UNITED STATES OF AMERICA

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BEFORE THE

ENVIRONMENTAL PROTECTION AGENCY

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In the Matter of the Hearing of::

2,4,5-T and SILVEX : Docket Nos. 415, et al

The Dow Chemical Company, et al :

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(This volume contains pages 16875 through 17065)

Room 2409
Environmental Protection Agency
Headquarters
401 M Street, Southwest
Washington, D. C.

Thursday, November 13, 1980

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The hearing was convened pursuant to adjournment, at 9:00 a.m., before Administrative Law Judge Edward B. Finch, when were present the following:

ON BEHALF OF THE ENVIRONMENTAL PROTECTION AGENCY:

DOROTHY PATTON, ESQ.	Office of General Counsel
KARL BAYER, ESQ.	Office of General Counsel
MICHAEL WINER, ESQ.	Office of General Counsel
ANDREW G. GORDON, ESQ.	Office of General Counsel

T5/S1 -1

JUDGE FINCH: We will resume the hearing.

Mr. McConnell.

MR. McCONNELL: Good afternoon, Your Honor.

Our next witness is Mr. V. K. Rowe, Mr. Rowe is the former director of Toxicological Affairs and Health and Environmental Research at Dow. He retired from Dow in 1979, but he is still active as a consultant.

Mr. Rowe was a charter member of the Society of Toxicology, and is a past president of the Society. He has, in addition, served on advisory committees for EPA, for OSHA and with the National Cancer Institute.

Mr. Rowe.

Whereupon,

V. K. ROWE

was called as a witness and, having first been duly sworn, was examined and testified as follows:

JUDGE FINCH: Are there any additions or corrections to your statement?

THE WITNESS: Yes, I have one minor one, in the educational section there, my Master's Degree was awarded in 1938, instead of '37.

JUDGE FINCH: Well, we want to make that change then, where does it appear?

THE WITNESS: It's in my CV.

JUDGE FINCH: Oh, in the CV.

Q And would he be one of the people that may have informed you that the careful medical surveillance was being conducted?

A I suspect that that is the case, but I cannot be certain.

Q Do you remember what he told you, or what you were told by people in the meetings?

A Simply that these people were being followed on a periodic basis.

Q You were not informed as to the tests that were actually being conducted on these workers, were you?

A I can't testify to that on a personal basis, no.

Q Let's turn to the next section of your witness statement. On page 5, which is entitled "Research Subsequent to the 1964 Chloracne Outbreak".

A (Perusing documents.) Yes.

Q This section of your testimony discusses experiments conducted by a Dr. ~~Alfred~~ Albert Kligman, which were initiated and funded by Dow Chemical Company, is that correct?

A That's right.

Q In these experiments varying doses of 2,3,7,8-TCDD were dermally applied to the forehead and back of human subjects incarcerated at a prison at Holmesburg, Pennsylvania, is that correct?

A The test procedures were as you describe, whether incarcerated is a proper word, I don't know, I presume it is.

Q They were prisoners, is that correct?

A That's my understanding.

Q You state, at the beginning of the bottom of page 5 that you contacted Dr. Albert Kligman and then at the top of page 6 you state, "Dr. Kligman agreed to test the chloracnegenic potential, TCDD in humans, under his existing program", is that correct?

A Yes.

Q Would it be fair to say that you were the Dow representative who initiated contact with Dr. Kligman, and requested that he conduct experiments in which human subjects would be dermally exposed to TCDD?

A Yes.

Q Now, Dr. Kligman conducted two separate sets of tests in which he applied TCDD to the skin of these human subjects, is that correct?

A You are talking about two different tests?

Q Two different sets of experiments.

A Well, there was one experiment to start with and then there was a subsequent experiment that he conducted, yes.

Q Did you not design the protocol for the first

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set of tests conducted by Dr. Kligman in which the researchers applied a range of doses of TCDD to the backs and the foreheads of 60 human subjects?

A Yes.

Q Was there a different protocol for the second series of tests which Dr. Kligman conducted?

A Well, not to my knowledge, that was his protocol. I did not know that this second experiment was to be done the way it was done.

