API RESEARCH PROJECT ADVISORY COMMITTEE 1951 - 1954

meeting 1-21-5;

ESSO LABORATORIES

STANDARD OIL DEVELOPMENT COMPANY
P. O. BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR
HORACE W. GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST

INDUSTRIAL HYGIENE SECTION
NATHAN V. HENDRICKS, CH.E.
HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

March 26, 1954

Dr. George M. Saunders
Socony-Vacuum Oil Company, Inc.
26 Broadway
New York 4, New York

Dear Dr. Saunders:

I am very happy to submit to you the progress report of the Subcommittee on Carcinogenicity. It has been agreed by the members of this Subcommittee that there is no longer any need for the RP(MC-1) Advisory Committee and with your approval, this Advisory Committee is now being abolished. The total Subcommittee on Carcinogenicity will in the future serve the functions that the RP(MC-1) Advisory Committee used to perform, including periodic meetings with the Kettering Laboratory group to learn of the progress of the work at the Kettering Laboratory.

It is my suggestion that you may wish to submit this report of the Subcommittee on Carcinogenicity to the Medical and Health Committee of the Board at the time of its meeting in New Orleans on April 21st.

Very truly yours,

R. E. ECKARDT, M. D.

REE:ilk
Encl.

cc with encl. - Mr. D. V. Streep
Dr. A. Healey Horton

PROGRESS REPORT OF RP(MC-1) ADVISORY COMMITTEE

TO THE SUBCOMMITTEE ON CARCINOGENESIS

FOLLOWING A MEETING WITH THE KETTERING LABORATORY

on

January 21-22, 1954

This report serves as a supplement to the RPA Committee report dated September, 1953.

1. The Kettering Laboratory has submitted a manuscript entitled "An Analytical Method for Determination of Benzo (a) Pyrene in Complex Mixtures". It is the plan of the Kettering Laboratory to submit this manuscript for publication in the Journal of Analytical Chemistry on or about April 1, 1954. The Committee reviewed the manuscript and believes it suitable for publication. It is being forwarded to the appropriate authorities in the AFI for suitable action. Two further manuscripts are in the process of preparation entitled "Carcinogenesis of the Skin I and II", dealing with biological standardization techniques for carcinogenic testing. It is the plan to submit these to a journal similar to Cancer Research. The Committee is prepared to review these articles and make its recommendations concerning publication after they are received.

2. The manuscript reviewed describes a method for determining benzo (a) pyrene in complex mixtures such as petroleum oils. In the data given, various oils were found to contain from 0.0005% to 0.3% benzo (a) pyrene. Especially in oils ~~with an initial boiling~~ point below 600°F and a final boiling point above below 800°F the biologic potency of these oils on mice does not ~~always~~ correlate ~~quite~~ with the benzo (a) pyrene content, thereby suggesting other materials which may influence the potency on mice. When the ~~initial~~ final boiling point is 800°F or above, fair correlation between benzo (a) pyrene content and biologic activity has been observed.

3. In pursuing other factors which may influence the carcinogenicity of an oil to mice, the following leads are being pursued by the Kettering Laboratory:

a) Most petroleum hydrocarbons boiling in the range 500-650°F are probably accelerators. This includes paraffins from normal decane to hexa- or heptadecane and naphthalenes which have at least a butyl chain attached.

b) Materials boiling between 700-725°F probably contain phenanthrene-like carcinogens similar to benzo (c) phenanthrene.

c) Materials boiling between 725-800°F probably contain anthracene-like carcinogens, possibly cyclopentano benzanthracene.

d) Materials boiling above 800°F probably contain the benzo (a) pyrene.

4. Public interest has recently been stimulated in petroleum products and/or their combustion or oxidation products because of their possible relationship to pulmonary cancer incidence. The petroleum industry should be aware of this interest and not let itself get in the present unenviable position that the tobacco industry finds itself. However, suitable experimental methods are not available for the study of this problem, other than epidemiological studies. The importance of the epidemiological studies now being sponsored by the API is therefore emphasized.

REE:ilk

TOPICS ON EXPERIMENTAL PROGRAM FOR DISCUSSION, JANUARY 21, 1954

API RESEARCH PROJECT MC-1

1. Manuscript, "Analytical Method for Determination of Benzo[a]-pyrene in Complex Materials".
2. Progress in identification of carcinogens which are extracted by maleic anhydride.
3. Progress in identification of carcinogens responsible for potency of cracked sidestreams.
4. Manuscripts on biological tests on standards of reference, "Carcinogenesis of the Skin. I and II.".
5. Biological tests involving limited numbers of applications of carcinogenic oils.
6. Accelerating activity of paraffins and alkylnaphthalenes.
7. Comparative effects of hygiene on susceptibility to carcinogenicity of straight run paraffin distillate versus cracked fuel oil.

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MEDICAL RESEARCH DIVISION
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GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

January 4, 1954

Dr. R. A. Kehoe
The Kettering Laboratory
University of Cincinnati
College of Medicine
Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

I wrote you previously concerning the dates of January 21st and 22nd for a meeting of the RPA Committee at the Kettering Laboratory in Cincinnati. I am now simply writing to reconfirm these dates and to indicate that the Committee would like to meet with the Kettering Laboratory beginning at 1 p.m. on January 21st and continuing until noon on January 22nd, if this can be arranged with your group. We could either interrupt the meeting at 5:00 or 5:30 on January 21st and reconvene at about 9 a.m. on January 22nd, or at your convenience could continue the meeting into the evening of January 21st in an attempt to finish up all business in one day, if that is more convenient to you. In any event, I do not believe it will be necessary to decide this prior to our arrival in Cincinnati. However, it is the plan of the Committee to meet together prior to coming to the Laboratory so that we may have a little greater unanimity of opinion before we convene with your group and that is why we would like to start the meeting at 1 p.m. on January 21st.

As a tentative agenda for the meeting with your group we would suggest the following:

(1) Minutes of the last meeting.
(2) Report by Dr. Horton.
(3) Report by Dr. Phair.
(4) Report by Dr. Kehoe on budgetary matters.
(5) Points for discussion which have been agreed upon by the members of the Committee.
(6) Date and place of the next meeting.

It would be very greatly appreciated if Dr. Horton and Dr. Phair could have their reports, if they are going to have reports, in the hands of the members of the RPA Committee well in advance of the January 21st date so that we might all have the opportunity to review the reports constructively prior to our meeting and, therefore, be in a much better position to hold our discussions with your group.

This represents a slight departure from previous meetings of the RPA Committe but has been brought about by some dissatisfaction on the part of the members of the Committee with the progress of previous meetings of the Committee, and is being tried to see if this plan will accomplish more than our previous meetings were able to.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:ilk

cc: Dr. A. Healey Horton
Dr. F. F. Heyroth

Copies - Dr. Horton
Dr. Heyroth
Dr. Phair

ESSO LABORATORIES
Standard Oil Development Company
P. O. Box 51, Linden, N. J.

December 31, 1953

Dr. R. A. Kehoe
Dr. C. H. Hine
Dr. E. K. Linder
Dr. N. M. Newquist
Mr. E. W. Adams
Mr. L. C. Beard, Jr.
Mr. L. M. Henderson
Mr. R. C. Mithoff

Gentlemen:

Majority opinion seems t o indicate January 21st and 22nd as the most desirable date for the meeting of the RPA Committee. At present it is planned that the RPA Committee will meet in a downtown Cincinnati hotel room the morning of the 21st, will convene at the Kettering Laboratory that afternoon, will continue the discussion the morning of the 22nd if necessary, and hold a meeting in a downtown hotel the afternoon of the 22nd if this seems necessary.

A more detailed letter will be sent to each of you next week outlining a proposed agenda for the coming meeting.

Sincerely yours,

/s/ R. E. Eckardt
R. E. Eckardt, M. D.

REE:ilk

December 15, 1953

Dr. R. E. Eckardt
Esso Laboratories
Standard Oil Development Company
P. O. Box 51
Linden, New Jersey

Dear Doctor Eckardt:

Dr. Kehoe has asked me to write to you to confirm the date of January 7 for the meeting of the RPA Committee at the Kettering Laboratory. If, however, you should find that January 8 is preferable, I believe that that date will be satisfactory also.

I presume that you will advise us shortly of the Committee's choice.

