomal enzyme induction), but no extensive fatty infiltration or necrosis occurred, as was characteristic of bioassays at higher dose levels (Kimbrough et al., 1975).

Test Results

1. Mice (Male)

   A. Kanechlor 300, 400, and 500 fed to groups of 12 eight-week-old male mice at 100, 250, and 500 ppm in the diet for 32 weeks produced hepatocellular carcinomas in 5 of 12 survivors in the high dose group fed Kanechlor 500. The remaining 7 mice in this group had nodular

hyperplasia (neoplastic nodules). No metastases or other tumors were present in this or other dosed groups. The control group (6 mice) was likewise tumor-free (Ito et al., 1973).

B. Aroclor 1254 administered to groups of 50 five to six-week-old male BALBc/J mice at dietary levels of 0 or 300 ppm (about 50 mg/kg body weight during the exposure) for 11 months produced neoplastic nodules (hepatomas or hyperplastic nodules) in 9 of 22 survivors in the dosed group. Other liver lesions (adenofibrosis) were present in all 22 survivors. Additional morphological changes in the livers of these animals included pleomorphism and areas of necrosis. Such changes and tumors were absent among survivors (24) in the control group (Kimbrough and Linder, 1974).

A. Kanechlor 400 administered to ten-week-old Donryu rats (10 males and 10 females) at dietary levels which varied from 40-600 ppm during the 400-day study produced liver tumors (multiple adenomatous nodules) in 6/10 treated female rats. Such lesions were absent from the controls (5 males and 5 females) and the treated males (Kimura and Baba, 1973).

B. Kanechlor 300, 400, or 500 administered to groups of 30 eight-week-old male Wistar rats at dietary levels of 0, 100, 500, or 1000 ppm produced increases in the incidence of cholangiofibrosis at the highest dose level of all Kanechlors (2/15, 2/10, and 4/13, respectively). All three compounds also produced hepatic nodular hyperplasia, the incidence of which increased with dose and extent of chlorination (Kanechlor 300 at 100 ppm: 1/22; Kanechlor 400 at 100 ppm: 2/16, and 1000 ppm: 3/10; Kanechlor 500 at 100 ppm: 3/25, at 500 ppm: 5/16, and at 1000 ppm: 5/13); (Ito et al., 1974).

C. Aroclor 1260 administered to groups of 200 three to four-week-old female Sherman rats at 0 and 100 ppm in the diet (varying between 5-10 mg/kg body weight during the 21 month exposure) produced at 23 months among the dosed survivors clearly significant increases of hepatocellular carcinomas (controls 0/173; dosed group 146/184) as well as neoplastic nodules (hyperplastic nodules: controls 0/173; dosed group 26/184). The incidences of non-hepatic tumors did not differ between the dosed and control groups (Kimbrough et al., 1975).

D. Aroclor 1254 administered to groups of 24 eight-week-old Fisher 344 rats of either sex at dietary levels of 0, 25, 50, or 100 ppm for 105 weeks was not carcinogenic to any of the treated groups under the test conditions. It is important to note that two of the dose levels used were lower than those which produced a positive response in Sherman rats. Rare adenocarcinomas and carcinomas of the gastrointestinal tract appeared in both sexes and may be related to the administration of the PCBs (males: historical controls 6/600, dosed group 2/24). In addition a high incidence of non-neoplastic liver hyperplasia was present among the dosed groups (males: controls 0/24, low-dose 5/24, mid-dose 8/24, high-dose 12/24; females: controls 0/23, low-dose 6/24, mid-dose 9/22, and high-dose 17/24); (NCI 1978).

E. Aroclor 1260 administered to groups of 50 male and female Sprague-Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, causing significant increases in liver hepatocellular carcinomas (Norbeck and Weltman, 1980).

F. A purified component of a PCB mixture, 2,4,5,2',4',5-hexachlorobiphenyl administered to groups of 50 male and female Sprague Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, producing an increased incidence of liver hepatocellular carcinomas among the dosed animals (Norback and Weltman, 1980).

Mutagenicity

PCB mixtures have not been observed to have mutagenic activity nor to measurably affect chromosomes in repeated studies using a variety of in vitro or in vivo test systems Evidence of genetic damage from PCB's in laboratory test systems including chromosomal aberrations, non-disjunction, loss of sex chromosomes or increased frequency of sister chromatid exchange has not been observed. Report of a weak effect of Aroclor 1221 and of a stronger effect of 4-chlorobiphenyl in Salmonella using PCB-induced rabbit liver homogenate as a liver activation system appears unfounded (Wyndham et al., 1976). Further attempts to repeat these results have been unsuccessful using a variety of Salmonella tester strains and liver activation systems (Katzenellenbogen and Ames, 1980; Safe, 1978).

However, PCB's belong to the class of heavily chlorinated animal carcinogens, most of which are not positive in short-term tests for mutagenicity. Examples in this class include dieldrin, chlordane, kepone, mirex, TCDD,* chloroform, and carbon tetrachloride. Whether this is because the in vitro metabolic activation systems do not produce the same spectrum of metabolites that occur in vivo or because heavily chlorinated compounds such as PCB's are carcinogenic by non-mutagenic mechanisms is not known at this time.

* TCDD: Tetrachlorodibenzodioxin

Validation of the carcinogenic effects in rodents is provided by a positive cell transformation assay using C3H10T1/2 clone eight mouse fibroblast cells in culture by two separate PCB mixtures (Aroclor 1254 and 1260) and a purified component 2,4,5,2',4'5' -hexachlorobiphenyl (Norback and Weltman, 1980).

Comments

A wide variety of PCB mixtures have been subjected to rodent cancer bioassays and to numerous in vitro and in vivo short-term tests for mutagenicity. Several of these PCB mixtures are carcinogenic. None of the PCB mixtures are active in short-term tests for mutagenicity, a finding that holds true for most heavily chlorinated carcinogens. However, substantial confirming evidence for carcinogenicity is provided by positive cell transformation assays using these same PCB mixtures. Thus, under OSHA published criteria, PCB mixtures should be considered Category I* carcinogens. Both IARC (IARC, 1978) and EPA (EPA, 1978) have concluded that based on available animal data PCB's should be considered as potential human carcinogens.

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* Category I: Human evidence or two positive mammalian bioassays or 1 positive mammalian bioassay with supporting results in short term tests.

Category II: One positive mammalian bioassay. (Source: Occupational Health and Safety Letter Vol. 9, No. 24 November 8, 1979)

VI. BIOCHEMICAL EFFECTS OF PCB'S

Enzyme Induction

The principal biochemical effect of PCB's is the stimulation and induction of certain enzyme systems. Enzyme induction occurs in both the microsomal monooxygenase or cytochrome P-450 system and the aryl hydrocarbon hydroxylase or cytochrome P-448 system, and it has been observed in both man and experimental animals. Induction is not restricted to the liver. It occurs in numerous other organs including kidney, adrenal, lung, gut, skin, and testes. Fetal enzyme induction may occur via transplacental exposure, and induction may also occur by exposure to contaminated milk. (ref)

Identification of structure-activity relationships for enzyme induction is difficult because of the large number of isomers in commercially prepared PCB's and because all commercial products contain trace amounts of polychlorinated dibenzofurans (PCDF's) which are orders of magnitude more potent as enzyme inducers than PCB's. (ref)

In early studies using commercial Aroclors, potency for enzyme induction was found to be dependent on chlorination of the PCB mixture. Later, when purified isomers were tested, potency was found to vary with the position of chlorine atom substitution (see Section III). (ref) Since rate of metabolism is also known to vary with isomeric configuration of the PCB molecule, it may be that potency for enzyme induction is simply a function of the relative rate of metabolism and excretion.

The enzyme induction properties of PCB's are utilized in the metabolic activation system of *in vitro* bioassays for mutagenicity. It is unlikely, however, that enzyme

induction would consistently enhance the effects of carcinogens or pro-carcinogens: It might function synergistically to activate a chemical, but they also might function to deactivate reactive carcinogens. Both phenomena have been observed in rodent cancer bioassays.

Porphyria

Porphyria cutanea tarda (PCT) in humans is an acquired defect in hepatic porphyrin metabolism characterized by uroporphorinuria, photosensitivity and mechanical fragility of the skin. PCT can be produced experimentally by a number of drugs, including tetrachlorodibenzodioxins and PCB's. All of these agents have the ability to stimulate the activity of 2-aminolevulinic acid (ALA) synthetase which is the initial enzyme in the heme synthetic pathway.

Experimental hepatic porphyria was observed in Sherman rats exposed to Aroclor 1254 in the diet. At doses of 100 ppm the animals became porphyric after a delay of approximately 2-4 months. The porphyria resembled hexachlorobenzene poisoning and human PCT (Goldstein et al., 1975).

In chronic feeding studies ALA-synthetase induction occurs after rats have become porphyric, although with large single doses the enzyme induction is seen almost immediately after dosing the animals (Goldstein et al., 1975).

It has not been established whether only certain isomers in the PCB mixtures or contamination with PCDF's is responsible for the production of hepatic PCT. Porphyria has not been reported in humans exposed to PCB's.

Comments

Enzyme induction has two important implications for human health:

1. The occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and

2. The interference with medical therapy due to increased metabolism of administered drugs.

PCB's are more potent enzyme inducers than phenobarbital, a drug that occasionally causes clinical problems due to its enzyme inducing effects. While the effects of phenobarbital decline after administration ceases, enzyme induction from PCB's persists long after cessation of exposure.

VII. HUMAN TOXICOLOGY AND EPIDEMIOLOGY

Few good epidemiologic studies of the health effects of PCB's are available. Most studies reported in the literature have been characterized by one or more of the following shortcomings:

1. Small study populations.
2. Lack of accurate exposure data.
3. Simultaneous exposure of workers to other potentially harmful chemicals.
4. Lack of control for confounding variables, such as alcohol consumption.
5. Inability to separate PCB's from contaminants and/or difficulty in comparing PCB's manufacture by different firms.

In spite of these problems, some health effects have been consistently reported in studies of workers occupationally exposed to PCB's. In addition, a large-scale poisoning which resulted from ingestion of PCB-contaminated rice oil has been well documented and resulted in multiple signs and symptoms attributable to PCB's.

The health effects identified in a review of the epidemiologic literature are summarized below, and Table II briefly describes the major epidemiological studies from 1954 through 1980.

Dermatologic Changes

Chloracne, contact or allergic dermatitis, and brown chromodermatosis have been consistently reported in studies of workers exposed to PCB's (Hara et al., 1975; Hasegawa et al., 1972; Inoue et al., 1975; Kitamura et al., 1973; Baker et al., 1980; Meigs et al., 1954; Ouw et al., 1976; Schwartz, 1936).

Systemic Symptoms

Nausea, digestive disturbances, headaches, upper respiratory problems, and persistent body odor have been reported as a result of occupational exposures (Ouw et al., 1976; Schwartz, 1936; Warshaw et al., 1979).

Liver Damage

This effect has been reported in some studies (Hasegawa et al., 1972; Higuchi, 1976; Meigs et al., 1954; Ouw et al., 1976). However, some investigators reporting abnormal liver function tests did not control for additional chemical exposures, previous medical problems, drinking patterns, etc. These confounding variables could explain some or all of the marginal differences encountered.

Yusho (Japenese word translated as "oil disease")

Both dermal and systemic health effects are well documented in the epidemiologic study of a poisoning epidemic in Japan caused by ingestion of contaminated rice oil in 1968 (Higuchi, 1976; Kuratsune et al., 1972)

It is not clear how much the health effects observed in Yusho victims can be extrapolated to occupational exposures for the following reasons:

1. The average amount of PCB (Kanechlor 400) ingested was estimated to be 2 grams and the minimum, 0.5 gram (Kuratsune et al., 1972). This is a higher dose than has been reported in most occupational exposures. In addition, the PCB's were ingested as opposed to inhaled or skin-absorbed as is the case with occupational exposures.
2. The contaminated oil contained "used" Kanechlor 400, the exact chemical compositon of which is unknown.
3. Frying of foods with the rice oil could have produced new compounds which may have altered the toxicity of the PCB's or the toxicity of possible contaminants.

4. Yusho oil was shown to contain high concentrations of dibenzofurans.

5. Reported concentration of PCB's in the oil may not have been accurate enough to permit a rigorous quantitative analysis since the methods for estimating PCB's in foods were not fully developed at the time.

Clinical features of the Yusho patients are listed in Table III. The Yusho incident is also important because it clearly documents the potential for reproductive and transplacental effects in humans:

A study was made of the thirteen infants of 11 mothers affected by Yusho and of 2 unaffected wives of patients: Two of the Yusho mothers had stillbirths; ten of the babies had transient greyish or dark-brown pigmentation of the skin, and 5 had similar pigmentation of the gingiva and/or nails; increased ocular discharge was present in 9; and 12 of the 13 infants were small when compared with the national average (Funatsu et al., 1972; Kikuchi et al., 1969; Kuratsune, 1976; Taki et al., 1969). Babies born to patients even 3 years after severe PCB exposure tended to show pigmentation of the skin on the back and the gingiva, although the degree of pigmentation was less than that of babies born to the same mothers up to one year after the poisoning (Kuratsune, 1976).