Q On page 8 -- let's turn to page 8.

A (Perusing documents.) Yes.

Q In the second full paragraph on that page, near the bottom of that page, at the bottom of that paragraph, you state, "Accordingly, I indicated to Dr. Kligman that Dow would fund a continuation of his studies" and then you go on to say, "In January of 1968, I was surprised to receive a letter from Dr. Kligman reporting new results".

Could you explain to us what you mean by "surprised"?

A Yes. As much of the first protocol had yielded absolutely negative results, we did agree, at his request, to fund a continuation, but I assumed it would be following the same progression that I had outlined in the first instance. Unfortunately, that was never confirmed in writing. And the next I heard from it was that the results

that he reported to me.

Now, each of these steps takes a considerable period of time. If you will look at the protocol, because I was very concerned that we approach this very cautiously. And raise the dosage in increments so as not to exceed a level which would produce a threshold response.

The reason for that was that in our studies on animals we had determined that concentrations of chloracnegens which produced an effect in humans, essentially always produced an effect in the animals.

And if the animal work was not positive, we never had a material that cause injury in humans.

Now, so what we wanted to do and what we felt we should do was to attempt to determine the relationship between the sensitivity of the rabbit's ear to that in humans. After we had identified the material had ~~quantative~~ quantitative -- it measured quantitatively, we determined that a certain dosage level was the minimum required to produce an effect on the rabbit's ears.

But our evidence from practical experience had indicated that the human was much more resistant, but we didn't know how much more resistant. And we were very concerned about what the margins of safety would be.

So, therefore, the purpose of this study was to incrementally increase the dosage, so that we would be able

to find out what that figure was.

Q You indicated to Dr. Kligman that Dow would continue its funding of the studies, is that correct?

A That's right.

Q And yet you assumed -- you said that you assumed that he would continue to follow the protocol that you had given him, is that correct?

A Yes.

Q Between the time you received the results of Dr. Kligman's first series of tests, in May and June of 1966; and the time that you received his letter in which he stated he had conducted a second set of tests, did you have no contact with Dr. Kligman concerning this second series of tests?

A I had none.

Q You mean you had said that Dow would continue to fund this study, and yet you did not bother to even contact Dr. Kligman to see what he was doing.

MR. McCONNELL: Your Honor, I think that question may be a little argumentative.

JUDGE FINCH: I think it is, too. He said he did not.

You can answer the question did you have any contact between the time you got the results?

THE WITNESS: If I did, I have no knowledge of

it. I don't believe I did.

BY MR. GORDON:

Q Does Dow normally fund studies and then not pay attention to what is being done with the money it grants?

A Well, it depends on what the situation is, this was a contract with the university and with a professional dermatologist who had conducted the first series of protocols, he knew what my philosophy, with respect to testing was. And it takes so much time between tests, that if you proceed according to the protocol, that I had designed, that I didn't feel it was necessary, and I didn't ask him about it.

As I said, it was a total surprise when the report came as it did.

Q Well, you say that Dow and yourself were concerned with the margins of safety, what was the highest dose level given -- applied to the skins of the prisoners in the first set of tests?

I believe you can find the answer to that on page 8, in Table 1.

A Yes, that's right, the total dose that was given was 16 microgram/kg -- per person.

Q What was the total dose given in the second set -- second series of tests that Dr. Kligman had conducted, in which Dow funded?

A 7500 micrograms.

Q So, Dr. Kligman went from 16 micrograms to 7500 micrograms, is that correct?

A That's what he says he did.

Q So, he increased the dosage somewhere in the neighborhood of 5,000 orders of magnitude?

A No, it would be closer to 40 to 50, 45 perhaps, something like that, wouldn't it?

Excuse me, I will make a calculation.

JUDGE FINCH: That's all right, wait until you get another question, unless you want him to.

BY MR. GORDON:

Q Would you work that out for us, please?

A Yes. You are closer to right, it's about 470.

MR. McCONNELL: Your Honor, if we might have a clarification on the question, was that phrased in terms of the magnification of the dose, or the order of magnitude of difference?