Very truly yours,

E. R. Fortiage, Secretary to
Dr. Kehoe

ef

C. C.: Dr. A. W. Horton
Dr. J. J. Phair
Dr. F. F. Heyroth

ESSO LABORATORIES

STANDARD OIL DEVELOPMENT COMPANY

P. O. BOX 51, LINDEN, N.J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR
HORACE W. GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST

November 30, 1953

INDUSTRIAL HYGIENE SECTION
NATHAN V. HENDRICKS, CH.E.
HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

Messrs. C. H. Hine
E. K. Linder
M. N. Newquist
E. W. Adams
L. C. Beard, Jr.
L. M. Henderson
R. C. Mithoff

Gentlemen:

Since we have not had a meeting of the Research Project MC-1 Advisory Committee for some time, I am writing to suggest that we plan for such a meeting the first week in January, 1954. In order to permit weekend travel for those who have to come a long distance, I would suggest that the meeting be held on Friday and, therefore, would tentatively at this time suggest January 8th, the meeting to be held as usual in the Kettering Laboratory and to start at about 9:30 a.m. I would furthermore suggest, as a result of our last meeting, that you may wish to give consideration to having the meeting with the Kettering group on the 7th of January, leaving the 8th of January open for a meeting of the RPA Committee itself at one of the Cincinnati hotels and still having the weekend free for those who have a long distance to travel to get back home.

In the meantime, I would appreciate receiving from each of you suggestions for the agenda of this meeting and an expression as to whether or not you wish to hold the two-day meeting the 7th and 8th, or a one day meeting confined to the 8th. By carbon copy of this letter to the investigators at Kettering Laboratory, I am also asking for their suggestions as to the best meeting time for them. As soon as I have heard from all of you, I will inform you of the definite meeting time and place and a tentative agenda for the meeting.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:ilk

cc: Dr. R. A. Kehoe
Dr. A. W. Horton
Dr. J. J. Phair
Dr. F. F. Heyroth
Mr. D. V. Stroop

9/11 & 9/28/5
Return to auth

Copy from D. V. Stroop for Information of All Members and Associates of the Medical Advisory Committee October 13, 1953

ESSO LABORATORIES
Standard Oil Development Company
P. O. Box 51, Linden, N.J.

Medical Research Division Industrial Hygiene Section

October 8, 1953

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am enclosing a revised copy of the report of the RP (MC-1) Advisory Committee submitted on September 29, 1953 to the Subcommittee on Carcinogenicity of the API Medical Advisory Committee. By verbal arrangement with Dr. Davis it is my suggestion that you have this report duplicated and distributed to all members and associates of the Medical Advisory Committee.

Sincerely yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk
Enclosure

REPORT OF RP (MC-1) ADVISORY COMMITTEE SUBMITTED ON SEPTEMBER 29, 1953,

TO SUBCOMMITTEE ON CARCINOGENICITY, API MEDICAL ADVISORY COMMITTEE

SUMMARY OF THE API PROJECT ON CARCINOGENICITY AT KETTERING LABORATORY

The original program of carcinogenic work at Kettering Laboratory grew out of the results obtained from testing a series of 8 oils. The conclusion of this work, reported on November 5, 1948, was that all 8 oils affected the skin. Two of them produced mild irritation, two produced a few verrucous papillomata, one produced papillomas and two questionable cancers, two produced a definite cancer each, and one was highly carcinogenic.

As a result of these preliminary studies, the Kettering Laboratory undertook a more extensive research program under the auspices of the API Medical Asvisory Committee designed to 1) survey refining processes and materials which might represent potential hazards from the cancer standpoint, 2)biological testing of indicated oils and tars, 3) chemical research to determine the nature of the carcinogenic components and to develop analytical techniques for their determination, and 4) an epidemiological program to develop sound information regarding the actual incidence of cancer among employees of the petroleum industry and to determine the efficacy over a period of years of the various safety programs which have been or are being set up by individual oil companies.

To implement this program, it was suggested that materials from a number of process be studied, in accordance with the outline on pages 2 and 3 of the Kettering report dated October 27, 1950.

Non-Accelerating Solvents

In order to have a reference standard to which the results of tests of these oils could be referred, the laboratory undertook a study of the carcinogenicity of solutions of methylcholanthrene in benzene. For reasons related to well known dose-response phenomena it was decided to use the average latent period for tumor production as a measure of carcinogenicity, the average latent period being defined as the length of time required to reach 50% tumor indices.

In the course of this work with reference standards, it soon became apparent that C3H mice gave fairly reproducible results, whereas CFW mice gave less reproducible results. It was therefore decided to standardize the mouse strain and to use only C3H mice in subsequent tests, even though a considerable number of tests on oils with CFW mice had already been started or completed.

In additon, it became apparent that if too strong a solution of methylcholanthrene is painted on the C3H mice too frequently, the health of the mice, as determined by non-tumor mortality and weight curves, is impaired, and, apparently, their ability to produce tumors is impaired at the same time. In addition, other factors which influence the health of the mice, such as infections, infestations with lice, etc., also reflected in non-tumor mortality and growth rates, and will seriously affect tumor production. Thus, unhealthy animals frequently do not produce tumors as readily as healthy animals, and the

average latent period is prolonged in the unhealthy animals. Since the average latent period is taken as a measure of carcinogenicity, it is obvious that the apparent carcinogenicity of a meterial could be profoundly influenced by the health of the animals, and misleading results thereby obtained.

The above observations led to the necessity of painting mice once, twice or three times per week, depending on the strength of solution being used, and to the establishment of three or more separate standard curves, depending on the frequency of painting. The most recent report from the Kettering Laboratory, however, has shown that these three curves can be united into a single curve when they are expressed in terms of the dose of carcinogen applied per unit area of skin per week. This has necessitated measuring the area of skin covered by a solution of methylcholanthrene in a solvent. Within limits this has been found to be constant for each solvent tested. The solvents thus far tested have been benzene, hydro-peroxide-free amyl benzene, cotton seed oil, technical white oil and fractions of refinery streams. The effect of these solvents is their effect on the spreading of the solution. Thus, if the same amount of the same concentration of methylcholanthrene in two different solvents were to be painted on the skin 3 times a week, the dose per unit area need not be the same. If one solvent caused the solution to spread over twice the area of the other solvent, the dose per unit area in the first case would be half that in the second case, and the average latent period for the two solutions would be different, leading to different P_{MC} values for the two solutions. The P_{MC} value refers only to concentration of methylcholanthrene in benzene, and serves only as a reference standard. What this work implies is that it will be necessary in carcinogenic work to determine not only the frequency of application and the amount applied per application, but also the area covered by this amount.

Accelerating Solvents

What has been said above applies only to solutions of pure carcinogens in non-accelerating solvents. In the course of the work at the Kettering Laboratory it was observed that certain solvents, in addition to having an effect on the area of spread of the solution, also have a specific effect on the carcinogenicity of the solution. Thus it was found that different concentrations of methylcholanthrene in some solvents, even though they spread over the same area, have essentially the same average latent period. According to the above, this should not be the case since the dose per unit area should be different. In this case the area remains constant, the amount applied per application remains constant; but the concentration varies, and hence dose per unit area varies. Theoretically, therefore, the average latent period should vary, but actually this was not found to be the case. The explanation for this effect is that the solvent exerts some specific accelerating action on carcinogenesis. To summarize these two concepts, it may be well to give some equations. Thus, dose per unit area per week may be defined as follows:

$$d = \frac{mgm \times c \times f}{a}$$

where mgm = mgm of solution applied per application
c = concentration
f = number of applications per week
a = area covered

In the first case of 2 non-accelerating solvents with different spreading, mgm, c, and f were constant, but a varied, thereby influencing d. In the second case, mgm, f, and a were constant, but c varied, and hence d also was variable; but this did not influence average latent period. Hence two situations exist, one in which the rate of tumor formation is related directly to d, the other in which it is not. To date, dodecyl benzene, normal hexadecane, methyl naphthalene, cyclohexyl decane, phenyl dodecane, cetane and phenyl decane have been found to be accelerating solvents, although gasoline is not.

An interesting observation recently made is that if dodecyl benzene is applied once to the skin, and then serial biopsies taken, holes in the epithelium can be observed microscopically but not grossly. It has been postulated by the Kettering Laboratory that these holes provide foci of rapidly regenerating epithelium which may be responsible for the accelerating action observed.

Refinery Streams

As a result of the above information of a fundamental nature developed over the past several years, the Kettering Laboratory now believes that carcinogenic refinery streams may be divided into two main classes:

1). Those streams or materials in which P_{MC} is related to d.

2). Those streams or materials in which P_{MC} is not related to d.