Congenital abnormalities have also been observed in PCB-intoxicated infants. In the population of 13 offspring of Yusho mothers, premature eruption of teeth was observed in 2 cases, and larger than normal frontal and occipital fontanelles, exophthalmos and the persistence of an abnormally wide sagittal suture were observed in 3 others. No other gross malformations were reported nor was any relationship between dose and outcome considered. (Funtasu et al., 1972).

Mothers' milk contaminated with PCB's also appears to be a source of exposure for infants: one baby showed signs of poisoning even though the mother had ingested the contaminated rice oil only after the baby was delivered. The infant began to show signs of PCB intoxication after 3-4 months of breast feeding (Kuratsune, 1972; Yoshimura, 1974).

Neurotoxicity

Paresthesias were reported in over 30% of Yusho patients (see Table III). In the Yusho epidemic more detailed neurologic examinations were performed in 21 cases admitted to a University hospital in northern Japan. Ten of the patients complained of numbness or pain in the distal extremities, and in five cases decreased pain, touch and temperature sensation was observed. Sensory conduction velocity in sural and radial nerves was below normal in 6 of 10 individuals with neuropathic symptoms (Murai and Kuroiwa, 1971). Headache and peripheral nervous system symptoms were also reported in a poisoning episode which occurred in a Finnish paper company (Hakkinen et al., 1973).

A decrease in amplitude of muscle action potential evoked by nerve stimulation, and a decrease in sciatic nerve conduction velocity has been reported in rats intoxicated with tetrachlorobiphenyl. Thus, PCB's can affect peripheral nerve function in both humans and experimental animals, but these have been reported only at doses which cause other systemic signs of poisoning.

Cancer

There is too little epidemiological evidence available yet to evaluate the potential of PCB's as human carcinogens (Bahn et al., 1980; Brown and Jones, 1980). A follow-up of the Yusho patients through 1977 has reported 51 deaths (31 with cause of death

confirmed) of the 1665 identified victims. There were 11 deaths from neoplasms, or 35.4% of the total. While this rate is higher than the 21.1% in the population of the same prefecture in 1977, these data were not age-adjusted. No particular site was elevated, and there were no deaths from malignant melanoma, a tumor previously suspected to be linked to PCB exposure (Bahn et al., 1976). Two liver cancers and two lung cancers were reported but smoking and drinking patterns were not available (Urabe et al., 1979).

A retrospective cohort mortality study of 2,567 workers in two capacitor manufacturing plants was recently completed by NIOSH. The reports, still in draft form, did not find any statistically significant excess mortality for any cause of death among the exposed workers. Deaths from liver cancer, cirrhosis of the liver, and rectal cancer were slightly higher than expected, but no information was available on medical histories, drinking patterns, etc. No correlation was observed between increased mortality and length of exposure, but the number of total deaths was small (163). NIOSH will continue to follow up the mortality experience of the cohort (Brown and Jones, 1980).

Ongoing Occupational Studies

Two additional cohort mortality studies are currently underway. The first is a mortality survey of the entire workforce employed between 1952-1957 at the largest U.S. facility that manufactured capacitors and transformers. There is detailed information available on exposure levels in the plant. While the duration from onset of exposure is shorter than optimal (only 25 years in some cases), the information will at least give data on the short-term mortality experience of a heavily exposed occupational group (Selikoff et al., in progress).

The second is a similar occupational mortality study, also of workers exposed in capacitor and transformer manufacturing. Over 2,000 workers have been identified for this study but no further details are yet available (Bertazzi et al., in progress). One case control study is currently being conducted to assess whether there is excess risk of malignant melanoma among PCB-exposed workers. This data will not be available until March, 1981 (Bahn et al., 1976).

There is also one cross-sectional clinical field survey of 326 capacitor manufacturing workers at two sites, encompassing a total workforce of 800 (Fischbein et al., 1979). Exposures were classified as none, low, medium, and high based on job description at the time of the survey (1975). Researchers were able to identify the PCB's used and had some data on environmental air levels in the plants. A number of parameters were measured, including complete history and physical exams, SMA panels and pulmonary function tests. Results have been published on respiratory function and general signs/symptoms, and results of serum lipids, endocrine function and dermatologic findings are forthcoming. To date, the only positive association involves dermatologic signs and symptoms.

Further investigations of the effects of PCB exposure on serum lipids have been done in both occupational and general environmental exposure settings. Smith et al., (1978), reported some statistically significant differences between exposed and non-exposed workers at two sites. They reported higher serum triglycerides and lower levels of high density lipo-proteins in the exposed group. Whether the magnitude of the difference is biologically significant is not clear from this study. For example, the non-exposed group at site #1 compared to the non-exposed group at site #2 showed a greater difference than the exposed and non-exposed comparison at either site. In another

study (Baker et al., 1980) workers and community residents with exposure to fertilizer made from sewage sludge contaminated with PCB's were studied. Plasma triglyceride levels were found to increase significantly with serum PCB concentration (both in drinkers and non-drinkers), and the authors concluded that PCB's may alter lipid metabolism at levels of exposure and bio-accumulation insufficient to produce other identifiable signs of toxicity.

Comments

Although many problems have been identified in the studies evaluating the health effects of PCB's, it is clear that occupational exposure, at a minimum, can produce dermatologic effects. The long half-life of PCB's and their bio-accumulation in various human tissues leaves open the possibility of substantial chronic and delayed effects analogous to those seen in animal bioassays. These effects have only recently begun to be studied in a rigorous manner, and although the epidemiological evidence is neither complete nor entirely consistent there can be no question of the necessity to protect the worker from exposure.

VIII. MEDICAL SURVEILLANCE AND BIOLOGIC MONITORING

Medical surveillance and biologic monitoring are of limited usefulness in predicting health hazards if dose-response relationships are not known. This certainly is the case with PCB's. Based on animal toxicology, there are many suspected adverse effects of PCB's which might result from exposure in occupational settings, but very few have been documented well enough to give even rough estimates of "no-effect" or "safe" levels. A large percentage of non-occupationally exposed people have detectable PCB levels in body fat, blood and milk. However, any attempt to estimate an adverse health effect associated with increases above this background level necessarily involves extrapolation from animal data and therefore is subject to considerable error, especially when the marked variation in sensitivity of various animal species is appreciated. Furthermore, not enough is known regarding the relative dose-response characteristics of the various documented effects (e.g., liver damage, skin changes) to state that in the absence of a particular sign, symptom or laboratory abnormality, the risk of long-term effect (cancer, reproductive toxicity) will be negligible (see Table I).

For the clinician confronted with a worker who has a history of exposure to PCB's the approach to management cannot be easily outlined. Given the current analytic methodology, residues can be measured in blood or tissue in the ppb range and compared to background; but assigning a health risk to a given level is virtually impossible, especially given the lack of pharmacokinetic data. Often patients are being evaluated after a considerable lag period (years) since last exposure occurred and extrapolation to peak blood levels is not possible. In fact, it may be that residue levels bear little relationship to the health risk. For example, the lower chlorinated compounds may be more toxic but they are more rapidly metabolized and excreted and therefore less

likely to persist in blood or fat. Further, with the possible exception of chloracne, the presence of specific signs, symptoms or laboratory abnormalities is very difficult to definitely relate to PCB exposure in any given patient.

Given these uncertainties and the potential for serious health effects, the approach to monitoring should emphasize environmental sampling and every attempt should be made to minimize exposure by engineering controls or personal protective measures in those settings where occupational exposure still occurs (e.g., utility repair workers). Biologic monitoring may be used to assess the effectiveness of environmental control, but it is really best utilized within a specific research protocol and probably has little value in the routine work-up of individual patients.

SUMMARY AND CONCLUSIONS

PCB's have low acute toxicity but are of public health concern because of their persistence in the environment and in human tissues and their demonstrated potential for chronic or delayed toxicity. They are potent inhibitors of reproductive function in both rodents and non-human primates and are positive in animal cancer bioassays. As potent inducers of hepatic enzyme systems, PCB's may have additional unpredictable long-term health effects.

Some of the conflicting reports in the toxicology literature are undoubtedly related to the variable composition and trace chemical contamination of the tested mixtures. Occupational and environmental exposure is usually to those mixtures; but if we are to accurately assess the associated health hazards, further animal studies are needed which carefully define the toxicology of the individual agents.

Epidemiologic studies of occupational exposures to PCB's to date have failed to detect serious adverse effects but are considered insufficient, and further studies are clearly needed. Of particular interest is the continued exposure among utility workers. Because of the potential ability to cause cancer and other long-term adverse effects such as infertility and hepatic injury, human exposure to PCB's should be kept to the lowest level technically possible. The persistence of PCB's in the body and the irreversibility of some of its effects make it necessary to act now, rather than to wait until more definitive data are available.

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TABLE I

DOSE-RESPONSE FOR ANIMAL TOXICOLOGY

Species	Age	Agent	Route	Dose mg/kg/day	Duration	Total Dose mg/kg	Effect	References
Rat	Adult	Aroclor 1254, 1260	Oral	4,000 - 10,000	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Weanling	Aroclor 1254, 1260	Oral	1,200 - 1,300	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Adult	Aroclor 1248, 1254, 1262	Oral	50	6 weeks	2100	Liver hypertrophy, fatty infiltration	Allen & Abrahamson, 1973
Rat	Weanling	Aroclor 1242, 1016	Oral	3.9-6.6	6 months	700-1200	Fatty liver	Burse et al., 1974
Rat	Adult	Aroclor	Oral	100	7-15 day gestation	700	↓survival - offspring no terata.	Linden et al., 1974
Rat	Adult	Aroclor 1260	Oral	25.0	2 months prior to mating	1500	↓litter size ↓survival offspring	Linden et al., 1974
Rat	Adult	Aroclor 1254	Oral	5.0	2 months prior to mating	300	↑mortality - offspring ↓mating behavior - offspring	Linden et al., 1974
Rat	Adult	Kanaclor 500	Oral	1.0	Day 8-14 or 15-21 gestation	6.0	↓various learning assays offspring	Shiota, 1976
Mice	Adult	"PCB's"	Oral	7.0	4 weeks starting at birth	200	↓implantations, litter size-offspring; changes in estrous cycle-offspring	Kihlstrom et al., 1975
Mice	Adult	Clophen A60	Oral	1.0	"chronic"	Unknown	lengthened estrous cycles ↓implantations	Oberg & Kihlstrom, 1973
Monkey	Adult	Aroclor 1248	Oral	10	4 weeks	840	weight loss, alopecia, facial edema, eye discharge	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	3.3	1 month	100	liver abnormalities (histological)	Allen, 1975
Monkey	"young"	Aroclor 1242	Oral	0.1-10	9 months	27-2700	death, gastric ulceration, facial edema, thymic atrophy	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	0.08-0.17	1 year	29-62	facial edema, alopecia acne, ↓fertility, irregular menses, ↑early abortions- offspring: ↓weight, head circumference, (detectable PCB's in tissue)	Allen, 1975
Rats	Adult	Aroclors	Dermal	≈100	25 days	2500	slight Δ's- liver histology	Miller, 1944
Guinea pig	Adult	Aroclors	Dermal	≈70	Single Exposure	----	death -- delayed up to 21 days with liver atrophy	Miller, 1944
Rabbit	Adult	Aroclor 1260	Dermal	≈20	38 days	760	skin, liver and kidney damage	Vos & Beems, 1971
Rat, Mouse, Guinea pig, and cat	Adult " "	Aroclor 1254 " "	Inhal. " "	2.5 *	17 weeks	650	microscopic liver Δ's	Treon, 1956
				0.7 *	31 weeks	217	reversible liver Δ's	Treon, 1956
Mice	8 weeks	Kanaclor 500	Oral	50	32 weeks	11.2 gm/kg	↑hepatocellular carcinomas (control 0/6; dosed 5/12) ↑neoplastic nodules (control 0/6; dosed 7/12)	Ito et al., 1973
Mice	5 weeks	Aroclor 1254	Oral	50	46 weeks	16.1 gm/kg	↑neoplastic nodules (control 0/24; dosed 9/22)	Kimbrough & Linden, 1974
Rats	4 weeks	Aroclor 1260	Oral	10	21 months	6.3 gm/kg	↑hepatocellular carcinomas (control 1/173; dosed 146/184) ↑neoplastic nodules (control 0/173; dosed 26/184)	Kimbrough et al., 1975
Rats	8 weeks	Aroclor 1260	Oral	10	104 weeks	7.2 gm/kg	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980
Rats	8 weeks	2,4,5,2',4',5' hexachlorobiphenyl	Oral	10	104 weeks	7.2 gm/kg	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980

* Animals were exposed to 5.4 or 1.5 mg/m^3 of Aroclor 1254 for 7 hours/day, 5 days/week for 17 weeks. To approximate dose in mg/kg/day, the following corrections were applied: 0.2 (volume of air breathed in m^3 by animal per day); 0.5 (weight of animal in kg); 24/7 (correction for 24 hour/day exposure); 7/5 (correction for 7 day/week exposure). Resulting value assumes 100% absorption.