MR. GORDON: Magnification, I'm sorry, I used the wrong terminology.

THE WITNESS: It's the difference between 16 and 7500, and if you divide 7500 by 16, you come out close to 470.

BY MR. GORDON:

Q Well, when you wrote the protocol for the first

series of tests, you increased the dosage for each group at what you would term a conservative amount, is that correct?

A That's right.

Q Would you call the increase that Dr. Kligman conducted in the second of tests a conservative increase?

A No, sir, I wouldn't.

Q Did you -- had Dow ever funded studies by Dr. Kligman previous to the ones that are discussed in your testimony?

A I can't answer that, I don't remember doing any of it myself, but Dow Chemical Company is a very large corporation and it could have been done by the medical department, or somebody, and I might not have known about it. Not to my knowledge.

Q So, to your knowledge, Dow had no prior experience with overseeing Dr. Kligman's studies, is that correct?

A I believe that is correct.

Q So, upon what basis did you determine that it was not important to oversee the second series of tests which he was going to conduct?

A I guess only that he was a professor of dermatology at the University of Pennsylvania, and we had reasonable confidence that he would proceed in a manner consistent with our original protocol.

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(This volume contains pages 17066 through 17238)

Room 2409
Environmental Protection Agency
Headquarters
401 M Street, Southwest
Washington, D. C.

Friday, November 14, 1980

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The hearing was convened pursuant to adjournment, at 9:05 a.m., before Administrative Law Judge Edward B. Finch, when were present the following:

ON BEHALF OF THE ENVIRONMENTAL PROTECTION AGENCY:

DOROTHY PATTON, ESQ. Office of General Counsel

KARL O. BAYER, ESQ. Office of General Counsel

ANDREW G. GORDON, ESQ. Office of General Counsel

Q Was Dow not interested at all in seeing those results?

A We accepted the statements that he and his internist made.

Q Does Dow normally, when they contract out to outside experimenters, do they normally not bother to acquire the results of the test that the experimenter performed?

A It generally depends on the -- and we, incidentally contract out very little work -- but it depends on what the purpose of that work is, where it is going and what the ultimate end is to be. Monitoring of laboratory work by consulting laboratories, in the time when this was done, was not done to the extent that it was done under the present GLPs, where every data point has to be monitored.

In those days we usually took what we considered to be competent people and expected them to conduct their studies in the normal course of their investigations. And Dr. Kligman was a professor of dermatology, he is an M.D., he did lots and lots of skin work in those days. And these are his results, we did not question his reporting.

Q In the second series of tests which is discussed in Dr. Kligman's January 23rd letter, he reports that eight of the 10 subjects developed chloracne. Did not Dow want

to see the clinical tests that were conducted on these eight subjects who did develop chloracne?

A I guess we really didn't think that it was necessary to see them.

Q Why did you think it was not necessary to see the results of these clinical tests which were conducted on eight human subjects which had developed chloracne?

A Well, in retrospect I will say it would have been nice to have seen them. But in those days we took their words that they had -- we had seen lots of chloracne, it wasn't a new phenomenon to us.

Q So for these human beings you are saying in retrospect, it would have been nice to see the results of these clinical tests?

A I think so, from a curiousity point of view.

Q Just for curiousity's sake? You were not interested in the health of these eight human beings?

A Well, of course we were --

Q Then why did you not ask to see the clinical results of the tests.

MR. McCONNELL: I don't believe Mr. Rowe had finished his answer there, if I am wrong, I will apologize. But it sounded to me like he was going to say something more.

THE WITNESS: I was only going to say that

follow-up on the health status of these three individuals?

A I do not.

Q Do you know whether Dow or Dr. Kligman has ever conducted a follow-up survey of the health status of the human subjects exposed to TCDD in Dr. Kligman's tests?

A Not to my knowledge, I do not know that he has, no. I have no knowledge of that.

Q Do you know whether Dow has conducted such a follow-up study?

A Dow has not.

Q Dow has not?

A Right.

MR. GORDON: Could I have just one moment, Your Honor?

JUDGE FINCH: Sure.