In the first group fall those materials such as catalytically cracked residua in which carcinogen concentration is so high or accelerators relatively so low that the carcinogen concentration becomes of first importance as a measure of tumor activity in mice. In the second group, characterized by medium distillates, the carcinogen concentration is so low and the accelerator concentration relatively so high that the accelerators are more important in the rate of tumor production of the mouse skin than the carcinogens.

The laboratory has developed information which indicates that the accelerators are present in those refinery streams boiling from 450-650°F., while carcinogens are present in those streams boiling above 650-700°F. Thus in mixtures which have a wide boiling range, say from 450-1000°F., the carcinogenicity of the mixture may not be dependent alone on the amount of 700°F.+ material present, but also on the amount and nature of the 450-650°F. fraction.

In partial support of this concept, the laboratory has analyzed a series of refinery streams for their benzpyrene content, in accordance with a method developed by the laboratory, and have related the determined benzpyrene content to the P_{MC} (appendix II of January-September, 1953 Progress Report). These determinations indicate that the % BP/P_{MC} ratio essentially divides into two groups, those that run from 0.30 and higher, and those that run from 0.10 and lower. The first group of materials falls in the first class of refinery materials, and the second group into the second class.

Tables of P_{MC}

In the newly distributed tables of P_{MC} values distributed on September 1, 1953, essentially three types of results are given:

1). Those in which both the average latent period and the P_{MC} values are given in parentheses. It is the feeling of the laboratory that these results are open to serious errors in their accuracy due to uncontrollable variables in the biological experiments such as poor health, toxicity of applied materials, etc.

2). Those in which the average latent period is enclosed in parentheses but the P_{MC} value is not. These are pretty good experiments from a biological standpoint, but the laboratory still has some reservations about the accuracy.

3). Those in which neither the average latent period nor the P_{MC} values are enclosed in parentheses. These experiments are believed to be as good a biological experiment as it is possible to obtain.

Of the samples in these tables for which a P_{MC} value is given, 57 fall into the first group, 93 fall into the second group, and 27 fall into the third group. It is the feeling that the 57 samples which fall into type 1 results should be examined critically and some of them repeated and brought into a type 2 or 3 experiment. Since much of the validation of the theories of the laboratory is dependent upon accurate P_{MC} values, it is highly desirable that these P_{MC} values be made as accurate as biological experimentation will permit.

Another serious defect of these tables is that in some experiments, animals have been eliminated from the experiment because the laboratory believed that biologically it was unsound to include them. In several cases the results are based on as few as 6 animals. It is to be desired that no results will be finally reported unless a minumum number of 20 animals are included in the experiment. The Committee recognizes the validity of throwing out some animals, but feels that where this has been done, the experiment should be repeated to include at least 20 animals.

Other Observations

The laboratory has determined that washing is an effective way of reducing the carcinogenicity of an oil to the skin of the mouse. In general, the sooner the oil is washed off, the better. Limited experiments with barrier creams are difficult to interpret but the laboratory feels the use of barrier creams in accordance with recognized practice followed by washing may offer advantages greater than washing alone.

Epidemiology

The epidemiological data is accumulating in the laboratory, with some 1200 cases now having been reported. No definite trends are as yet

discernible but it was not anticipated that any such trends would be discernible prior to at least 5 years experience. It is hoped that the support which the General Committee, Division of Refining has given to the epidemiological study will stimulate renewed reporting of the cases with sufficient medical and occupational histories to permit some early correlations to be made about 1956.

Summary

1. The RP (MC-1) Advisory Committee believes that the Kettering Laboratory is performing important work in the field of carcinogenesis of refinery streams and materials. They believe that although a great many practical answers have already been obtained, the work should be pursued because the work of the laboratory promises to provide many fundamental answers to questions which now exist concerning industrial and occupational carcinogenesis.

2. It is believed that the work with non-accelerating solvents which relates the carcinogenic responses of a solution of pure carcinogen to the dose applied per unit area per week to the skin is of extreme fundamental importance. The Committee urges that additional work be conducted to establish firmly the curve which expresses this relationship.

3. It is also believed that the work with accelerating solvents is also of extreme fundamental importance and that this should be pursued vigorously in an attempt to develop a complete understanding of the relative role of carcinogens and accelerators in refinery streams and materials.

4. Since much of the correlation of chemical analyses with biological potency is dependent upon the accuracy of P_{MC} values, the Committee laments the fact that many of the P_{MC} values thus far reported are based on data which the laboratory recognizes as not having been obtained from the best biological experiment possible. The Committee suggests, therefore, that the laboratory devote considerable effort to repeating those experiments in an effort to develop P_{MC} values that are based on the soundest possible biological experiment.

5. The Committee believes that the work with washing techniques and protective creams may provide intensely practical guides to refinery hygiene practice and suggests that this work be pursued as new approaches appear to the laboratory.

6. The Committee recognizes that the epidemiological studies cannot be expected to produce significant results until at least 1956, and, therefore, urges that renewed efforts at adequate case and occupational history reporting be made during the next several years. It believes that adequate medical staffs can do most to insure the success of this program, and in this connection it acknowledges the stimulus that the General Committee, Division of Refining has given to the attainment of this objective.

7. The laboratory has already determined that a number of refinery streams and materials have a relatively high degree of carcinogenicity. Although data obtained with mice cannot be directly transposed to humans, there is sufficient data in occupational cancer experience to indicate that the

petroleum industry cannot take lightly the observations of the laboratory on the carcinogenicity of these refinery streams and materials.

8. The Committee recognizes that the laboratory at best can determine from its biological and chemical work only the relative carcinogenicity of various refinery streams and materials. The determination of the hazard is dependent upon factors of extent, frequency, duration, and length of exposure. As recognized by the laboratory in Dr. Kehoe's talk to the members of the General Committee, Division of Refining the determination of the hazard is at present a function of the individual petroleum companies. Adequate medical and industrial hygiene staffs are essential in these individual companies if they are adequately to appraise the hazard. The Committee supports Dr. Kehoe's plea that petroleum company managements recognize this truism and make plans for the development of such adequate medical and industrial hygiene staffs.

9. It is apparent that the laboratory has accumulated sufficient data that publication of results will be deemed desirable in the near future. The Committee recognizes the right of the laboratory to publish, and urges that the mechanism be established so that these publications can be reviewed in a finite period of time. As a suggestion, it is proposed that this mechanism be so established that review by API management and suggestions and criticisms for the laboratory from API management be made available within sixty (60) days. If no criticisms or suggestions are obtained by the laboratory at the expiration of this time, the laboratory can assume that none are forthcoming and proceed with publication. It should be recognized that this review is for the purpose of helpful criticisms and suggestions, and not for the determination of whether or not there will be publication, since the contract with the laboratory clearly states that the laboratory determines if and when publication occurs.

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October 7, 1953

Page 6 of 7 pages
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ESSO LABORATORIES
STANDARD OIL DEVELOPMENT COMPANY
P. O. BOX 51, LINDEN, N.J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D., DIRECTOR
HORACE W. GERARDE, PH.D., M.D., HEAD TOXICOLOGIST

September 22, 1953

INDUSTRIAL HYGIENE SECTION
NATHAN V. HENDRICKS, CH.E., HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S., INDUSTRIAL HYGIENISTS

Dr. Kieffer Davis
Phillips Petroleum Company
Bartlesville, Oklahoma

Dear Dr. Davis:

As new Chairman of the RPA Committee, I have prepared the attached report summarizing the activities of the Kettering Laboratory as I see them to the present time. It would be my intention to present this to the Subcommittee on Carcinogenicity meeting in Houston as a formal report of our RPA Committee to the Subcommittee. Because of the unavailability of time to obtain approval from each of the RPA Committee members, I am unable to claim this as a full RPA Committee report. However, I plan to arrive in Houston at about two o'clock Monday afternoon, September 28th, and have a reservation at the Shamrock Hotel beginning in the evening. I would be happy to go over this report with any and/or all members of the RPA Committee that evening in order to introduce any corrections or suggestions that might seem warranted, or, if the Committee so decides, to abandon this report altogether. For any members of the RPA Committee who will not be in Houston Monday evening, I would suggest that they write me their criticisms and suggestions at the Shamrock Hotel and they will be taken into consideration at the discussions which the rest of the Committee will hold that evening.

I am sending three copies of this report to Dr. Horton with the suggestion that if he has any comments which he feels I should have included in this report, or if he disagrees with our interpretation of the work of the Kettering Laboratory, he will be in a position to advise me of the opinion of the Laboratory Monday evening in Houston. The two extra copies of the report being sent to Dr. Horton are for Dr. Kehoe and Dr. Flair.