** Total dose in gm/kg

TABLE II - OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure	Study Population		Findings				
	Level & Time	Exposed	Controls	Dermal Effects	Liver Function	Blood Concentrations	Cancer/ Mortality	Comments
Meigs 1954 - Outbreak of dermatitis in a chemical plant	0.1 mg/M^3 Arochlor - 5 to 19 moths intermittent exposure through vapor leakage	14	0	7/14 mild to moderate chloracne;	6 normal, 1 borderline (in chloracne cases)			Since blood concentrations of PCBs could not be measured, no correlation of individual dose and skin effects was possible.
Hasegawa et al, 1972 Study of 6 industrial plants including PCB manufacture, capacitor, manufacture, and biphenyl recovery	Vapors 13-965 µg/M^3 Particulates 4-650 (6,270 in a spill) <1 to 20 years	99	32	Various	Slightly abnormal (elevated liver enzymes)	Exposed: 370 ppm non-exposed: 20 ppb		Dermal ailments were unrelated to blood concentrations. Based on 3 plants, there was no relationship of exposure to blood concentration; fat metabolism was apparently affected
Hara et al 1973-1974	Level of exposure not reported in NIOSH Criteria Document	118 (study concentrated on 17 immersion process workers)		45% blackheads, 37% acne, 13% irritation	not reported	Exposed 7-300 ppb		Blood concentrations closely related to years of exposure; Follow-up study after exposure ceased allowed calculation of serum half-life: The longer the duration of exposure, the longer the PCB half-life. (range 3 - 30 months)
Kitamura 1 73 Study of workers medical exams in a capacitor manufact-	Exposure level not reported in NIOSH Criteria Document Time 2.5 years	13		Various: acne, seborrhea adiposa, folliculitis	Normal	820 ppb average (320-2100 ppb)		No relationship was found between concentration in blood and duration of exposure.

OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure	Study Population		Findings				
	Level & Time	Exposed	Controls	Dermal Effects	Liver Function	Blood Concentrations	Cancer/ Mortality	Comments
.w et al 76 Study of pacitor anufacturer	Arochlor 1242 1.08-1.44 mg/M^3 (19 fillers) .32 mg/M^3 (15 assemblers) Workers wore no protective clothing Time 1 month to 23 years	34	30	Mild burning, irritation of face, eyes and skin; 5 had rashes, 1 chloracne, several dermatitis	Bromsul phothallum tests elevated 4 of 7 fillers with blood levels > 500 ppb	E xposed 100-602 ppb (mean 400 ppb) Not detected in non-exposed		Systemic effects reported such as nausea and persistent body odor. There was no adverse response at blood concentrations below 200 ppb
ahn, et al 976 Study of orkers in a efinery	Arochlor 1254 over a 9 year period	51 researchers and development; 41 refinery workers					2 malignant melanomas observed, .04 expected (based on TNCS data)	These were preliminary results reported in a letter to the editor. Workers were also exposed to other chemicals. Study is in progress.
Brown and Jones 1980 cohort mortality study of capacitor manufactureres (draft report)	Plant #1: 1.24 µg/M^3 - 3.93 µg/M^3; Plant #2: 170 µg/M^3 - 1260 µg/M^3	Plant #1-968 Plant #2-1599				All cause mortality was lower than expected (163 obs. vs 174 exp) All cancer mortality was lower than expected (39 obs. vs 40.6 exp.) Rectal and liver cancer were slightly elevated but not significantly.		Lower observed mortality may be attributable to the "health worker" effect. NIOSH will continue to follow-up mortality experience

OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure	Study Population		Findings				
	Level & Time	Exposed	Controls	Dermal Effects	Liver Function	Blood Concentrations	Cancer/ Mortality	Comments
Inoue et al 1975 Study of a family silk thread glossing operation	Not reported in NIOSH Criteria Document 0.15-1.2 μ/M^3 0.13-4.4 $\mu g/M^3$	Number studied not reported in NIOSH document (Later 54 more persons were studied)		Mild skin skin lesions including comedones	Unknown	130-520 ppb		Good correlation between degree of exposure and blood PCB levels.
Sato and Hasegawa 1974 Pressure sensitive carbonless paper manufacturer	measured 2 yrs. past PCB use	Not reported in NIOSH Criteria Document				Exposed 73 ppb non-exposed 20 ppb		
Karppanen and Kolho 1972 Study of 3 groups: 1) no exposure 2) analytical lab 3) capacitor impregnation	High exposure (capacitor manufacturing); low exposure (analytical Lab)	High - 12 Low - 6	4 males 5 females			Unexposed 5.6-12 ppb Medium exposure 36-63 ppb High exposure 74-1,900 ppb		Unable to detect any "Biologic Effects"; type of monitoring not reported in NIOSH review
Bumgarner et al 1973 Study of refuse workers exposed to PCB in incineration of waste	Incinerated waste	37	36 lumber yard workers			Control: max. 4.2 ppb Exposed: max. 14 ppb (4-14 ppb)		Concentrations not well correlated with duration of exposure, age or race

OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure	Study Population		Findings				
	Level & Time	Exposed	Controls	Dermal Effects	Liver Function	Blood Concentrations	Cancer/ Mortality	Comments
Baker, Landrigan et al 1980 Study of exposure to PCBs in sewage sludge	Liquid sewage entering plant 30-470 ppb. Upstream sewage 1250-5500 ppb (Aroclor 1016) Concentrations in sludges (Aroclor 1242) were as high as 1700 ppm (mean 479.1 ppb) and 107.3 ppm in treated soil (mean 17.1 ppm)	89 sludge users, 18 workers exposed to PCBs, 19 members workers families	22 community members	Acne, increased pigmentation in 4 workers		Sludge users 17.4 ppb, workers 75.1 ppb Families 33.6 ppb, community 24.2 ppb		Plasma triglyceride levels increased significantly with serum PCB concentrations. Data indicate that PCBs may alter lipid metabolism.

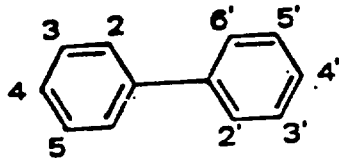
TABLE III

PERCENT DISTRIBUTION OF SYMPTOMS OF YUSHO REPORTED BY 189 PATIENTS EXAMINED BEFORE OCTOBER 31, 1968.

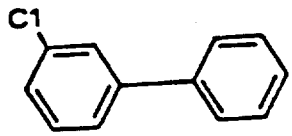
Symptoms	Males (N-89)	Females (N- 100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	24.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

Source: Kuratsune et al, 1972

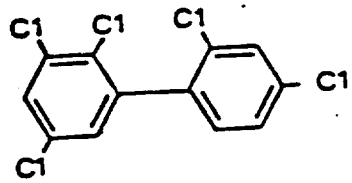
FIGURE I



BIPHENYL MOLECULE AND RING NUMBERING SYSTEM



3-chlorobiphenyl



2,2',3,4',5-pentachlorobiphenyl

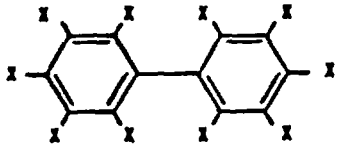
EXAMPLES OF NOMENCLATURE SYSTEM OF CHLOROBIPHENYL COMPOUNDS

NUMBER OF ISOMERS AND PERCENT CHLORINE FOR THE 10 CHLOROBIPHENYL (PCB) CLASSES

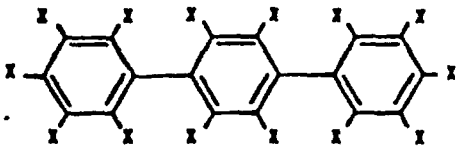
Chlorobiphenyl	Empirical Formula	No. of Isomers	Weight % Cl
mono	$C_{12}H_9Cl$	3	18.79
di	$C_{12}H_8Cl_2$	12	31.77
tri	$C_{12}H_7Cl_3$	24	41.30
tetra	$C_{12}H_6Cl_4$	42	48.56
penta	$C_{12}H_5Cl_5$	46	54.30
hexa	$C_{12}H_4Cl_6$	42	58.93
hepta	$C_{12}H_3Cl_7$	24	62.77
octa	$C_{12}H_2Cl_8$	12	65.98
nona	$C_{12}HCl_9$	3	68.73
deca	$C_{12}Cl_{10}$	1	71.18

Source: NIOSH, 1977

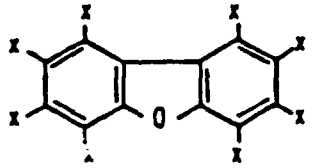
FIGURE II



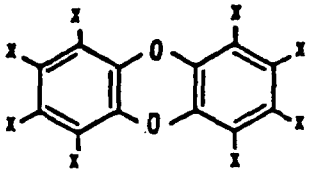
Polychlorinated Biphenyls (PCB's)



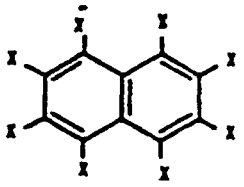
Polychlorinated Terphenyls



Chlorinated Dibenzofurans



Chlorinated Dibenzodioxin



Polychlorinated Naphthalenes

Source: Kimbrough, 1974

FIGURE III
CHLORODIBENZOFURAN TYPES AND CONCENTRATIONS (µg g)
IN COMMERCIAL PCB PREPARATIONS

	Chlorodibenzofurans						
Mixture*	di	tri	tetra	penta	hexa	hepta	Total
(1) 1016	0.5						0.5
(1) 1016			<0.0001	<0.0001	<0.0001		
(1) 1248			0.5	1.2	0.3		2.0
(1) 1254			0.1	0.2	1.4		1.7
(1) 1254			0.2	0.4	0.9		1.5
(1) 1260			0.1	0.4	0.5		1.0
(1) 1260			0.2	0.3	0.3		0.8
(2) A-60			1.4	5.0	2.2		8.4
(3) DP-6			0.7	10.0	2.9		13.6
(4) K300			(a)	(a)			1-1.5
(4) K400	(c)***	(e)	(e)	(c)			17-18
(4) K500				(a)	(c)	(a)	2,5-4
(4) K600			(a)	(a)	(b)	(b)	3-5

*(1) Aroclor, (2) Clophen, (3) Phenoclor, (4) Kanechlor
**(a), (b), (c), (d), (e) represent relative amounts in increasing order

Source NI^SH, 1977

FIGURE IV

Responses of primates and rats to PCB's*

Response	Man	Monkey	Rat
Susceptibility to toxicity	High	High	Moderate
Acne	Yes	Yes	No
Hyperpigmentation of skin	Yes	Only infants	No
Alopecia	NA	Yes	No
Hyperactive Meibomian glands	Yes	Yes	No
Conjunctivitis	Yes	Yes	No
Oedema of eyelids	Yes	Yes	No
Subcutaneous oedema	Yes	Yes	No
Keratin cysts in hair follicles	Yes	Yes	No
Hyperplasia of hair follicle epithelium	NA	Yes	No
Gastric hyperplasia	NA	NA	Yes
Thymic atrophy	Yes	Yes	Yes
Hepatic hypertrophy	NA	Yes	Yes
Liver enzyme change	Yes	Yes	No
Decreased no. of red-blood cells	Yes	Yes	No
Decreased haemoglobin	Yes	Hypolipidaemia	Yes
Serum hyperlipidaemia	Yes	Yes	No
Leucocytosis			

Source: IARC, 1978

* This table summarizes acute and subacute clinical effects but does not include chronic or delayed effects such as reproductive effects or cancer.

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Levels and Gas Chromatographic Patterns of Polychlorinated Biphenyls in the Blood of Patients after PCB Poisoning in Taiwan

P. H. Chen, J. M. Gaw, C. K. Wong, and C. J. Chen

Department of Biochemistry, National Yang Ming Medical College, Taipei, Taiwan, R.O.C., Department of Dermatology, Veterans General Hospital, Taipei, Taiwan, R.O.C.

In March 1979, an epidemic of a peculiar skin disease was reported in Taichung and Changhwa of the central Taiwan. In October, the cause of the disease was identified to be the ingestion of rice oil contaminated with polychlorinated biphenyls(PCB). At the end of April 1980, the victims numbered 1900. The magnitude of this PCB poisoning is likely to surpass a similar mass outbreak of "Yusho" in Japan in 1968(KURATSUNE et al. 1972).

Since December 1979, we have been engaged in the analysis of PCB levels in the blood of these PCB-intoxicated patients. We have been using both GC/MS and ECD-Gas Chromatography for the quantification of PCB levels in the blood of patients. We report here the blood PCB levels of sixty-six patients determined by ECD-Gas Chromatography. Quantification of PCB residues by GC/MS method will be published elsewhere.

MATERIALS AND METHODS

Blood samples were collected at the hospital ward and the out-patient clinic of the Department of Dermatology, Veterans General Hospital, Taipei, or at patients' residential areas in Taichung during the period of December 1979 to March 1980. The blood(about 10 ml) drawn from each patient was transferred to a 20-ml glass tube containing 200 USP units of heparin in 0.2 ml solution. For isolation of PCB from the blood sample we used the alkali decomposition method similar to the one used by AKIYAMA et al.(1975). The procedure is as follows: To 10 g of whole blood was added 20 ml of ethanol. Five g of potassium hydroxide was added to this and the whole mixture was refluxed in a steam bath for one hour. After cooling, the content was extracted with 20 ml of redistilled n-hexane for three times. The combined n-hexane extract was washed with 20 ml of water for three times, followed by drying over anhydrous sodium sulfate. The dried extract was concentrated in a Kuderna-Danish evaporator to about 5 ml, then carefully blown with a very mild stream of nitrogen to about 1 ml.