MR. GORDON: I am going to provide the witness, and Counsel with Exhibit No. 15, entitled, "Results of the Two-Year Chronic Toxicity and Oncogenicity Study on 2,3,7,8-Tetrachlorodibenzo-p-dioxin, TCDD in Rats" by Kociba, et al.

MR. McCONNELL: Did you say Exhibit 15 or Exhibit 13? I believe this is Exhibit 13.

MR. GORDON: Oh, I meant to say 13, yes.

BY MR. GORDON:

Q Are you familiar with this document, Mr. Rowe?

A I am generally familiar with it, not in detail because I am not a pathologist and I certainly don't intend to get into pathology.

Q Let's look at the abstract on the first page, in the seventh line from the top, does it not state that "Ingestion of 0.1 ug/kg/day caused an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, heart, palate, nasal turbinates, or tongue, whereas a reduced incidence of the pituitary, uterus, mammary glands, pancreas and adrenal gland was noted"?

A Yes.

Q After you became aware of the oncogenic effects of TCDD reported in the Kociba Study, did you or Dow consider whether the human subjects you had exposed to TCDD had developed cancers in the years subsequent to the conduct of the study?

A We have not followed up on that.

Q Did you consider whether the human subjects had developed cancers from the study in 1966?

A I don't remember entering into any discussions on that subject.

Q Well, you had entered into no discussions as to whether these human subjects had developed cancer, but had you considered that they might have developed cancer on your own?

July 9, 1965

Albert M. Kligman, M.D., Ph.D.
Department of Dermatology
Hospital of the University of Pennsylvania
36th and Spruce Streets
Philadelphia 4, Pennsylvania

Dear Dr. Kligman:

I am sending you under separate cover a small amount of 2,3,7,8-tetrachlorodibenzo-p-dioxin. This is the material which is a potent acnegen and is highly toxic. I have checked back on our figures and find that the single dose oral LD_{50} for rabbits is in the neighborhood of 100 micrograms/kilogram, and we had one animal die which had received a single dose of 16 micrograms/kilogram. It is safe to say, however, that doses of 0.5 to 1.0 mg/kg are always fatal, although deaths may be delayed for 10 to 20 days post treatment. The typical clinical picture is severe liver and kidney injury.

In regard to the skin response on rabbits, we have attempted to quantitate this by applying 0.1 ml of test solution to one to two square inches of the surface of the inner face of the rabbit ear. We find that when the total dose does not exceed about 0.2 of a microgram of the acnegen, no follicular prominence or epithelial hyperplasia develops. When the total dose is about 0.5 of a microgram on this area, the response is marginal; 1 to 2 micrograms almost always produces a response, and 4 to 8 micrograms usually produce a severe response. We have not as yet been able to quantitate the dose required to cause 50% mortality from skin exposure, but we are sure it is well above the total dosages noted above.

In view of this information, it does not seem probable that the dosages shown in the accompanying suggested protocol for the human work would be likely to constitute any serious systemic hazard because the dose on a per kilogram basis would be far below that which produces any significant effect systemically in the rabbit. I might add that the rabbit is far more sensitive than the rat to this type of compound. Nevertheless, the seriousness of the consequences that might develop from testing with this type of compound require that we approach the matter in a highly conservative manner. It

is with this thought in mind that I have developed the attached protocol. The number of persons per experiment is your decision; I would suggest two as a starter. When applications are repeated, I would like to have them made on consecutive days, if it is convenient to do so. Although the time required to conduct these experiments will require several months, I believe it is the safe way to proceed, using a few people at a time with careful observations on each. The observations are to be made at your discretion, but I would urge routine SGOT's and alkaline phosphatases as a minimum.

There is another item upon which comment should be made. I have indicated in the suggested protocol that a two week observation period should be used prior to starting the next series of experiments. This is because our experience with both animals and man indicates that there is an induction period. In a few instances, we believe an eruption in the human has developed four to six weeks post exposure. Also, we have had a few serious flare-ups which have developed within a matter of days, post exposure. I have compromised on a two-week observation period, but of course, any treated individual should be watched for at least two months post test.