I realize that this report cannot be a complete summary of all of the work done by the Kettering Laboratory, otherwise it would have to be too long, but I do feel that it represents, at least in my mind, the important observations which have been made thus far by the Kettering Laboratory, and in the summary emphasizes the important points that should be pursued in the work of the Laboratory. It is my hope that our RPA Committee, if not wishing to accept this report, will deem it advisable to prepare a report somewhat similar to this one which can be submitted to the Subcommittee on Carcinogenesis at the Houston meeting. If it is agreeable with this Committee and with you, it would be my plan to read this report

before the Subcommittee on Tuesday morning and then to have copies made available to each of the members of the Subcommittee on Carcinogenesis following the Houston meeting. Furthermore, it would be my suggestion that the Subcommittee may wish to consider sending a report similar to this to the Medical Advisory Committee with the suggestion that it be forwarded to the Safety Committee of the Board of Directors of the API.

As I have indicated above, the report which I am sending to you now should be considered only as my own rough draft of such a report, representing only my ideas, and subject to the approval of the other members of the RPA Committee. I trust that our RPA Committee will be able to come to some agreement on this report Monday evening in Houston prior to the meeting of the Subcommittee on Carcinogenesis.

Sincerely,

R. E. ECKARDT, M. D.

REE:ilk

Attachment

cc with attachment: Dr. C. H. Hine
Dr. P. K. Linder
Dr. M. N. Hoxquist
Mr. E. J. Adams
Dr. L. C. Beard, Jr.
Mr. L. M. Henderson
Mr. R. C. Mithoff
Dr. A. Wesley Horton (3) ✓
Mr. D. V. Stroop

REPORT OF RPA COMMITTEE SUBMITTED ON SEPTEMBER 29, 1953.

TO SUBCOMMITTEE ON CARCINOGENESIS, API MEDICAL ADVISORY COMMITTEE

SUMMARY OF THE API PROJECT ON CARCINOGENESIS AT KETTERING LABORATORY

The original program of carcinogenic work at Kettering Laboratory grew out of the results obtained from testing a series of 8 oils. The conclusion of this work, reported on November 5, 1948, was that all 8 oils affected the skin. Two of them produced mild irritation, two produced a few verrucous papillomata, one produced papillomas and two questionable cancers, two produced a definite cancer each, and one was highly carcinogenic.

As a result of these preliminary studies, the Kettering Laboratory undertook a more extensive research program under the auspices of the API Medical Advisory Committee designed to 1) survey refining processes and materials which might represent potential hazards from the cancer standpoint, 2) biological testing of indicated oils and tars, 3) chemical research to determine the nature of the carcinogenic components and to develop analytical techniques for their determination, and, 4) an epidemiological program to develop sound information regarding the actual incidence of cancer among employees of the petroleum industry and to determine the efficacy over a period of years of the various safety programs which have been or are being set up by individual oil companies.

To implement this program, it was suggested that materials from a number of processes be studied, in accordance with the outline on pages 2 and 3 of the Kettering report dated October 27, 1950.

Non-accelerating Solvents

In order to have a reference standard to which the results of tests of these oils could be referred, the laboratory undertook a study of the carcinogenicity of solutions of methyl cholanthrene in benzene. For reasons related to well known dose-response phenomena it was decided to use the average latent period for tumor production as a measure of carcinogenicity, the average latent period being defined as the length of time required to reach 50% tumor indices.

In the course of this work with reference standards, it soon became apparent that C3H mice gave fairly reproducible results, whereas CFW mice gave less reproducible results. It was, therefore, decided to standardize the mouse strain and to use only C3H mice in subsequent tests, even though a considerable number of tests on oils with CFW mice had already been started or completed.

In addition, it became apparent that if too strong a solution of methyl cholanthrene is painted on the C3H mice too frequently, the health of the mice, as determined by non-tumor mortality and weight curves, is impaired, and, apparently, their ability to produce tumors is impaired at the same time. In addition, other factors which influence the health of the mice, such as infections, infestations with lice, etc., are also reflected in non-tumor mortality and growth rates, and will seriously affect tumor production. Thus unhealthy animals ~~from any cause~~ frequently do not produce tumors as readily as healthy animals, and the average latent period is prolonged in the unhealthy animals. Since the average latent period is taken as a measure of carcinogenicity, it is obvious that the apparent carcinogenicity of a material could be profoundly influenced by the health of the animals, and misleading results thereby obtained.

The above observations led to the necessity of painting mice once, twice, or three times per week depending on the strength of solution being used, and to the establishment of three or more separate standard curves depending on the frequency of painting. The most recent report from the Kettering Laboratory, however, has shown that these three curves can be united into a single curve when they are expressed in terms of the dose of carcinogen applied per unit area of skin per week. This has necessitated measuring the area of skin covered by a solution of methyl cholanthrene in a solvent. Within limits this has been found to be constant for each solvent tested. The solvents thus far tested have been benzene, hydro-peroxide-free amyl benzene, cotton seed oil, technical white oil and fractions of refinery streams. The effect of these solvents is their effect on the spreading of the solution. Thus if the same amount of the same concentration of methyl cholanthrene in two different solvents were to be painted on the skin 3 times a week, the dose per unit area need not be the same. If one solvent caused the solution to spread over twice the area of the other solvent, the dose per unit area in the first case would be half that in the second case, and the average latent period for the two solutions would be different, leading to different P_{MC} values for the two solutions. The P_{MC} value refers only to concentration of methyl cholanthrene in benzene, and serves only as a reference standard. What this work implies is that it will be necessary in carcinogenic work to determine not only the frequency of application and the amount applied per application, but also the area covered by this amount.

Accelerating Solvents

What has been said above applies only to solutions of pure carcinogens in non-accelerating solvents. In the course of the work at the Kettering Laboratory it was observed that certain solvents, in addition to having an effect on the area of spread of the solution also have a specific effect on the carcinogenicity of the solution. Thus it was found that different concentrations of methyl cholanthrene in some solvents, even though they spread over the same area, have essentially the same average latent period. According to the above, this should not be the case since the dose per unit area should be different. In this case the area remains constant, the amount applied per application remains constant, but the concentration varies, and hence dose per unit area varies. Theoretically, therefore, the average latent period should vary, but actually this was not found to be the case. The explanation for this effect is that the solvent exerts some specific accelerating action on carcinogenesis. To summarize these two concepts, it may be well to give some equations. Thus dose per unit area per week may be defined as follows:

$$d = \frac{mgm \times c \times f}{a}$$

where mgm = mgm of solution applied per application

c = concentration (wt %)

f = number of applications per week

a = area covered

In the first case of 2 non-accelerating solvents with different spreading, mgm, c, and f were constant but a varied, thereby influencing d. In the second case, mgm, f, and a were constant but c varied and hence d also was variable.

but this did not influence average latent period. Hence two situations exist, one in which the rate of tumor formation is related directly to d, the other in which it is not. To date dodecyl benzene and normal hexadecane have been found to be accelerating solvents, although gasoline is not.

An interesting observation recently made is that if dodecyl benzene is applied once to the skin, and then serial biopsies taken, holes in the epithelium can be observed microscopically but not grossly. It has been postulated by the Kettering Laboratory that these holes provide foci of rapidly regenerating epithelium which may be responsible for the accelerating action observed.

Refinery Streams

As a result of the above information of a fundamental nature developed over the past several years, the Kettering Laboratory now believes that carcinogenic refinery streams may be divided into two main classes:

1). Those streams or materials in which P_{MC} is related to d.

2). Those streams or materials in which P_{MC} is not related to d.

In the first group fall those materials such as catalytically cracked residua in which carcinogen concentration is so high or accelerators relatively so low that the carcinogen concentration becomes of first importance as a measure of tumor activity in mice. In the second group, characterized by medium distillates, the carcinogen concentration is so low and the accelerator concentration relatively so high that the accelerators are more important in determining the incidence of producing tumors of the mouse skin than the carcinogens.

The laboratory has developed information which indicates that the accelerators are present in those refinery streams boiling from 450-650°F., while carcinogens are present in those streams boiling above 650-700°F. Thus in mixtures which

have a wide boiling range, say from 450-1000°F., the carcinogenicity of the mixture may not be dependent alone on the amount of 700°F. + material present, but also on the amount and nature of the 450-650°F. fraction.