The condensed extract was cleaned up by silica gel column chromatography. A mixture of 3 g of activated silica gel(Wakogel S-1) and 20 ml n-hexane was poured into a 1.7 x 22 cm glass column. After washing the column with about 25 ml of n-hexane, PCB extract was applied to the top of the column; then the column was eluted

0007-4861/80/0025-0325 $01.00

with n-hexane. Discard the first 25 ml, then collect the next 100 ml of eluant. Concentrate the eluant in a Kuderna-Danish evaporator to about 5 ml, then carefully blow with a very mild stream of nitrogen to below 1 ml. The condensed extract was analyzed by ECD-Gas Chromatography for PCB.

The gas chromatograph used was a Shimadzu GC-6AM equipped with ^{63}Ni Electron Capture Detector. The column used was a 2.5 m x 2.6 mm i.d. glass column packed with 5% SE-30 on Chromosorb WAW-DMCS, carrier gas nitrogen flow rate was 40 ml/min. The column and detector temperatures were maintained at 220°C and 270°C, respectively.

Quantitation of PCB residues was made by comparing respective area of PCB peaks in the sample with the area of the corresponding peak in the chromatogram of KC-500. For the calculation of PCB quantity in each peak of KC-500, we followed the method presented by UGAWA et al.(1973).

RESULTS AND DISCUSSION

Gas chromatograms of KC-500, KC-400/KC-500(1:1), and PCB residues in the contaminated rice oil are shown in Fig. 1. Three typical chromatograms of PCB residues in the patients' blood are shown in Fig. 2. The peak numbering system in the chromatograms are the same as that used by UGAWA et al.(1973). In the portion of peaks 9 to 25, gas chromatographic pattern of PCB in the contaminated rice oil(Fig. 1-C) is similar to that of KC-400/KC-500 (1:1) (Fig. 1-B). The chlorine content of PCB residues in the rice oil as determined by GC/MS method was about 52-53%, this is between those of KC-400(47.9%) and KC-500(54.6%).

Gas chromatographic patterns of PCB in the blood of patients can be classified into three types, i.e., types A, B, and C. In type A, peaks 15 and 16 are larger than peak 18(see Fig. 2-A), whereas in type B, the reverse is true(see Fig. 2-B). Other than this difference, the relative intensities of other peaks in the two chromatograms are about the same. In type C, pattern of peaks 15 to 25 is similar to that of type A, however, peaks 9 and 11 are much larger than those of either type A or B(see Fig. 2-C). The chlorine numbers of PCB components corresponding to peaks 9,11,15, 16, and 18, as determined by GC/MS, are 4,5,5,5 and 6, and 6, respectively. Examination of GC patterns of a large numbers of blood samples revealed that among PCB components corresponding to peaks 15, 16, and 18, the component of peak 18(a hexachlorobiphenyl) was retained in human body longer than the PCB components of peak 15(a pentachlorobiphenyl) and of peak 16(a mixture of penta- and hexachlorobiphenyls). The faster excretion of PCB components of peaks 15 and 16 than that of peak 18 likely contributes to the formation of type B pattern.

Patients whose blood analyzed by us are mostly from Taichung. The blood PCB patterns of these patients belong to types A and B.

Only five out of sixty six patients are from Changhwa area or have ingested rice oil bought from Changhwa. The blood PCB pattern of these five patients belongs to type C. This suggests that either the rice oil ingested by the patients from Changhwa contained PCB of higher percentages of lower chlorine numbers than the rice oil

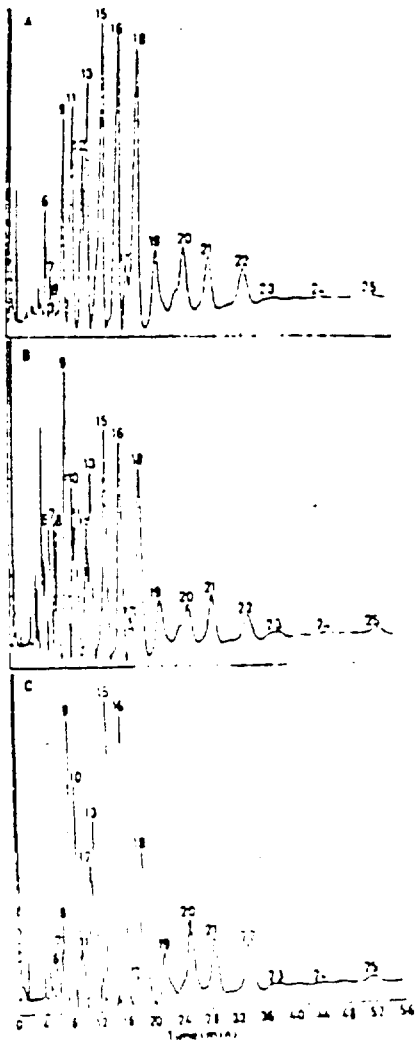

Fig. 1. Gas chromatograms of PCB.
A: KC-500, B: KC-400/KC-500 (1:1), C: Rice oil.

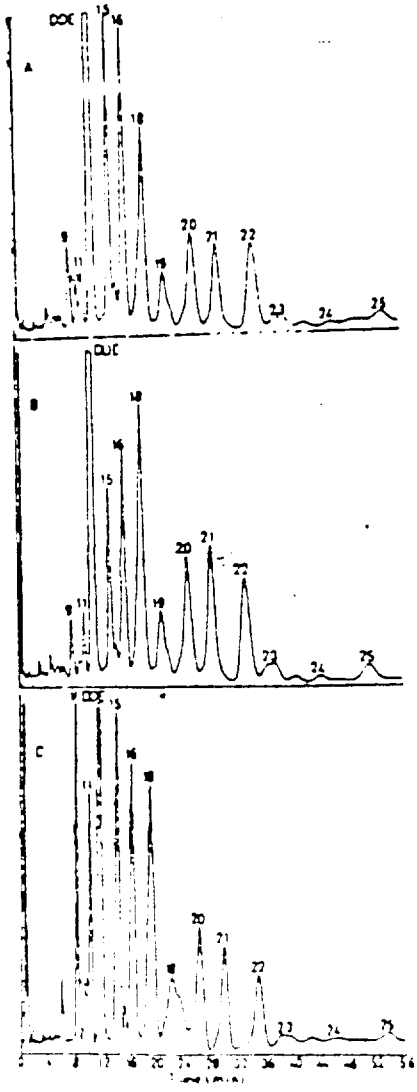

Fig. 2. Gas chromatograms of PCB residues in human blood. A, B, and C: Patterns of types A, B, and C.

TABLE 1. PCB Levels in the Blood of PCB-Intoxicated Patients

No.	Age	Sex	Sampling date	PCB level (ppb)	No.	Age	Sex	Sampling date	PCB level (ppb)
1	22	F	12/21/79	40	34	25	F	2/26/80	22
2	23	F	12/21/79	61	35	17	F	2/26/80	28
3	37	F	12/21/79	40	36	17	F	2/26/80	16
4	22	M	12/21/79	62	37	22	F	2/26/80	17
5	39	M	1/13/80	59	38	21	F	2/26/80	20
6	34	F	1/13/80	62	39	31	F	3/ 4/80	34
7	28	F	1/14/80	52	40	24	F	3/ 4/80	25
8	45	F	1/14/80	35	41	16	F	3/ 4/80	29
9	27	F	1/14/80	66	42	56	F	3/ 5/80	720
10	69	F	1/14/80	50	43	12	F	3/ 7/80	56
11	30	M	1/15/80	50	44	11	M	3/ 7/80	48
12	26	F	1/31/80	37	45	8	M	3/ 7/80	82
13	48	M	1/31/80	19	46	13	M	3/ 7/80	71
14	24	F	1/31/80	21	47	20	F	3/11/80	28
15	20	F	2/ 1/80	41	48	16	F	3/11/80	11
16	24	F	2/ 1/80	33	49	17	F	3/11/80	21
17	31	M	2/ 1/80	37	50	60	M	3/11/80	26
18	31	M	2/ 1/80	67	51	60	M	3/12/80	35
19	24	F	2/ 1/80	41	52	25	M	3/12/80	42
20	21	F	2/ 1/80	31	53	58	M	3/14/80	76
21	30	M	2/ 1/80	27	54	31	M	3/14/80	26
22	18	F	2/ 1/80	31	55	42	M	3/14/80	120
23	29	F	2/ 1/80	17	56	66	F	3/14/80	51
24	26	M	2/ 1/80	58	57	24	M	3/18/80	21
25	48	M	2/ 1/80	83	58	28	M	3/18/80	24
26	B	M	2/ 4/80	15	59	8	M	3/18/80	76
27	B	M	2/ 4/80	21	60	25	M	3/18/80	24
28	25	F	2/ 5/80	71	61	19	F	3/18/80	26
29	20	F	2/13/80	24	62	17	F	3/18/80	21
30	19	F	2/23/80	32	63	19	F	3/18/80	26
31	28	M	2/26/80	34	64	20	F	3/18/80	16
32	20	F	2/26/80	14	65	21	M	3/25/80	21
33	16	M	2/26/80	25	66	56	M	3/28/80	21

M, F, and B designate male, female, and baby(one month old), respectively.

from Taichung, or these patients from Changhwa happened to excrete PCB components of peak 9(a tetrachlorobiphenyl) and peak 11(a pentachlorobiphenyl) slower than normal patients. As a matter of fact, two of the five patients have abnormal liver function which might explain the slower elimination of PCB components of peaks 9 and 11 by these two patients. The gas chromatogram of PCB residues in the blood of one of these two patients is shown in Fig. 2-C.

In the chromatograms of PCB residues in the blood of patients, peaks 12 and 13 overlap with a large peak due to DDE(see Fig. 2). Therefore, peaks 12 and 13 were not included in the calculation of PCB quantity. Fortunately, the exclusion of these two peaks in the quantification of PCB would presumably not lead to a large error. This is based on the data from the selected ion chromatograms in GC/MS analysis which showed that, in most cases, peaks 12 and 13 were relatively small in the blood samples.

Blood PCB concentrations of 66 patients are tabulated in Table 1. They range from 11 to 720 ppb. The mean value is 49 ppb. The high value of 720 ppb(patient no. 42) is much higher than the mean value. If this very high value of 720 is excluded in the calculation of the mean, then the mean value drops to 39 ppb. The very high PCB concentration in the blood of patient no. 42 is at least in part due to his difficulty in metabolizing and subsequen excretion of PCB components from his body. This is supported by clinical data which indicated that the patient's hepatic and renal functions were both abnormal. It may also be due to the ingestion of unusually high quantities of PCB by this patient. The GC pattern of PCB residues in the blood of this patient is shown in Fig. 2-C.

The blood PCB levels of the PCB-intoxicated patients reported in this study are much higher than those of Japanese Yusho patients. For the Yusho patients, the mean PCB value of seventy-two patients was 5.9 ± 4.5 S. D. ppb(KODA and MASUDA 1975). This difference is, to a large extent, presumably due to the difference in time lags between PCB intoxication and blood PCB analysis. For Yusho patients, the blood PCB analysis was done about five years after the ingestion of the toxic rice oil, whereas for our patients, the blood PCB measurement was made about nine months to one year after intoxication. It is expected that the blood PCB level of Yusho patients would drop significantly five years after intoxication. Other factor which is attributable to the higher blood PCB level in our patients than in Japanese Yusho patients may be due to the difference in the degree of intoxication between Chinese and Japanese patients. It should be noted that the PCB ingested by Chinese patients contained larger percentages of high numbers of chlorine(such as 5, 6, and 7) than that ingested by Japanese Yusho patients. These highly chlorinated PCBs, i.e., penta-, hexa-, and heptachlorobiphenyls, will be retained in human body longer than the lower chlorinated PCBs such as tri- and tetrachlorobiphenyls.

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Role of Polychlorinated Dibenzofuran in Yusho (PCB Poisoning)

TAKASHI KASHIMOTO, Ph.D.
HIDEAKI MIYATA, Ph.D.
SHINJI KUNITA, Ph.D.
Osaka Prefectural Institute of Public Health
1-3-69, Nakamichi, Higashinari-ku
Osaka, Japan

TA-CHENG TUNG, M.D., Ph.D.
SHU-TAO HSU, M.D., Ph.D.
KING-JEN CHANG, M.D.
SHU-YING TANG, M.D.
Department of Biochemistry
National Taiwan University
College of Medicine
1 Jen-Ai Road
Taipei, Taiwan

GEN OHI, M.D., Ph.D.
JUNICHI NAKAGAWA
SHUN-ICHI YAMAMOTO, M.D., Ph.D.
Department of Hygiene and Preventive Medicine
Faculty of Medicine
University of Tokyo
7-3-1, Hongo, Bunkyo ku
Tokyo 113, Japan

ABSTRACT. In the blood of 15 patients with Yusho or "polychlorinated biphenyl poisoning" that occurred in 1979 in Taiwan, was found polychlorinated dibenzofurans (14 of 15) and polychlorinated quaterphenyls (15 of 15), as well as polychlorinated biphenyls (15 of 15). The mean concentration ratio of these substances was approximately 1 : 160 : 500. Based on the following evidence, we propose that polychlorinated quaterphenyls were major pathogenic substances in the development of Yushu: (1) Clinical manifestations and course of Yusho patients are disproportionately severe and persistent for the observed blood levels of polychlorinated biphenyls, while patients who were occupationally exposed to pure polychlorinated biphenyls take characteristically mild and benign clinical course despite polychlorinated biphenyl levels often much higher than those noted in Yusho patients; (2) Polychlorinated debenzofurans show a marked tendency to accumulate in the liver, which might explain frequent presence of jaundice and other abdominal symptoms in Yusho, which are, again, not observed in those with occupational polychlorinated biphenyl poisoning; (3) Toxicity of polychlorinated dibenzofurans is a hundred to ten thousand times greater than that of polychlorinated biphenyls and polychlorinated quaterphenyls in animal experiments.