You asked about materials in which this test substance is soluble. I have indicated it is quite soluble in chloroform and benzene and slightly soluble in alcohol. I believe that a solution in 50/50 alcohol and chloroform would be quite appropriate for your work. In regard to covering the exposed area, I would suggest that when the treated area has dried that it be covered lightly with a gauze simply to keep the material from being brushed away or having a person contaminate his hands or clothing inadvertently.

I hope I have answered your questions, but if you have any others, please do not hesitate to contact me.

Sincerely yours,

V. K. Rowe
Biochemical Research Laboratory
1701 Building

VKR/jd

Attach.

cc: Medical Department:
Gordon, Holder, Kramer
J. E. Peterson
L. Silverstein
H. R. Hoyle
V. K. Rowe (2)
TB6.25-66681-7

TO DETERMINE THE ACNEGENIC POTENTIAL OF 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN AND TO STUDY THE PATHOGENESIS OF CHEMICALLY INDUCED ACNE

Volume/Application - 0.04 ml.

Area Treated - Approximately 1 square inch

Solvent - 50/50 Chloroform and Ethanol

Test Solution	µg/ml	µg/0.04 ml
A	2.5	0.1
B	12.5	0.5
C	25.0	1.0
D	50.0	2.0
E	100.0	4.0

Label all solutions with appropriate warnings as: Danger! This material is extremely toxic.

Handle with special care to prevent inadvertent contamination of laboratory equipment (tables, papers, desks, etc.) or otherwise "clean" facilities.

Experiment Number	Total Dose/Test Site µg	Number of Applications	Solution
1	0.2	2	A
2	0.2	2	A
3	0.5	1	B
4	0.5	5	A
5	1.0	1	C - 25
6	1.0	1	B - 12.5
7	2.0	1	D - 50
8	2.0	4	B - 12.5
9	4.0	1	E - 100
10	4.0	4	C - 25
11	8.0	2	E - 100
12	8.0	8	C - 25

ALBERT M. KLIGMAN, M.D., Ph.D.
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
36TH AND SPRUCE STREETS
PHILADELPHIA, PA 19104

January 23, 1968

Mr. V. K. Rowe
Biochemical Research Laboratory
1803 Building
The Dow Chemical Company
Midland, Michigan 48640

Dear V. K.:

This note is a follow-up to my report of July 8, 1966. In that study, you will recall that 6 groups of healthy adult subjects received small and increasing doses of tetrachlorodibenzo-p-dioxin. We followed a specific protocol laid down by you. Unfortunately, not a single subject developed acne nor was there any evidence of toxicity.

This encouraged me to proceed more vigorously. We then assembled a new panel of 10 subjects and applied 0.05 ml of a 1% solution in alcohol chloroform to a one inch square on the back. These applications were made every other day for one month. The treated sites were covered with a non-occlusive gauze square. Each week for 6 weeks, the following laboratory tests were done: Urinalysis, CBC, BUN, SGOT, Alkaline phosphatase, and Creatinine clearance.

Clearly, this exposure was immensely greater than the former one. 8 of 10 subjects showed acne form lesions usually beginning 3 to 4 weeks. This began as with a typical development of comedones. In 3 instances, the lesions progressed to inflammatory pustules and papules. These lesions lasted for 4 to 7 months, since no effort was made to speed healing by active treatment. Biopsies were obtained in 5 instances at various stages. The histologic and clinical manifestations were in every way comparable to classical chloracne. The lesions were indistinguishable from those obtained by Dow 6X and Halowax.

In no instance was there laboratory or clinical evidence of toxicity. The subjects remained well throughout the study.

These results implement the conclusions formerly drawn, namely: it is much more difficult to induce acne in the human than in the rabbit ear. The process begins more slowly and the doses required are very much greater. However, unlike the rabbit ear, the comedones often become inflammatory. It is a certainty that the rabbit ear is exceptionally sensitive to acneigenic chemicals and is an excellent system for the detection of such chemicals. Finally, it may be said that chloracne closely mimics acne vulgaris. The only difference is the paucity of anaerobic organisms in the comedo. One may conclude that bacteria are not very significant in the pathogenesis of chloracne.