In partial support of this concept, the laboratory has analyzed a series of refinery streams for their benzpyrene content, in accordance with a method developed [redacted] and have related the determined benzpyrene content to the P_{MC} (appendix II of January - September, 1953, Progress Report). These determinations indicate that the % BP/P_{MC} ratio essentially divides into two groups, those that run from 0.30 and higher, and those that run from 0.10 and lower. The first group of materials falls in the first class of refinery materials, and the second group into the second class. In three instances (API[6], 71 and 91) this ratio lay between 0.1 and 0.3, and these three oils may warrant further study. —— why these 3 particularly?

Tables of P_{MC}

In the newly distributed tables of P_{MC} values distributed on September 1, 1953, essentially three types of results are given:

1). Those in which both the average latent period and the P_{MC} values are given in parentheses. It is the feeling of the laboratory that these results are open to serious errors in their accuracy due to uncontrollable variables in the biological experiments such as poor health, toxicity of applied materials, etc.

2). Those in which the average latent period is enclosed in parentheses but the P_{MC} value is not. These are pretty good experiments from a biological standpoint, but the laboratory still has some reservations about the accuracy.

3). Those in which neither the average latent period nor the P_{MC} value are enclosed in parentheses. These experiments are believed to be as good a biological experiment as it is possible to obtain.

Of the samples in these tables for which a P_{MC} value is given, 57 fall into the first group, 93 fall into the second group, and 27 fall into the third group. It is the feeling of this writer (and I hope the remaining members of the RPA Committee) that the [redacted] samples which fall into type 1 and [redacted] results can be repeated and brought into a type 3 experiment. Since much of the validation of the theories of the laboratory is dependent upon accurate P_{MC} values, it is highly desirable that these P_{MC} values be made as accurate as biological experimentation will permit.

Another serious defect of these tables is that in some experiments, animals have been eliminated from the experiment because the laboratory believed that biologically it was unsound to include them. In several cases the results are based on as few as 6 animals. It is to be desired that no results will be reported unless a minimum number of 20 animals are included in the experiment. The Committee recognizes the validity of throwing out some animals, but feels that where this has been done the experiment should be repeated to include at least 20 animals.

Other Observations

The laboratory has determined that washing is an effective way of reducing the carcinogenicity of an oil to the skin of the mouse. In general, the sooner the oil is washed off the better. Limited experiments with white oil wash and barrier creams are difficult to interpret, [redacted], or the use of barrier creams in association with washing, may offer advantages greater than with washing alone.

Epidemiology

The epidemiological data is accumulating in the laboratory, with some 1200 cases now having been reported. No definite trends are as yet discernible but it was not anticipated that any such trends would be discernible prior to at least 5 years experience. It is hoped that the support which the General Committee, Division of Refining has given to the epidemiological study will stimulate renewed reporting of cases with sufficient medical and occupational histories to permit some early correlations to be made about 1956.

Summary

1. The RPA Committee believes that the Kettering Laboratory is performing important work in the field of carcinogenesis of refinery streams and materials. They believe that although a great many practical answers have already been obtained, the work should be pursued because the work of the laboratory promises to provide many fundamental answers to questions which now exist concerning industrial and occupational carcinogenesis.

2. It is believed that the work with non-accelerating solvents which relates the carcinogenic response of a solution of pure carcinogen to the dose applied per unit area per week to the skin is of extreme fundamental importance. The Committee urges that additional work be conducted to establish firmly the curve which expresses this relationship.

3. It is also believed that the work with accelerating solvents is also of extreme fundamental importance and that this should be pursued vigorously in an attempt to develop a complete understanding of the relative role of carcinogens and accelerators in refinery streams and materials.

4. Since much of the correlation of chemical analyses with biological potency is dependent upon the accuracy of P_{MC} values, the Committee laments the fact that many of the P_{MC} values thus far reported are based on data which the laboratory recognizes as not having been obtained from the best biological experiment possible. The Committee suggests, therefore, that the laboratory devote considerable effort to repeating those experiments in an effort to develop P_{MC} values that are based on the soundest possible biological experiment.

5. The Committee believes that the work with washing techniques and protective creams may provide intensely practical guides to refinery hygiene practice and suggests that this work be pursued as new approaches appear to the laboratory.

6. The Committee recognizes that the epidemiological studies cannot be expected to produce significant results until at least 1956, and, therefore, urges that renewed efforts at adequate case and occupational history reporting be made during the next several years. It believes that adequate medical staffs can do most to insure the success of this program, and in this connection it acknowledges the stimulus that the General Committee, Division of Refining has given to the attainment of this objective.

7. The laboratory has already determined that a number of refinery streams and materials have a relatively high degree of carcinogenicity. Although data obtained with mice cannot be directly transposed to humans, there is sufficient data in occupational cancer experience to indicate that the petroleum industry cannot take lightly the observations of the laboratory on the carcinogenicity of these refinery streams and materials.

8. The Committee recognizes that the laboratory at best can determine from its biological and chemical work only the relative carcinogenicity of various refinery streams and materials. The determination of the hazard is

dependent upon factors of extent, frequency, duration, and length of exposure. As recognized by the laboratory in Dr. Kehoe's talk to the members of the General Committee, Division of Refining the determination of the hazard is at present a function of the individual petroleum companies. Adequate medical and industrial hygiene staffs are essential in these individual companies if they are adequately to appraise the hazard. The Committee supports Dr. Kehoe's plea that petroleum company managements recognize this truism and make plans for the development of such adequate medical and industrial hygiene staffs.

9. It is apparent that the laboratory has accumulated sufficient data that publication of results will be deemed desirable in the near future. The Committee recognizes the right of the Laboratory to publish, and urges that the mechanism be established so that these publications can be reviewed in a finite period of time. As a suggestion, it is proposed that this mechanism be so established that review by API management and suggestions and criticisms for the laboratory from API management be made available within sixty (60) days. If no criticisms or suggestions are obtained by the laboratory at the expiration of this time, the laboratory can assume that none are forthcoming and proceed with publication. It should be recognized that this review is for the purpose of helpful criticisms and suggestions, and not for the determination of whether or not there will be publication, since the contract with the laboratory clearly states that the laboratory determines if and when publication occurs.

ESSO LABORATORIES

STANDARD OIL DEVELOPMENT COMPANY

P.O. BOX 51, LINDEN, N.J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D. DIRECTOR
HORACE W. GERARDE, PH.D., M.D. HEAD TOXICOLOGIST

August 20, 1953

INDUSTRIAL HYGIENE SECTION
NATHAN V. HENDRICKS, CH.E. HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S. INDUSTRIAL HYGIENISTS

Dr. R. C. Mithoff
California Research Corporation
200 Bush Street
San Francisco 4, California

Dear Dr. Mithoff:

In response to your letter of August 17, 1953, I am listing the seven points which Dr. Beard outlined in his letter to me of April 22, 1953.

In view of the fact that you have expressed interest in these seven points prior to the meeting, I am also sending a copy of Dr. Beard's questions to all of the other members of our committee.

I shall look forward to seeing you in Cincinnati.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:ilk

Attach.

cc with attach. - Messrs. C. H. Hine
E. K. Linder
M. N. Newquist
E. W. Adams
L. C. Beard, Jr.
L. M. Henderson
R. A. Kehoe
A. W. Horton
J. J. Phair
F. F. Heyroth
K. Davis
D. V. Stroop

(Taken from letter to Dr. R. E. Eckardt from Dr. L. C. Beard, Jr., 4/22/53)

1) Establish by mouse tests on successive raffinates the efficacy of multiple extractions with furfural to remove carcinogens from a carcinogenic lubricating oil fraction; say from a 100" paraffin oil from Mid-Continent crude.

Trying to establish first relationship between case of carcinogens, case of accelerators and latent period

2) Continue to completion work to determine if viscosity has a physical effect in delaying the appearance of papilloma.

114 and 114-1

3) Determine if asphalts from catalytic cracked residua have carcinogenic properties. Refer Dr. Kieffer Davis' letter March 9, 1953. Does their solid nature prevent skin absorption and subsequent cancer? – Not in humans – see pitch workers, chimney sweeps, etc

4) Mr. Mackenzie at one time urged to paint a cage of mice with a carcinogenic petroleum fraction until the appearance of the first papilloma in any one mouse and then to stop painting and just observe. These data are requisite to answer the question as to whether we may have latent cases which can bloom forth later. I know that with beta naphthylamine this can occur. Can it occur with petroleum aromatics?