"YUSHO" is a poisoning characterized clinically by acne-like dermal lesions and a variety of constitutional symptoms. In 1968, an outbreak occurred in western parts of Japanese Archipelago and as a result, more than a thousand persons suffered. The outbreak was initially thought to result from polychlorinated biphenyl (PCB) poisoning[1-3] caused by the consumption of rice oil contaminated with Kanechlor 400, a heat transfer medium.[2] Subsequently, the "toxic" rice oil was also found to contain elevated levels of polychlorodibenzofurans (PCDFs)[4]; highly toxic contaminants of PCBs[5]; and polychlorinated quaterphenyls (PCQs)[6]—toxicologically ill-defined, but substances perhaps equally toxic as PCBs.[7,8] Both PCDFs and PCQs can be generated when PCBs are heated.[9] The ratio of PCDFs or PCQs to PCBs can become high during the deodorization process of rice oil under high temperature and reduced pressure.[10] Toxicolog

ical contribution of PCDFs in Yusho was further implicated by discovering that the liver of Yusho patients who died from other causes after the outbreak of the poisoning contained PCDFs one thousand times higher than that found in normal populations.[11,12] A recent analysis of the blood of Yusho patients conducted 11 yr after the Yusho outbreak, detected PCQs but not PCDFs, suggesting the role of PCQs as a suitable marker for the past episode of exposure to toxic oils.[12]

During the spring and summer of 1979, cases of peculiar skin disease characterized mainly by acne; cheese-like discharge from the Meibomian gland; pigmentation of the skin, gingiva and the nail beds; and abdominal pains were reported in two prefectures in the middle part of Taiwan, Republic of China.[13] Samples of suspected "toxic" rice oil delivered to us in the autumn were found to contain PCBs. Gas chromatographic patterns of these samples were similar to those found in Japanese "toxic" rice oils. All blood samples from the patients likewise contained PCBs ranging from 54 to 136 ppb (unpublished data). The number of patients exceeded 1,800 at the end of 1980; a detailed epidemiological and clinical report will be made elsewhere.

Of the 15 patients in the present study, PCDFs were found in the blood of all except for one who had mild clinical manifestations. In this study strong evidence suggesting a major role of PCDFs in developing clinical manifestations and prognosis which characterize Yusho (not mere "pure PCB" poisoning) is presented.

METHODS AND MATERIALS

Three samples of "toxic" oil, and 10-ml blood samples were collected from 15 patients with various clinical severities, who were pupils living in the dormitories on the school campus. Every meal was provided by the school. The pupils were estimated to have consumed the contaminated oil in the school chow served during a 4-month period, up to 6 months prior to the time of blood sampling.

Analytical methods for PCBs, PCQs, and PCDFs. Ten milliliters of blood were saponified with 20 ml of 2 *N* KOH ethanol solution for 1 hr under refluxing. After addition of 20 ml water, the saponified sample was extracted with 30 ml of *n*-hexane. The *n*-hexane layer was then washed with 50 ml of water, dried over anhydrous sodium sulfate and concentrated to approximately 5 ml in a K.D. concentrator. The *n*-hexane extract was put on a Florisil column (20 g of 60–100 mesh Florisil, activation at 130°C overnight; 1.8 cm ID) and eluted successively with 130 ml of *n*-hexane, 50 ml of 2% diethyl ether in *n*-hexane, 100 ml of 5% diethyl ether in *n*-hexane, 250 ml of 50% diethyl ether in *n*-hexane, and 250 ml of acetone at a rate of approximately 2 ml/min. The first and second eluates were combined, concentrated, and analyzed for PCBs by gas chromatography (GC) on a Varian Aerograph 2100 machine equipped with ^{63}Ni-ECD, as described previously.[1]

Polychlorinated quaterphenyls eluted in the third fraction were chlorinated exhaustively with antimony-pentachloride, cleaned up on an alumina column to remove impurities, and determined by a Shimadzu GC-6A gas chromatograph fitted with ^{63}Ni-ECD.

Polychlorinated dibenzofurans were eluted in the fourth and fifth fractions from a Florisil column, and after careful evaporation to dryness were subjected to a final clean-up on an alumina column (20 g alumina, Merck Co., Ltd., Art. No. 1077; 1.5 cm ID). To achieve more efficient removal of impurities, 200 ml of 2% methylene chloride in *n*-hexane was used as the first eluate. Polychlorinated dibenzofurans were recovered with 200 ml of 20% methylene chloride in *n*-hexane. The eluate was evaporated to dryness and the residue was dissolved in *n*-hexane and analyzed by GC using a Varian Aerograph 2100 gas chromatograph machine with ^{63}Ni-ECD. Gas chromatograph conditions were as follows: column, 2 m X 2 mm glass column packed with 2% OV-17 on Gas Chrom Q (100/120 mesh); injection, detection, and column temperatures, 255, 320, and 250°C, respectively; carrier gas, N_2 (30 ml/min). Polychlorinated dibenzofurans were estimated by comparing the peak heights of the gas chromatogram with those of PCDF standard, assuming that PCDF isomers with the same number of chlorine atoms all had the same sensitivity, regardless of the sites of chlorine substitution (Fig. 1).

Polychlorinated dibenzofurans in the samples were identified (Fig. 2) by gaschromoto-masspectrographic (GC-MS) methods, using a JEOL-20KP gas chromatograph-JMS-300 mass spectrometer with a computer system. The conditions were as follows: column, 2 m X 2 mm glass column packed with 3% OV-17 on Gas Chrom Q (80/100 mesh); inlet and column temperatures, 300 and 300°C, respectively; ionizing energy, 70eV; acceleration, 3.0 KV, carrier gas, He (2.0 kg /cm^2).

GC-MS Chromatograms at m/z (M^+) and (M^+ – 63) of PCDF in "toxic" oil in Taiwan (Fig. 2). The PCDF fraction of the oil was injected into a GC-MS using a JEOL-20KP gas chromatograph-JMS-300 mass spectrometer with a computer system. The GC-MS conditions were as follows: column, 2 m X 2 mm glass column packed with 3% OV-17 on Gas Chrom Q (80/100 mesh); inlet and column temperatures, 300 and 300°C, respectively; ionizing energy, 70 eV; acceleration, 3.0 KV; carrier gas, He (2.0 kg/cm^2).

RESULTS

The gas chromatographic patterns of PCDFs (Fig. 1) extracted and purified from toxic oil samples in both countries show fair resemblance in peaks 10 through 16, indicating similarity of constituent isomers between the two. A GC-MS confirmation was also done on each PCDF peak for toxic oil and Taiwanese blood samples. A similar relationship was likewise present between the blood of a Yusho patient (No. 11) in Taiwan and the liver of a Japanese patient. A GC-MS chromatographic analysis of the toxic oil from Taiwan indicates that peaks 5 through 14 represent 4–6 chlorinated dibenzofurans with molecular ion (M^+) and fragmental ion (M^+ – 63) resulting from the deletion of COCl (Fig. 2).[5]

The blood concentrations of PCBs, PCQs, and PCDFs found in patients from Taiwan and Japan, Japanese workers occupationally exposed to PCBs, and control Japanese subjects are shown in Table 1. Polychlorinated dibenzofurans were detected in all the Taiwanese patients (6 months after termination of toxic oil ingestion), except for one who had

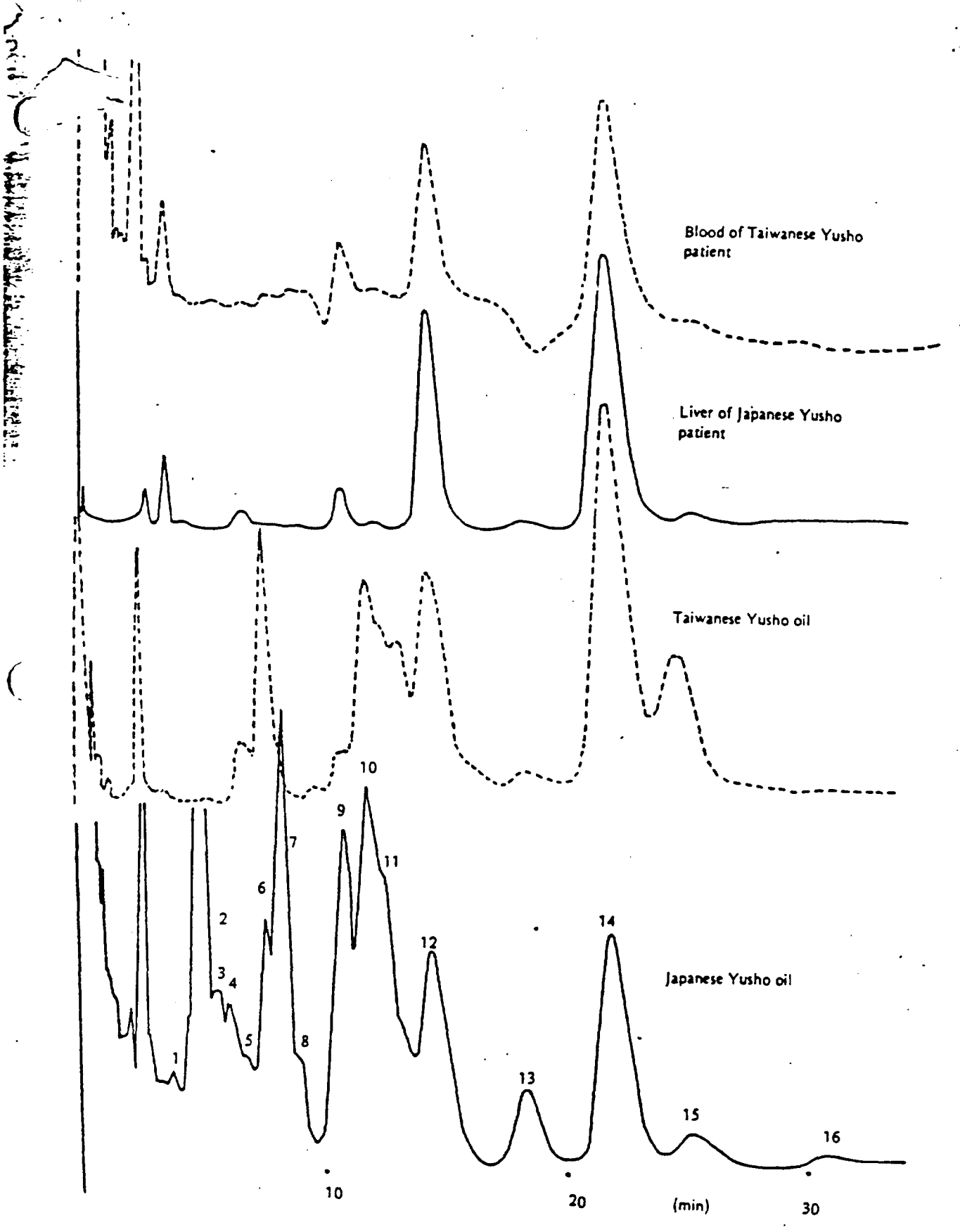

Fig. 1. Gas chromatograms of PCDF fraction: (A) blood of Taiwanese "Yusho" patient (No. 11); (B) liver of Japanese "Yusho" patient; (C) "toxic" oil in Taiwan; (D) "toxic oil in Japan. Compound of each peak shown in gas chromatograms was confirmed as follows by GC-MS analysis: peak No. 2, tetrachlorobiphenyl; peak Nos. 3–7, tetrachlorodibenzofuran; peak Nos. 8, 9, 11, and 12, pentachlorodibenzofuran; peak Nos. 13, 14, and 16, hexachlorodibenzofuran.