Very sincerely yours,

Albert M. Kligman, M. D.

AMK/klf

THE DOW CHEMICAL COMPANY

MIDLAND
December 24, 1964

D. D. Irish
E. M. Adams
H. R. Hoyle
H. H. Gay
H. L. Gordon
B. B. Holder
C. G. Kramer
M. B. Lilly
R. D. Stewart
D. J. Kilian

RESEARCH ON CHEMICAL ACNEGENS USING HUMAN SUBJECTS

As a result of our discussion with Dr. Albert M. Kligman, Professor of Dermatology at the University of Pennsylvania, when he visited us on December 11, 1964, Dr. Kligman has drawn up a proposed program for a basic study on acne. As I am sure you are all aware, one of our basic problems is to learn how to correlate the response observed in humans with that observed in rabbit ears. We need to know of the quantitative as well as of the qualitative relationships between the sensitivity of the rabbit and man. Aside from this quantitative aspect, we also need to know something about the basic changes that occur in the skin in response to given acnegens. What is the effect of these materials upon the microflora of the skin and what, if any, treatments can be instituted to alleviate the condition once it begins to develop? Dr. Kligman is very desirous of searching for the answers to these questions. It would be our intention to correlate his work on humans with rabbit work done here with exactly the same compositions, thereby hopefully establishing quantitative and qualitative relationships.

I should like to have opinions from each of you relative to the merits of Dr. Kligman's proposal. If the consensus is that such a project would be worth the anticipated expenditure, I shall attempt to obtain authorization to proceed.

If any of you have any questions, I will be glad to try to answer them.

V. K. Rowe
Biochemical Research Laboratory
1701 Building
ME 6-2376

VKR/jd

MIDLAND
March 4, 1965

L. C. Chamberlain
Director of Independent Laboratories
Executive Research
566 Building

C. O. Hutchenreuther
Chemicals Production
258 Building

REQUEST FOR AUTHORIZATION FOR $10,000 FOR RESEARCH ON CHEMICAL ACNEGENS USING HUMAN SUBJECTS

Attached is a copy of a letter dated December 24, 1964, addressed to a number of persons who at that time I thought would be interested in the subject. Attached to this letter is an outline of a proposed study, an estimate of the cost of such a study, and a copy of a letter from Dr. Kligman which relieves the Company of any liability which may be incurred by Dr. Kligman's experimental work and which is acceptable as far as Mr. O'Connor of the Dow Legal Department is concerned.

This program has been discussed with all of the addressees of my letter of December 24th, and also with Mr. Hutchenreuther Mr. Georgen and Dr. Trapp. All have agreed that this would be a desirable project to support.

In view of the fact that this work is of direct interest to the chloracne problem and because it is research in nature and the results are expected to be useful in other applications, I suggested that the cost be split evenly between our laboratory and Mr. Hutchenreuther's production unit.

I should like to have the approval of each of you so that I can get the program under way. If you have any questions I would be glad to discuss them with you.

V. K. Rowe
Biochemical Research Laboratory
1701 Building
ME 6-2376

VKR/jd

cc: E. M. Adams
H. R. Boyle
H. E. Cay, M.D.
J. M. O'Connor
Authorization Book
V. K. Rowe (2)
Correspondence

ALBERT M. KLIGMAN, M. D., PH. D.
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
36TH AND SPRUCE STREETS
PHILADELPHIA 4, PA.

DEPARTMENT OF DERMATOLOGY

EVERGREEN 2-4000
EXTENSION 431

Mr. V. K. Rowe
Biochemical Research Laboratory
1701 Building,
The Dow Chemical Company
Midland, Michigan

March 2, 1965

Dear Mr. Rowe:

This letter will indicate that The Dow Chemical Company is released from liability in case of adverse effects developing in human volunteers in the course of certain studies in which The Dow Chemical Company is interested. I assume full responsibility for any liabilities which may arise in connection with human testing. I might add that we have never encountered a problem in this respect. These are the terms which are obtained in all of our contracts with industry.

Very sincerely yours,

Albert M. Kligman, M.D.

AMK/a