See new sig! on Table IV

5) What are the comparative carcinogenic effects of concentration x on 2y square centimeters versus concentration 2x on y square centimeters? In other words, what are the relative effects of concentration and surface area painted? Oils must be classified according to chem. composition to answer this quest

6) Using a relative weak carcinogen such as Mid-Continent 100" paraffin oil, what lengthening of the latent period is obtained in cycles comparable to cutting-oil operators washing for lunch and at the end of an 8-hour shift?

See washing exp. on A PI-56

7) Should we implement a critical survey of the epidemiologic literature to determine the relative incidence of cancer of the skin in metal workers (cutting oils), garage mechanics (motor oils)?

(Very little literature; see eg (Muhlbock) ask JP

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FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S. INDUSTRIAL HYGIENISTS

August 6, 1953

C. H. Hine, M. D.
E. K. Linder, M. D.
M. N. Newquist, M. D.
E. W. Adams
L. C. Beard, Jr.
L. M. Henderson
R. C. Mithoff

Gentlemen:

Having just returned from a pleasant three weeks in New Hampshire, I am now in a position to tally your suggestions as to the meeting at the Kettering Laboratory in Cincinnati. Thus far, six members of the Committee and Dr. Kehoe have felt that a meeting somewhat in advance of the Houston meetings would be advisable and all have agreed that Friday, September 11 would be a satisfactory date. May I offer my apologies to all of you for having stated that this Friday was September 10 in my first correspondence with you all. Each of you carefully pointed out that Friday is September 11, and on checking my calendar, I find that you are all quite correct. Therefore, I would suggest that our Committee plan to meet in the Kettering Laboratory at about 9 a.m. on the morning of Friday, September 11, 1953.

At the moment, I would suggest the following as a tentative agenda:

(1) Approval of the minutes of the last meeting.
(2) Progress report and outline of future work by Dr. Horton.
(3) Progress report and outline of future work by Dr. Phair.
(4) Budgetary discussion by Dr. Kehoe.
(5) Summary of Dr. Horton's visit to Europe this summer.
(6) Seven proposals by Dr. Beard which should receive discussion by the Committee.
(7) Any new items by members of the Committee.
(8) The time and place of the next meeting of the Committee. (Presumably to be held at the Shamrock Hotel in Houston in conjunction of the meeting of the full Subcommittee on Carcinogenicity on September 29, 1953.)

I shall look forward to seeing you all at the meeting in Cincinnati and to receiving from any of you additional suggestions for items to be included on the agenda of our September 11th meeting.

Sincerely yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:gch
cc: Dr. R. A. Kehoe
Dr. A. W. Horton
Dr. J. J. Phair
Dr. F. F. Heyroth
Dr. K. Davis
Mr. D. V. Stroop

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INDUSTRIAL HYGIENE SECTION
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HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

June 26, 1953

C. H. Hine, M. D.
H. K. Linder, M. D.
M. M. Newquist, M. D.
E. V. Adams
L. C. Beard, Jr.
L. M. Henderson
R. C. Mithoff

Gentlemen:

It has been suggested by several of the members of the Research Project NC-1 Advisory Committee that our committee should meet in Cincinnati sometime prior to the scheduled meeting in Houston on September 29th. You will remember that the September 29th meeting is being planned as a joint meeting of our Research Project NC-1 Committee with the whole Subcommittee on Carcinogenicity and several members of the smaller committee have felt that it would make it impossible to accomplish our best effectively in such a large meeting. Therefore, a preliminary meeting at Cincinnati has been suggested in order to dispose of some of the details of the Kettering Laboratory work which could not so easily be presented to the total Subcommittee on Carcinogenicity. Such things as budget and detailed discussion of some of the results could be accomplished in the smaller meeting. I am writing therefore to suggest that our RPNC-1 Committee meet in Cincinnati on Friday, September 10, 1953. I am suggesting this date in order that those who have far to travel will be able to return on the weekend without loss of time from work and because I will be in attendance at the Gordon Research Conference on Cancer until September 4th.

I would appreciate hearing from each of you whether this date is satisfactory and whether I should proceed with plans with the Kettering Laboratory to arrange such a meeting.

Sincerely yours,

R. E. Eckardt.

R. E. ECKARDT, M. D.

cc: Dr. R. A. Kehoe
Dr. A. W. Horton
Dr. J. J. Fhair
Dr. F. F. Heyroth

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MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH. D., M. D.
DIRECTOR
N. V. HENDRICKS, B. E., CH. E.
DIRECTOR, INDUSTRIAL HYGIENE SECTION

P. O. BOX 51, LINDEN, N. J.

April 7, 1953

To: M. N. Newquist, M. D.
E. K. Linder, M. D.
C. H. Hine, M. D.
L. C. Beard, Jr.
K. G. Mackenzie
R. M. Landon
R. C. Mithoff
E. W. Adams
R. M. Shepardson

Gentlemen:

Tentatively, the Sixth Meeting of the RP (MC-1) Advisory Committee is being scheduled as a joint meeting with the Subcommittee on Carcinogenicity for September 29, 1953 at the Shamrock Hotel, Houston, Texas.

I would very greatly appreciate it if each of you would send to me suggested topics for inclusion in the agenda of this joint meeting prior to September 1, 1953. This will permit me to circularize the agenda of the meeting to you and to the members of the Subcommittee on Carcinogenicity prior to the time of this meeting.

Very truly yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:gah

cc: Kieffer Davis, M. D.
R. A. Kehoe, M. D.
J. J. Phair, M. D.
A. W. Horton ✓
F. F. Heyroth, M. D.

Meeting 1-16-

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

March 13, 1953

To Members and Associates
Subcommittee on Carcinogenicity

Phillips	Kieffer Davis M.D. (Chairman)	R. C. Cole
Sinclair	Marshall Clinton M.D.	L. C. Beard, Jr.
Std Cal	L. E. Curtis M.D.	R. C. Mithoff
SOD	Robert E. Eckardt M.D.	R. M. Shepardson
Gulf	F. D. Gassoway M.D.	R. M. Landon
Shell	C. H. Hine M.D.	L. C. Burroughs
Carbide	E. K. Linder M.D.	R. D. Bent
Texas	M. N. Newquist M.D.	Allan E. Dooley
Schw	James W. Osborn M.D.	F. J. Sanders
SO Indiana	B. B. Reeve, M.D.	E. W. Adams
Pure		
	L. M. Henderson	

Gentlemen:

At the request of Doctor Newquist, we enclose agenda and minutes of Fifth Meeting - RP (MC-1) Advisory Committee held January 16, 1953.

Very truly yours,

WStroop

DVS: jb
mc: Members and Associates
Medical Advisory Committee
Drs. A. Wesley Horton
Robert A. Kehoe
John J. Phair

FOR INFORMATION ONLY NOT FOR PUBLICATION

AGENDA AND MINUTES OF THE FIFTH MEETING RP(MC-1) ADVISORY COMMITTEE KETTERING LABORATORY, UNIVERSITY OF CINCINNATI January 16, 1953 9:30 A.M. E.S.T.

AGENDA

1. Approval of minutes of Fourth Meeting held 9/24/52
2. Progress report - Dr. A. W. Horton, Ph.D.
3. Progress report on Epidemiological Survey - Dr. J. J. Phair
4. Research activities for the year beginning 7/1/53
   - Chemical and biological - Dr. A. W. Horton, Ph.D
   - Epidemiological - Dr. J. J. Phair
   - Budgetary allocations - Dr. R. A. Kehoe
5. Report of the Committee on the Carcinogenic action of Mineral Oils to the Medical Research Council (Great Britain) on their "First Three Years' Work"
6. Communications with Dr. Paul Kotin, University of Southern California
7. Other
8. Time and place of next meeting (MAC meets Hotel Shamrock - Houston 9/30/53)

MINUTES

The Fifth Meeting of the RP(MC-1) Advisory Committee was convened in Dr. Kehoe's office at the Kettering Laboratory of the University of Cincinnati at 9:30 A.M., January 16, 1953. In attendance were the following:

M. N. Newquist, M.D.
R. E. Eckhardt, M.D., Ph.D.
E. K. Linder, M.D.
Kieffer Davis, M.D.
C. H. Hine, M.D., Ph.D.
R. A. Kehoe, M.D.
F. F. Heyroth, M.D., Ph.D.
J. J. Phair, M.D.
A. W. Horton, Ph.D
L. C. Beard, Jr., Ph.D.
K. G. Mackenzie B.S. (M.S.?)
R. M. Landon, B.E.?
R. C. Mithoff, Ph.D
E. W. Adams, Ph.D
R. M. Shepardson B.E.?