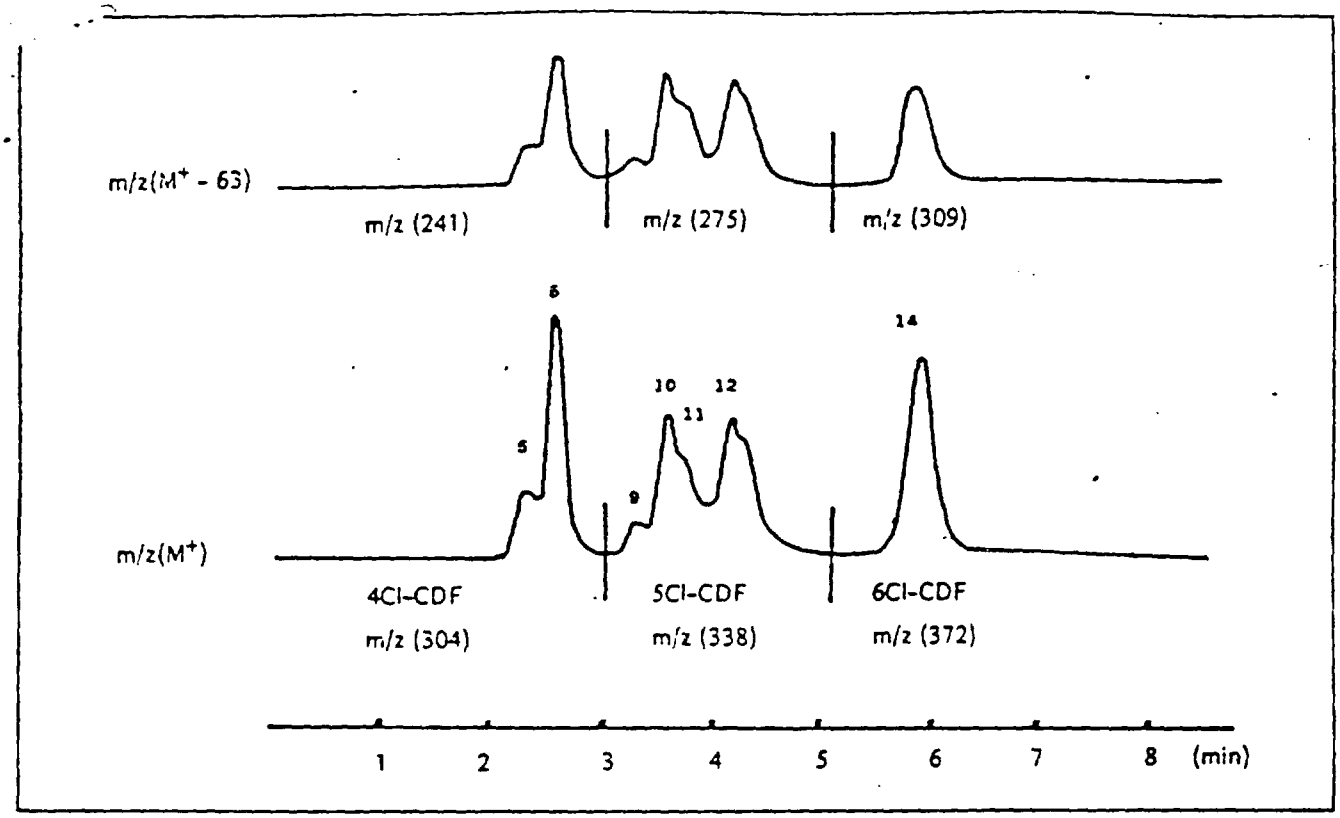

Fig. 2. GC-MS chromatograms at m/z (M^+) and (M^+ - 63) of PCDF in "toxic" oil in Taiwan. Each figure shown in the lower mass chromatogram was equal to the peak number in the gas chromatogram of Figure 1.

the mildest clinical manifestations and corresponding low levels of PCBs and PCQs.

DISCUSSION

Although attempts to identify PCDFs in the blood of Japanese Yusho patients 11 yr after the outbreak failed, PCDF concentrations exceeding those found in the present cases, in relation to PCB levels, would have been found shortly after the outbreak. Japanese toxic oils have a greater PCDF : PCB ratio, and roughly 10 times higher contamination with both substances than Taiwanese toxic oils (Table 1). However, a direct comparison between the two outbreaks with regard to the intake of toxic substances and severity of poisoning is impossible because only some "toxic" lot samples from the Taiwanese incident are available for analysis.

What do the PCDF levels noted in our study signify? We believe that the following evidence strongly suggests that PCDFs were mainly responsible in the pathogenesis of Yusho.

(1) Those individuals occupationally exposed to pure PCBs are usually symptom-free; sometimes mild dermal manifestations such as chloracne accompanied by mild constitutional symptoms occur.[14-16] This occurs despite that blood concentrations of PCBs in individuals 7 yr after leaving their workplace are equal to or greater by one digit than concentrations observed among Taiwanese patients in the current study (Table 1). When occupational exposure to PCBs was terminated, their dermal lesions quickly improved[15] in contrast to persistent clinical signs and symptoms among Yusho patients that have lingered more than 10 yr.[19] It should be again emphasized that most Japanese Yusho patients now have blood PCB levels that barely exceed those of the general population.[12]

(2) PCDFs show strong hepatotropism,[17] as do their analogue[18]—polychlorinated dibenzodioxines. While the PCDF to PCB ratio in the blood of Taiwanese patients is approximately 1 : 500, which is similar to that found in Taiwanese toxic oils (i.e., 1 : 300), the ratio found in the liver of Japanese patients, who succumbed 1 to 9 yr after the incident, is 1 : 5—a value far above the ratios noted in the Japanese toxic oils [1 : 100 in average (Table 1)]. Clinically, no abdominal pains nor jaundice have been described among the three series of workers occupationally exposed to PCBs,[14-16] while 45 to 73% of Japanese Yusho patients experienced abdominal pains[20] and 11% had jaundice accompanied by other abdominal symptoms.[21] Presence of hepatotropic and hepatotoxic[22] PCDFs in Yusho can account for this symptomatic discrepancy.

(3) Although toxicity of PCDFs varies depending on the biological parameters (e.g., chick embryo,[5] liver necrosis,[22] thymic atrophy,[23,24] animal species,[25] etc.) and on the structural difference of isomers,[25,26] most of these

Table 1.—PCB, PCQ, and PCDF Levels in Taiwanese and Japanese Patients with "Yusho" Disease, Workers Occupationally Exposed to PCBs, Healthy Persons, and in Toxic Oils Causing "Yusho" Disease

	Sample	No.	Period after Termination of Exposure (yr)	PCB Level (ppb)	PCQ Level (ppb)	PCDF Level (ppb)	PCB : PCQ : PCDF
BLOOD	Yusho patients in Taiwan		0.5	43	14.5	0.072	100 : 33 : 0.16
				54	24.5	0.14	100 : 45 : 0.26
				43	24.0	0.092	100 : 56 : 0.21
				90	17.0	0.11	100 : 19 : 0.12
				54	8.4	0.066	100 : 16 : 0.12
				68	21.0	0.10	100 : 31 : 0.16
				35	11.0	0.17	100 : 31 : 0.17
				4	0.9	N.D.*	100 : 26 : < 0.13
				56	9.0	0.055	100 : 16 : 0.14
				64	15.5	0.069	100 : 24 : 0.11
				186	63.6	0.27	100 : 34 : 0.14
				34	16.9	0.091	100 : 50 : 0.27
				78	24.4	0.086	100 : 31 : 0.11
				37	16.9	0.067	100 : 46 : 0.18
				53	14.4	0.036	100 : 27 : 0.07
		15		60 ± 39§	19.3 ± 13.0§	0.14 ± 0.07§	100 : 32 : 0.16
	Yusho patients in Japan	56	11	5.9 ± 4.4	2.0 ± 2.0	N.D.†	100 : 34 : < 0.17
	Japanese workers occupationally exposed to PCB[13]	17	4	33.3 ± 22.8	N.D.‡	—	100 : < 0.06 : –
	Japanese workers occupationally exposed to PCB[14]	19	7	149.4 ± 170.2	--	—	
	Healthy subjects in Japan	60		2.0 ± 1.3	N.D.‡	—	100 : < 1 : –
LIVER	Yusho patients in Japan	3	1	225.9	217.5	64.7	100 : 96 : 29
			7	114.4	51.7	6.2	100 : 45 : 5
			9	48.4	27.0	6.1	100 : 39 : 9
				130.7 ± 72.0	98.7 ± 84.6	25.7 ± 27.6	100 : 76 : 20
	Healthy subjects in Japan[15]	4		27.5 ± 15.4	--	0.0061 ± 0.0063	100 : – : 0.02
	Toxic oil in Taiwan	3		43,900 ± 12,400	17,300 ± 3,800	141 ± 33	100 : 39 : 0.32
	Toxic oil in Japan[9]	3		[illegible]	630,000 ± 167,000	3,850 ± 2,510	100 : 147 : 0.90

*0.005 ppb detection limit.
†0.01 ppb detection limit.
‡0.02 ppb detection limit.
§Values expressed as mean ± SD.

...ological comparisons were made using the PCDF and ...samples which directly arrived "fresh" and "pure" ...om manufactures. Utilizing PCDFs and PCBs that were either reproduced under the original conditions (i.e., temperature and coexisting air) at the rice oil production plant, or purified from the "toxic oil"—the causative agent of Japanese Yusho—we observed that the toxicity of PCDFs was hundreds to ten thousand times greater than PCB toxicity in monkey,[8] mouse,[26] and rat.[7] In addition to hepatotropism of PCDFs, the blood PCDF : PCB ratio in the current study alerts one to the toxic contribution of PCDFs in Yusho

(4) Although the toxicologic role of PCQs has been barely defined in Yusho, the present study shows that the toxicity of PCQs is almost equal to that of PCBs.[7,8] Therefore, the blood levels of PCQs observed among Taiwanese Yusho patients suggest that these substances were relatively insignificant in toxicological contribution. Perhaps PCQs are more important in enabling one to differentiate whether the patient has had a past exposure to "Yusho-type" chlorinated hydrocarbons (i.e., PCBs, PCQs, and PCDFs) or to only PCBs.[12]

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Requests for reprints should be sent to: Gen Ohi, M.D., Ph.D., Department of Hygiene and Preventive Medicine, School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo ku, Tokyo 113, Japan.

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Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls

DAVID P. BROWN, M.P.H.
MARK JONES, M.S.
U.S. Department of Health, Education and Welfare
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations and
Field Studies
Cincinnati, Ohio 45226

ABSTRACT. Because of the demonstrated toxic effects on animals resulting from exposure to polychlorinated biphenyls (PCBs), the National Institute for Occupational Safety and Health conducted a retrospective cohort mortality study of 2,567 workers in two plants where PCBs were used in the manufacture of electrical capacitors. All workers included in the study were employed for at least 3 months in areas of the plants where PCBs were used. The vital status of 98% of the two cohorts was determined, and 39,018 person-years were accumulated. All-cause mortality was lower than expected (163 obs. vs 182.4 exp.) as well as all cancer mortality (39 obs. vs 43.8 exp.). Excess mortality was noted for rectal cancer (4 obs. vs 1.19 exp.) and liver cancer (3 obs. vs 1.07 exp.), although neither excess was statistically significant. In one of the plants the observed mortality due to cirrhosis of the liver was also elevated. The results of detailed industrial hygiene surveys conducted in each plant are also presented.

POLYCHLORINATED BIPHENYLS (PCBs) are a class of compounds composed of biphenyl molecules with a varying number of substituted chlorine atoms. In commercially prepared PCB mixtures, the weight-percent of chlorine has varied from 21 to 68%. In some preparations, there has also been some degree of contamination by chlorodibenzofurans.[1]

The primary use of PCBs has been as a liquid insulating material in electrical capacitors and transformers, therefore, the greatest potential for occupational exposure has been in the manufacture and repair of these components. Polychlorinated biphenyls have also been used in heat exchange units, hydraulic systems, vacuum pumps, gas transmission turbines, plasticizers, adhesives, pesticide extenders, paints, and carbonless copying papers.

Since 1971, PCBs were sold in the United States only for use in closed systems. According to the Toxic Substances Control Act of 1976, rules and regulations were promulgated to limit the manufacture and use of PCBs. This Act stipulated that all U.S. production of PCBs end January 1, 1979, and that all U.S. sale and distribution of PCBs end July 1, 1979. However, continual exposure to PCBs will occur among workers who maintain transformers and capacitors, and among the general population via contaminated food.

During the past few years, interest in the health effects among individuals exposed to PCBs has been stimulated by (a) the tendency for PCBs to accumulate in tissues and certain organs;[2,3] (b) the stability of PCBs and their persistence in the environment;[4,5] and (c) the demonstrated long-term toxic effects, including liver tumors and other liver diseases, in exposed laboratory animals.[6-13] Much of this interest was expressed at the National Conference on Polychlorinated Biphenyls in November, 1975,[14] and the toxicity of PCBs has been extensively reviewed in the NIOSH Criteria Document on PCBs.[15] In comparison to

the accumulated information on acute toxic effects in humans and adverse effects in animals, little is known about the chronic effects from long-term exposure in man.

To determine whether past occupational exposure to commercially produced PCBs has caused any long-term health effects, NIOSH initiated an epidemiologic study among workers in two capacitor manufacturing plants. In conjunction with this study, detailed industrial hygiene surveys were also conducted by NIOSH to document the levels of exposure to PCBs and other chemicals.

Description of Facilities

Both of the plants chosen for study manufacture electrical capacitors and were selected because: (a) each had a large work force; (b) PCBs had been used for more than 30 yr; (c) there was considerable potential for exposure to PCBs with little potential for exposure to other known toxic contaminants; and (d) the records necessary to identify individuals to be included in the study population were readily available. At the time the study was initiated, both plants were still using PCBs. Plant 1 is located in New York State and is divided into two manufacturing facilities within close proximity. One facility that has used PCBs since 1946 produced small industrial capacitors and the other facility has produced large PCB-filled power capacitors since 1951. The type of PCBs used has varied during the years from "Aroclor" (Monsanto trade name) 1254 (54% chlorine) to 1242 (42% chlorine) to 1016 (41% chlorine). In addition, several other kinds of oils were used, but in a limited number of capacitors.

Plant 2, located in Massachusetts, began to use PCBs to manufacture capacitors in 1938. This plant also changed the type of PCBs used from "Aroclor" 1254 to 1242 to 1016. Until 1972, other types of capacitors which did not contain PCBs were made at this plant. Castor oil was used in lieu of PCBs to produce the large power capacitors at this plant.

Both plants assembled small and large type capacitors using the same general techniques. The following briefly describes the assembly process.

Winding and pre-assembly. The inner components of the capacitor were made of paper, foil, and sometimes plastic film; wound together; and subsequently loaded into metal casings. This job was done in an enclosed dust-free room where there was minimal exposure to PCBs. Therefore, the workers in these jobs were not considered "exposed" when choosing the study cohort.

Impregnation. The pre-assembled capacitors were filled or impregnated with the PCBs. Within this area there was potential for exposure to PCBs, and therefore, those employed in this area were considered "exposed" when choosing the study cohort.

Final assembly. The tops of the capacitors were closed by crimping, rubber stoppers, or soldering, which involved some exposure to PCBs. The capacitors were washed to remove excess PCBs by running them through a detergent wash or a degreaser such as trichloroethylene. Finally, they were sent through the final operations involving drying, testing, and painting. Those employed in several of these jobs were considered "exposed" when choosing the study cohort.

Other areas where there was potential exposure to PCBs in the plants included the laboratory and the area where rejected capacitors were rebuilt. Approximately 10% of the two work forces were employed in areas where there had been potential exposure to PCBs. Those employed in these jobs were considered "PCB exposed" for purposes of choosing the study cohorts.

Historically, the work force at Plant 1 has been composed of approximately 50% white males and 50% white females. Plant 2 has had a less homogeneous work force, with two-thirds being female, and reflects the general ethnic make-up of the area, which is largely Cape Verdean and Portuguese.

METHODS

Mortality study. A retrospective cohort mortality study was conducted to determine whether individuals occupationally exposed to PCBs have experienced any increase in cause-specific mortality. The study cohorts were defined as all workers who accumulated at least 3 months of employment at any time in areas of the plants where there was a potential for exposure to PCBs. These "exposure jobs" were designated by the companies and verified by the labor unions (at Plant 1), and by the NIOSH industrial hygiene surveys to represent the high-exposure jobs. Trichloroethylene (TCE) was used as a degreaser in both plants. Therefore, if the work history records indicated that an employee had potential exposure to TCE, the individual was not included in the cohort. This included very few workers.

An effort was made to determine the vital status (living or deceased) of each individual in the cohorts as of January 1, 1976. Vital status was determined through records maintained by Federal and State agencies, including the Social Security Administration, state motor vehicle registration, and state vital statistics offices. For those individuals who could not be located through these sources, U.S. Postal Mail Correction Services and other follow-up searches were used. For all those known to be deceased, death certificates were requested and causes of death were interpreted by a qualified nosologist according to the International Classification of Diseases (ICDA) in effect at the time of death, and then converted to the 7th Revision of the ICDA. Those who had an unknown vital status were assumed to be alive as of January 1, 1976, therefore the true risk of mortality was not overestimated. Those who died after January 1, 1976, were considered to be alive for purposes of analysis.

Person-years were accumulated for each worker starting after 1940 when 3 months of employment in exposed jobs were completed, and ending at the date of death or the study end date (1/1/76)—whichever occurred first. Using a modified life table computer program similar to that described by Cutler,[16] the person-years for each cohort were combined into 5-yr calendar time periods and 5-yr age groups and multiplied by the corresponding U.S. white male (for male cohort members) and U.S. white female (for female cohort members) cause-specific mortality rates to yield the expected number of deaths. Person-years were additionally distributed by 5-yr exposure and 5-yr latency (number of years from date first employed in exposed

Table 1.—Vital Status of PCB Workers

	Plant 1			Plant 2			
	Males	Females	Total	Males	Females	Total	Grand Total
Known to be alive	520	360	880	633	836	1,469	2,349
Known to be deceased	55	18	73	28	62	90	163
Unknown vital status	8	7	15	14	26	40	55 (2%)
Total	583	385	968	675	924	1,599	2,567
Person-years	7,825	5,185	13,010	9,229	16,779	26,008	39,018

jobs) categories. Observed and expected cause-specific deaths were compared and differences were tested using the Poisson distribution.

Industrial hygiene survey. The detailed industrial hygiene surveys included personal time-weighted air samples from selected job titles, as well as area air samples. In both plants, samples were taken for PCBs (Aroclor 1016), trichloroethylene, lead, tin, and zinc. In addition, samples for toluene, methyl isobutyl ketone (MIBK), aluminum, and iron were taken at Plant 1. These surveys were designed to characterize the exposures occurring at the time of the survey and may not represent exposures of previous years, especially those of Plant 1 where exposures may have been reduced because of new production techniques recently initiated.

RESULTS

Mortality study. A total of 2,567 workers met the definition of the study cohort. Table 1 gives a breakdown of the vital status ascertainment and the number of person-years within each sub-cohort. The vital status ascertainment is 98% complete.

The possibility that records might be missing from the personnel files used to assemble the Plant 1 cohort was cited at the beginning of the study. In an effort to determine whether eligible workers were missing from the Plant 1 cohort, a validity check was conducted by the New York State Department of Health[30] using methodology similar to that described by Marsh et al.[17] Social Security Administration (SSA) quarterly earning statements (SSA form 941) from 1945-1965 were obtained and compared to the names appearing on the microfilmed personnel records that were used to assemble the cohort. The results of this comparison yielded 35 additional workers (3.5% of cohort) not included in the Plant 1 study cohort. This small portion of the population at risk that is missing from the study cohort should not seriously bias the results. A similar validity check was not done at Plant 2, as it appeared from our inspection that the personnel file system had been maintained intact.

Table 2 shows the distribution of the cohorts by duration of employment in jobs where PCB exposure occurred. The distribution within the two plants is somewhat similar, with the exception of the female workers in Plant 2, where

Table 2.—Duration of Employment among Cohort Members in PCB Exposure Jobs

Plant 1	Males		Females		Total	
	N	(RF)*	N	(RF)	N	(RF)
3-6 mo	137	(23.5)	79	(20.5)	216	(22.3)
6 mo-1 yr	88	(15.1)	59	(15.3)	147	(15.2)
1-2 yr	93	(16.0)	92	(23.9)	185	(19.1)
2-3 yr	53	(9.1)	41	(10.6)	94	(9.7)
3-10 yr	165	(28.3)	82	(21.3)	247	(25.5)
10 yr	47	(8.1)	32	(8.3)	79	(8.2)
Total	583		385		968	
Plant 2	**Males**		**Females**		**Total**	
	N	(RF)	N	(RF)	N	(RF)
3-6 mo	211	(31.3)	207	(22.4)	418	(26.1)
6 mo-1 yr	127	(18.8)	161	(17.4)	288	(18.0)
1-2 yr	118	(17.5)	175	(18.9)	293	(18.3)
2-3 yr	64	(9.5)	82	(8.9)	146	(9.1)
3-10 yr	123	(18.2)	188	(20.3)	311	(19.4)
10 yr	32	(4.7)	111	(12.0)	143	(8.9)
Total	675		924		1599	

*RF = Relative frequency.

Table 3.—Observed and Expected Deaths (O/E) According to Major Causes among PCB Workers

Cause of Death (7th Revision ICD No.)	Plant 1		Plant 2				
	Males	Females	Males	Females	Total	(SMR)	95% Confidence Interval
All malignant neoplasms (140-205)	9/ 9.70	4/ 7.26	3/ 6.83	23/ 20.00	39/ 43.79	(89)	(63 - 122)
Nervous system (330-334, 345)	3/ 3.14	1/ 1.97	2/ 1.84	5/ 5.60	11/ 12.55	(88)	(44 - 157)
Circulatory system (400-468)	26/ 22.31	7/ 6.83	14/ 14.15	13/ 19.64	60/ 62.93	(95)	(73 - 123)
Accidents (800-962)	7/ 6.02	1/ 1.17	3/ 7.43	2/ 3.67	13/ 18.29	(71)	(38 - 122)
All other causes	10/ 12.80	5/ 5.54	6/ 10.26	19/ 16.19	40/ 44.79	(89)	(64 - 122)
All causes	55/ 53.97	18/ 22.77	28/ 40.51	62/ 65.10	163/ 182.35	(89)	(76 - 104)

more employees had worked for 10 or more yr, and in male workers where there was a high frequency of short-term (3-6 months) employees.

When the two cohorts are examined by year first employed in jobs where PCB exposure occurred, the females in Plant 2 are seen to have had an earlier initial date of exposure. In Plant 1, 49.4% of the males and 45.1% of the females were first employed in PCB exposure jobs before 1955. In Plant 2, 49.3% of the males and 69.6% of the females were first employed in PCB exposure jobs before 1955.

Tables 3 and 4 summarize the number of deaths observed (obs.) from the study cohorts and the number of deaths expected (exp.). The all-cause mortality is lower than expected in each cohort, with an SMR [Standardized Mortality Ratio (SMR = observed deaths/expected deaths X 100)] of 95 (73 obs. vs 76.7 exp.) for Plant 1 and an SMR of 85 (90 obs. vs 105.6 exp.) for Plant 2. These SMRs may be influenced by the "healthy worker effect."[18] There is no increase in observed mortality among the total cohort for any of the major causes of death listed in Table 3.

Table 4 lists the observed and expected number of deaths by specific cancer cause and for cirrhosis of the liver. When both cohorts are combined, the observed number of deaths is more than that expected for cancer of the rectum (4 obs. vs 1.19 exp.) and liver cancer—ICDA = 155, 156A (3 obs. vs 1.07 exp.). The only statistically significant difference ($P < .05$) in observed versus expected deaths occurred in females from Plant 2 for cancer of the rectum (3 obs. vs 0.50 exp., $P < .05$). For both cohorts combined, there are 6 deaths due to cirrhosis of the liver, while 5.60 were expected. Five of these cases are from the Plant 2 cohort, while 3.2 were expected. According to hospital reports, at least 3 of the 6 persons who died of cirrhosis of the liver were known to have consumed alcohol regularly.

The relationship between latency and the mortality from all cancer, cancer of the rectum, liver cancer, and cirrhosis of the liver is shown in Table 5. For "all cancer" there is no apparent pattern in either cohort. For cancer of the rectum, there is a slight increase with an increase in the latency periods. All of the deaths due to liver cancer occur before 20 yr of latency and there is no trend of increasing risk with an increase in the latency period. The risk of mortality due to cirrhosis of the liver does not show a consistent increase with an increase in the latency periods; there is however, a greater risk after a 20-yr period.

The relationship between these same causes of death and length of employment in PCB exposure areas of the plants is given in Table 6. As indicated in the Table, there is no increase in mortality with increasing lengths of exposure, except for cirrhosis of the liver; however, the numbers in this comparison are small.

Industrial hygiene survey. The industrial hygiene survey results of area and personal sampling for PCBs (Aroclor 1016) are summarized in Tables 7 and 8. Because of differences in the production processes, the results by specific jobs or work areas are not comparable between the two plants. However, relative comparisons can be made, and the range of concentrations observed in Plant 1 are lower than those in Plant 2. In Plant 1, the time-weighted average (TWA) personal air samples ranged from 24 $\mu g/m^3$ to 393 $\mu g/m^3$, and the TWA area air samples ranged from 3 $\mu g/m^3$ to 476 $\mu g/m^3$. The TWA personal air samples in Plant 2 ranged from 170 $\mu g/m^3$ to 1260 $\mu g/m^3$, and the TWA area air samples ranged from 50 $\mu g/m^3$ to 810 $\mu g/m^3$.

Trichloroethylene was measured near the degreasers in both plants. Of 11 area air samples from Plant 1, all were less than 35 ppm, except for two which measured 195 ppm and 321 ppm. At Plant 2, three area air samples were taken which ranged from 53.4 ppm to 77.5 ppm.

Area air samples were measured for tin, lead, and zinc near the soldering operations. There were no detectable levels for tin at either plant. Of four samples collected for lead and zinc at Plant 1, lead was detected in one sample at a level of 12 $\mu g/m^3$, and zinc was detected on two samples at levels of 8 and 24 $\mu g/m^3$. At Plant 2, 15 samples were collected for lead and zinc; all but one (41.2 $\mu g/m^3$) of these samples showed no detectable levels for lead. Six of the 15 samples revealed concentrations of zinc ranging from 2.3 to 94.1 $\mu g/m^3$.