ITEM 1

The minutes of the Fourth Meeting of the RP(MC-1) Advisory Committee were approved. Subsequently the meeting followed the agenda which had been prepared by Dr. Newquist prior to the meeting with slight modification in that the progress report and the research activities for the year beginning 7/1/53 were combined in both Dr. Horton's and Dr. Phair's reports.

ITEMS 2 AND 4 - DR. HORTON'S REPORT

As the basis for his discussions, Dr. Horton used the attached "Memorandum from the Kettering Laboratory-Fifth Meeting of the Advisory Committee API Research Project MC-1" dated January 16, 1953. Considerable discussion was given to the opening two paragraphs which justified the use of mice in appraising the hazards of skin cancer in workmen. In response to a specific question from Dr. Adams, Dr. Horton stated that washing is more effective in reducing carcinogenic potency than a reduction in the dosage of carcinogen applied. As evidence he presented the experimental evidence which was obtained with washing experiments with API-8 and API-113. It was then suggested that consideration be given to a washing experiment with API-113 and API-57 in which these oils would be painted on at a level of 100 mg. two times a week and washed off after 9 hours in contact with the skin.

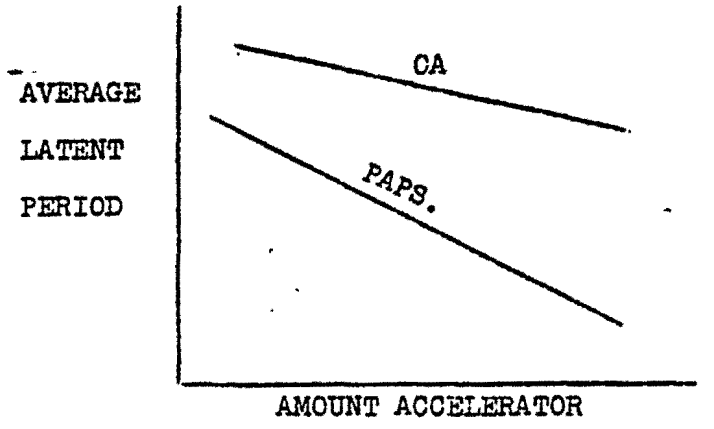
Perhaps the greatest interests in Dr. Horton's report are his observations or theories that the potency of a particular material is dependent less on the amount of carcinogen than on its concentration; whereas, the effect of accelerators is dependent less on the concentration than on the total amount applied at each application. Although this is an interesting thought, it appears somewhat

difficult to understand how this could be the situation and how the proper definitive experiments could be conducted in order to conclusively establish these observations. The concept that accelerators may act because of their similarity in structural configuration with the carcinogenic agents is an interesting one insofar as it applies to benzo(c)phenanthrene and highly branched dodecylbenzene. It is difficult, however, to see how this concept could apply to compounds like 3,4-benzpyrene or to dodecylbenzene in which the side chain is not highly branched.

The formula presented by Dr. Horton on page 9 of his report is an extremely interesting formula from a theoretical standpoint, but whether it will ever have any practical application seems highly problemmatical since the determination of the effective concentration of accelerator in an oil may be extremely difficult, particularly if there is more than one accelerator present in such an oil. Similarly, such a formula allows for the presence of only two carcinogens, namely, benzpyrene and one C4 aromatic. It seems highly unlikely that there would be only two carcinogens present in as complex a mixture as slurry oil, and this is partially borne out by the observations reported by the Standard Oil Development Company in which 6-isopropyl benzanthracene was determined in a relative state of purity from one of these oils. It therefore seems likely that this formula will be exceedingly complicated by a great number of accelerators and inhibitors, such that the effective concentration of accelerator will have to be determined for each individual oil, and also by the presence of a large number of carcinogenic compounds, which will highly complicate the usefulness of any such equation.

Another interesting observation made by Dr. Horton during

his discussion was that the average latent period decreases more rapidly for papillomas, depending upon the amount of accelerator, than the average latent period for carcinomas. This may be graphically expressed somewhat as follows:



ITEMS 2 AND 4 - DR. PHAIR'S REPORT

Dr. Phair used as a basis of his report the attached memorandum, which is essentially a tabular summary of the number of cases which he has thus far collected from the various companies. It appears that an increasing number of companies are participating in reporting cases to Dr. Phair but that there is a heavy imponderance of cases being reported from companies along the eastern seaboard as compared with companies in southwestern United States. It was agreed that Dr. Phair would outline briefly and send to the Chairman of the Subcommittee on Carcinogenicity his latest thoughts on pertinent data which he wishes to have included in the current reporting of cancer cases among employes in the petroleum industry, and that the Chairman of the Subcommittee on Carcinogenicity would then reattempt to stimulate all medical directors to report current cases to Dr. Phair.

ITEM 4 - DR. KEHOE'S REPORT

Dr. Kehoe discussed the budgetary allocations of funds and indicated that it would be possible for the Kettering Laboratory to live within the presently assigned budget of $79,000, but that it must be remembered that this will result in approximately one-quarter less work being done during the year July 1, 1953-June 30, 1954. Dr. Kehoe wished to reserve the right to allocate funds under any of the headings given, depending upon the Kettering Laboratory's estimation of how the funds should be allocated. Thus, for instance, if full cooperation with Dr. Phair is not obtained, it may well be that the $17,500 allocated for epidemiological work may be re-allocated into other phases of the Research Project. There seems to be a general agreement among the members of the committee that Dr. Kehoe should have freedom in allocating the total funds to any of the four phases of the project that he feels the funds should be allocated to. Dr. Kehoe also made a plea that if there is a determined effort to have a gradual reduction in the budget of this project during the coming years, he would like to be informed of this as far in advance as possible so that he might make his plans accordingly. Thus, if the budget is to be cut one-half in the Year July 1, 1954-June 30, 1955, and to a quarter of its present figure in the succeeding years, Dr. Kehoe would like to know of this as soon as possible.

ITEM 5

Dr. Horton discussed the report from the British on the carcinogenicity of the mineral oils. He felt that their tests had been performed with applications of oil which were so small that they are not getting tumors in the mice, yet they were observing

tumors in the rabbits due to the effects of accelerators. He seemed to feel that the fractionation of their oils left much to be desired, and that same fractionation of oils in his laboratories, which were then applied on his own animals by his own techniques, had resulted in the appearance of a considerable number of tumors, particularly in the K-4, L-4 and O-4 fractions. He felt that this was probably the result principally of accelerators, and that the carcinogens would be found in the highest concentrations in the K-5, L-5 and O-5 residues. It was suggested at the meeting that the workers at the Kettering Laboratory feel free to communicate on a professional basis with the workers in England in discussing their mutual work, and furthermore, it was felt that if the Kettering Laboratory felt they would like to keep this communication in the established channels, this could be done by having Dr. Horton prepare a critique of the British work and then having Dr. Newquist forward this to the British workers through Colonel Auld. It is evident that it is too early to draw conclusions with respect to the British work which has been reported thus far.

ITEM 6

Dr. Kehoe indicated that he has written a supplemental letter to Dr. Kotin suggesting that Dr. Kotin more definitely outline what information he would like to receive in order that the Kettering Laboratory might be able to provide it to him. Dr. Kehoe did not feel that any of the Kettering Laboratory reports should be sent to Dr. Kotin or anyone else since they are at the present time so tentative. It was also suggested that a possible means of handling this situation would be to have Dr. Kotin come in to the Kettering Laboratory and discuss their mutual problems verbally,

and that such a discussion could get to Dr. Kotin all the information which he might need and yet not jeopardize the position of the Kettering Laboratory.

ITEM 7

Dr. Eckardt reported to the committee that 5 additional cases of skin cancer resulting from cutting oils have recently come to his attention. One of these cases was a scrotal cancer and none of the cases had previously been reported to the group. This simply served to emphasize the growing importance of cutting oils as a possible carcinogenic agent in industry.

ITEM 8

Some discussion was given to the possibility of holding the next meeting of the Advisory Committee at the Hotel Shamrock on the 29th of September, 1953, and that at this time it would be a joint meeting with the Subcommittee on Carcinogenicity. Decision on this matter was left to the Chairman of the Subcommittee, with the recommendation that if the meeting is to be held on that date, members should be notified and hotel reservations should be made well in advance.

R. E. Eckhardt, M. D.
Acting Secretary

M. N. Newquist, M. D.,
Chairman

MEMORANDUM FROM THE KETTERING LABORATORY

FIFTH MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

January 16, 1953

A. The use of mice in the experimental appraisal of the relative hazards of cancer of the skin of workmen from exposure to various petroleum products.