Both personal and area samples were taken in the area

Table 4.—Observed and Expected Deaths (O/E) According to Specific Cancer Causes and Cirrhosis of the Liver among PCB Workers

Cause of Death (7th Revision ICD No.)	Plant 1		Plant 2		Total	(SMR)	95% Confidence Interval
	Males	Females	Males	Females			
All malignant neoplasms (140-205)	9/ 9.70	4/ 7.26	3/ 6.83	23/ 20.00	39/ 43.79	(89)	(63 - 122)
Stomach (151)	0/ 0.51	0/ 0.22	1/ 0.31	0/ 0.62	1/ 1.66	(60)	
Intestine exp. rectum (152, 153)	1/ 0.82	0/ 0.70	0/ 0.54	3/ 1.97	4/ 4.03	(99)	(27 - 254)
Rectum (154)	1/ 0.31	0/ 0.18	0/ 0.20	3/ 0.50*	4/ 1.19	(336)	(92 - 860)
Biliary pass liver Liver not specified (155, 156A)	1/ 0.23	0/ 0.18	0/ 0.15	2/ 0.51	3/ 1.07	(280)	(58 - 820)
Pancreas (157)	0/ 0.53	1/ 0.27	0/ 0.35	0/ 0.75	1/ 1.90	(53)	
Respiratory system (160-164)	5/ 3.22	1/ 0.71	0/ 2.22	1/ 1.83	7/ 7.98	(88)	(35 - 181)
Breast (170)	------	1/ 1.86	------	6/ 4.98	7/ 6.84	(102)	(41 - 211)
Lymphatic and hematopoietic (200-205)	0/ 1.10	0/ 0.59	0/ 0.94	2/ 1.71	2/ 4.34	(46)	
Other	1/ 2.98	1/ 2.55	2/ 2.12	6/ 7.13	10/ 14.78	(68)	(32 - 124)
Cirrhosis of liver (581)	1/ 1.69	0/ 0.73	2/ 1.26	3/ 1.92	6/ 5.60	(107)	(39 - 233)

*$P < .05$

Table 5.—Observed and Expected Deaths According to Latency* among Male and Female PCB Workers

Latency (yr)	Plant 1 O†	Plant 1 E‡	Plant 1 SMR	Plant 2 O	Plant 2 E	Plant 2 SMR	Plants 1 2 O	Plants 1 2 E	Plants 1 2 SMR
I. All Cancers									
<10 yr	6	5.27	114	6	7.76	77	12	13.03	93
10-<20 yr	3	6.61	45	16	10.91	147	19	17.52	108
>20 yr	4	5.07	79	4	8.17	49	8	13.24	60
II. Cancer of Rectum (ICD = 154)									
<10 yr	0	0.15	---	0	0.21	---	0	0.36	---
10-<20 yr	0	0.19	---	2	0.29	690	2	0.48	417
>20 yr	1	0.15	667	1	0.21	476	2	0.36	556
III. Liver Cancer (ICD = 155, 156A)									
<10 yr	1	0.12	833	1	0.18	556	2	0.30	667
10-<20 yr	0	0.16	---	1	0.27	370	1	0.43	233
>20 yr	0	0.12	---	0	0.21	---	0	0.33	---
IV. Cirrhosis of Liver (ICD = 581)									
<10 yr	1	0.80	125	1	0.95	105	2	1.75	114
10-<20 yr	0	1.01	---	1	1.35	74	1	2.36	424
>20 yr	0	0.61	---	3	0.88	341	3	1.49	201

* Latency = number of years from date first employed in exposed job.
† O = observed deaths.
‡ E = expected deaths.

of welding operations for measuring aluminum and iron at Plant 1. The aluminum samples ranged from nondetectable to 233 $\mu g/m^3$, and the iron samples ranged from 47 $\mu g/m^3$ to 123 $\mu g/m^3$.

Twelve personal samples were collected for toluene and MIBK during painting operations at Plant 1. Toluene concentrations ranged from 0.48 to 22 ppm and MIBK ranged from 2 to 5 ppm.

Although the exposures to PCBs at the dates of survey (Plant 1—April 1977, Plant 2—March 1977), were relatively higher in Plant 2, the historic levels of exposure may have been more equivalent. The exposures that occurred 20 to 30 yr ago are more relevant when considering the occupational cancer risk among the study cohorts. The PCB mixtures used during these time periods were Aroclor 1254 and 1242, whereas Aroclor 1016 was first used in 1971. In addition, several different stabilizers have been added to the PCBs (1% or less by weight) used at Plant 1 since the early 1960s. These include potential carcinogens such as diglyceride ether-disphenol-a and, more recently, vinyl cyclohexene dioxide. It is not known which stabilizers have been used at Plant 2.

DISCUSSION

There are few previous epidemiologic studies that have examined the long-term health effects on humans exposed to PCBs. Individuals poisoned by rice oil heavily contaminated with PCBs (Yusho Disease) have been studied extensively years after the incident took place in Japan in 1968.[19,20] However, the rice oil contaminant also contained polychlorinated dibenzofurans and other contaminants in higher concentrations than those found in commercially prepared PCBs. A high prevalence of skin and eye conditions were noted in the Yusho patients. In addtion, there were clinical and laboratory findings that included changes in the microanatomy of liver cells and a decreased concentration of bilirubin in the serum of these individuals.[21,22]

Early reports regarding the health effects from occupational exposure to PCBs include chloracne,[23] digestive disturbances, eye irritation, liver injury, and impotence.[24,25] Most of these findings have been reported as case histories.

In a recent study of volunteers conducted by the Mount Sinai School of Medicine,[26] 326 workers who were em-

Table 6.—Observed and Expected Deaths According to Length of Exposure among Male and Female PCB Workers

Length of Employment	Plant 1			Plant 2			Plants 1 2		
	O*	E†	SMR	O	E	SMR	O	E	SMR
				I. All Cancers (ICD = 140-205)					
3 mo -5 yr	11	12.21	90	20	18.78	106	31	30.99	100
5-9 yr	1	2.95	34	2	4.10	49	3	7.05	43
10-14 yr	0	1.00	---	3	2.28	132	3	3.28	91
15-19 yr	1	0.69	145	1	1.04	96	2	1.73	116
⩾ 20 yr	0	0.11	---	0	0.63	---	0	0.74	---
				II. Cancer of Rectum (ICD = 154)					
3 mo -5 yr	1	0.35	286	1	0.48	208	2	0.83	241
5-9 yr	0	0.09	---	0	0.11	---	0	0.20	---
10-14 yr	0	0.03	---	2	0.06	3333‡	2	0.09	2222‡
15-19 yr	0	0.02	---	0	0.03	---	0	0.05	---
⩾ 20 yr	0	0.001	---	0	0.02	---	0	0.02	---
				III. Liver Cancer (ICD = 155, 156A)					
3 mo -5 yr	1	0.29	345	2	0.45	444	3	0.74	405
5-9 yr	0	0.08	---	0	0.11	---	0	0.19	---
10-14 yr	0	0.02	---	0	0.06	---	0	0.08	---
15-19 yr	0	0.02	---	0	0.02	---	0	0.04	---
⩾ 20 yr	0	0.002	---	0	0.02	---	0	0.02	---
				IV. Cirrhosis of the Liver (ICD = 581)					
3 mo -5 yr	1	1.79	56	2	2.26	88	3	4.05	74
5-9 yr	0	0.39	---	1	0.48	208	1	0.87	115
10-14 yr	0	0.12	---	1	0.24	416	1	0.36	278
15-19 yr	0	0.10	---	1	0.13	769	1	0.23	435
⩾ 20 yr	0	0.02	---	0	0.08	---	0	0.10	---

*O = observed deaths.
†E = expected deaths.
‡$P < .01$

ployed at Plant 1 were examined. The most prevalent symptoms noted were dermatological and those of the central nervous system. There was a low prevalence of abnormal liver findings on physical examination. However, a subgroup exposed to PCBs were found to have liver enzyme changes different from those of a normal, non-exposed group. In addition, abnormal serum glutamic oxalacetic transaminase (SGOT) levels were associated with plasma levels of PCBs. There was a relatively high prevalence of decreased lung capacity among a subgroup of 243 workers tested.[27]

In a preliminary report, Bahn[28] reported an increase in deaths due to malignant melanoma (2 obs. vs 0.04 exp.) and cancer of the pancreas among 51 research and development employees and 41 refinery plant employees at a New Jersey petrochemical facility. These individuals were exposed to Aroclor 1254 during various periods between 1949 and 1957, along with exposure to other toxic and potentially carcinogenic compounds.

In a summary of case histories among approximately 300 workers employed in the manufacturing of PCBs,[29] no malignant melanomas or pancreatic cancers were observed. However, among the death certificates of 50 former workers at this manufacturing facility, 7 cases of lung cancer were observed whereas 2.7 cases were expected. The findings were preliminary and were not adjusted for age or smoking.

These previously reported findings of an increased risk of mortality due to malignant melanoma, cancer of the pancreas, and lung cancer among workers exposed to PCBs are not corroborated in the present study. There are no observed deaths due to malignant melanoma and only 1 observed death from pancreatic cancer while 1.89 are expected. There are 7 observed deaths from respiratory

system cancer, whereas 7.69 are expected. The only categories of cancer in which the number of observed deaths are greater than expected are for cancer of the rectum and cancer of the liver and only a slight increase for breast cancer. When both cohorts and sex groups are combined, none of the excesses are statistically significant at $P < .05$. However, the excess in liver cancer is noteworthy because it is consistent with the toxicology data observed in laboratory animals exposed to PCBs, where effects have been noted in the liver.[6-13] The slight increase in deaths due to cirrhosis of the liver in the Plant 2 cohort is also consistent with the notion that PCBs have a toxic effect on the liver.

In most occupational health studies where cancer mortality is being assessed, latency is an important variable; the hypothesis being that there is an increased risk of mortality once a certain time period has elapsed after initial exposure. In this study, this hypothesis is difficult to examine because of the small number of deaths. None of the causes of death analyzed according to latency clearly demonstrates this association. Rectal cancer shows a slight increase with an increase in latency, and cirrhosis of the liver shows an increase in risk with an increase in latency after 20 yr.

There is no relationship between increasing durations of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver.

When cancer mortality is examined by Plant, it is evident that most of the excesses occur in Plant 2—especially among the female group. This finding may be related to more exposures to PCBs at Plant 2, as indicated by the industrial hygiene results. In addition, there was an opportunity for earlier exposures at Plant 2, potentially allowing for a longer latency period. However, this difference in mortality may be a function of the size of the cohorts (Plant 1 only has half the number of person-years as Plant 2), and thus, simply be a statistical quirk.

Table 7.—Concentrations of PCBs (Aroclor 1016) at Plant 1 (April 1977)

	A. Power Capacitor Manufacturing Facility						
	Personal Air Samples				Area Air Samples		
Job Titles	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)	Location	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)
Recovery Repair	2	840	298	Test and Paint	2	840	41
Salvage Operator	1	426	155	Assembly	2	851	29
EMF operator	1	431	115	Shipping	1	426	16
Treat helper	2	867	80	Storage	1	427	14
Treat operator	2	731	66	Winding	1	420	3
Repair	1	422	50				
	B. Small Capacitor Manufacturing Facility						
Moveman (Sealing area)	2	689	393	Soldering	2	782	476
Moveman (Testing and soldering area)	3	1306	220	Assembly	2	827	115
Testing	3	1290	218	Shipping	2	838	56
Packer	3	1287	199	Winding	2	828	54
Treat operator	2	845	160	Can Manufacturing	2	836	51
Rework and final assembly	2	824	152	Cover Manufacturing	2	834	45
Maintenance	1	404	150				
Rework tester	1	433	140				
Rework packer	1	435	132				
Rework tester solder	1	271	24				

*TWA is calculated during the total sampling time period.

Table 8.—Concentrations of PCBs (Aroclor 1016) at Plant 2 (March 1977)

	Personal Air Samples				Area Air Samples		
Job Titles	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)	Location	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)
Degreaser	1	381	1,260	Impregnation	2	176	810
Solder	3	884	1,060	Pump room	3	1079	490
Tanker	9	2120	850	Testing	5	1424	320
Moveman (soldering area)	3	752	720	Pre-assembly	4	1213	140
Heat soak operator	3	872	630	Shipping	2	741	90
Tester	3	917	290	Winding	4	637	70
Pump Mechanic	1	377	280	Cover manufacturing	3	1089	60
Floorman (pre-assembly)	6	1683	170	Office	2	741	50

*The TWA is calculated during the total sampling time period.

A potential confounding variable or interaction variable in this study is the possible effect of alcohol ingestion on the observed increase (at Plant 2) in mortality from cirrhosis of the liver. However, this cannot be properly assessed in the present study, since not enough is known about the ingestion of alcohol among the entire study cohort.

CONCLUSIONS

Because a relatively small number of deaths were observed, conclusions drawn from the results of this study are tentative.

All-cause mortality is lower than expected, and there was no increase in mortality for the major causes of death that were examined. Among the cancer causes, there was increased cancer of the liver and rectum. Cirrhosis of the liver was also elevated in one of the plants. The slight excesses for liver cancer and cirrhosis of the liver are consistent with previously reported findings on experimental animals exposed to PCBs, and suggest that there may be an association between these causes of death and occupational exposure to PCBs (i.e., Aroclor 1254 and 1242). However, the findings for liver cancer do not reflect a relationship with latency that has been observed for other carcinogens found in the workplace. The observed excess in cancer of the rectum related to PCB workers was unexpected and requires further investigation.

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Mr. Jones is now employed at Kaiser Aluminum and Chemical Corp., Ravenswood, West Virginia, 26164.

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Requests for reprints should be sent to: David P. Brown, I.W.S.B., NIOSH, 4676 Columbia Parkway, Cincinnati, OH 45226.

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