1. Materials which in industrial experience have caused cancer of the skin of workmen have been shown to be carcinogenic to mice.

2. The correlation of the responses of men and mice is particularly close in the case of straight run wax distillates, cancers having resulted in both species from intermittent, severe exposure (100 mg. doses applied three times per week on the skin of the mice), when the carcinogenic material was not removed by washing. Data reported by the New York University group indicate that mice develop very few tumors when low dosages (15 mg. per application) of wax distillates are applied. The mouse, like man, seems to be affected adversely by these oils only when exposure is severe. A confirmatory test at low dosage will be carried out on C3H mice with the Midcontinent paraffin distillate, API-56 (P_{MC} 0.1 at the 100 mg. level of dosage).

B. Relationships between potency of oils and the level of dosage applied upon the skin per application.

1. Variation of the relative potency, P_{MC}, with the level of dosage (over certain ranges of dosage) is just what one

would expect on the basis of human experience with such alleged carcinogens as coal tar, shale oil or the distillates which have been handled in wax presses in the petroleum industry, i.e., the higher the level of exposure, the greater the chance of skin cancer. The results of the tests on mice at different levels of dosage which have been reported for the catalytically cracked residua, API-8 and 71, are therefore neither surprising nor distressing when considered from the overall aspect of the program. Really unexpected results are coming from the tests on standard solutions and refinery streams containing either very low or very high levels of concentration of accelerating constituents.

2. Certain materials demonstrate a constant potency over a broad range of dosage:

   (1) Solutions of methylcholanthrene or benzpyrene in benzene

   (2) Some blended industrial fuel oils, e.g., API-113

   (3) Some thermal tars from virgin feeds, e.g., API-108

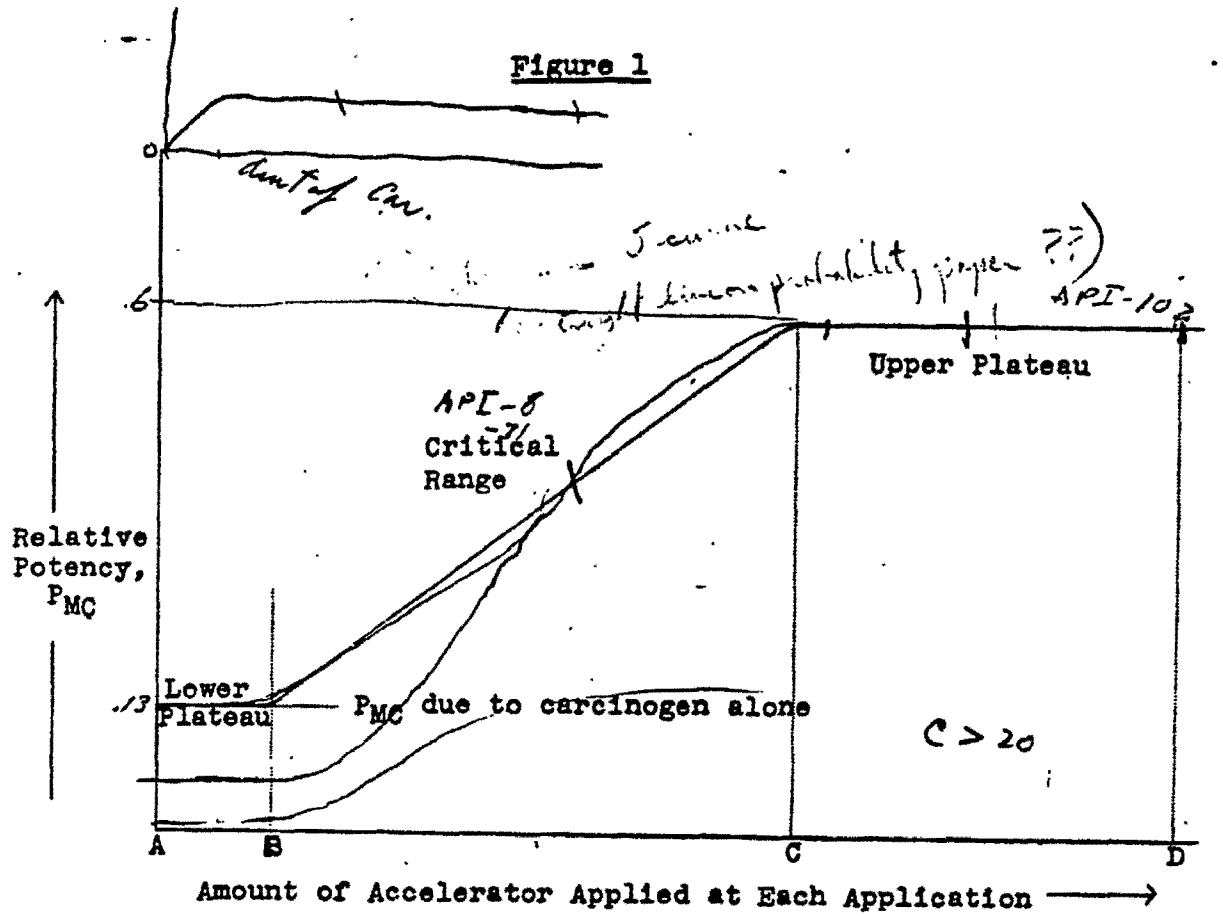
   (4) Solutions of methylcholanthrene or benzpyrene in dodecylbenzene

   (5) Some catalytically cracked gas oils, e.g., API-102.

   Types (1), (2), and (3) probably contain, at the most, very low concentrations of accelerating constituents,

types (4) and (5) relatively high concentrations. The types of oils discussed in section B.1. apparently have a critical level of concentration of such components. The situation may best be pictured graphically (see Figure 1):

Figure 1



Thus, if no accelerators are present in an oil (A), it will exhibit only the potency due to its carcinogen content. Similarly, oils containing accelerators will show only their base level of potency if the dosage per application is kept sufficiently low so that the amount of the

accelerator applied to the skin of the mouse each time does not exceed B. What dosage this will be for any given oil obviously depends on the concentration of accelerators in the oil.

If the dosage per application of such oils is increased until the amount of the accelerating constituent actually being applied each time reaches the critical range between B and C, the relative potency, P_{MC}, as measured by a shortened latent period for tumor induction, will rise. This effect will then increase as higher levels of dosage are tested until the maximum response for a given concentration of carcinogen is obtained (upper plateau in Figure 1).

Proceeding in the reverse direction (from D towards C) it will be apparent that the higher the level of the concentration of accelerators in an oil, the more the dosage per application may be reduced before a significant reduction in potency will be observed. This category probably includes a large number of the current distillate gas oils with End Boiling Points >700°F. from fractionators of catalytic cracking units.

Because of the obvious importance of these relationships between the amount of accelerator applied and the rate at which an oil containing carcinogens will induce cancer in exposed animals, steps are being taken to establish:

(1) the exact magnitude of levels B and C (with blends of synthetic hydrocarbons),

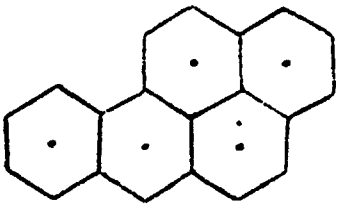
(2) the classes and boiling ranges of the hydrocarbons in catalytically cracked gas oils and residua responsible for the acceleration observed, and

(3) the levels of concentration of such hydrocarbons in various refinery streams.

C. The nature of the compounds contributing to the carcinogenic potencies of refinery streams.

1. Polycyclic carcinogenic compounds.

a.



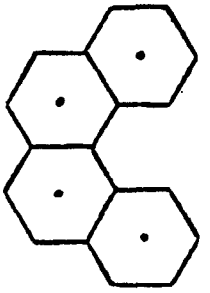
3,4-Benzpyrene

A direct method of analysis for the 5-ringed carcinogen, 3,4-benzpyrene, has been developed. Its reliability has been tested and confirmed with four of the major types of refinery streams under consideration, including cycle gas oils and bottoms products from catalytic cracking, tars from thermal cracking of catalytic feeds, and straight run distillates.

By application of this method, it has been shown that about 70% of the base potency exhibited by the FCC decanted oil, API-8, at 5-20 mg. levels of dosage is

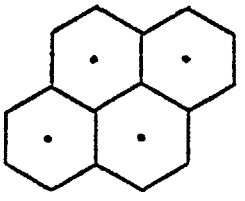
contributed by benzpyrene. Approximately 40% of the constant P_{MC} value of the No. 4 fuel oil blend, API-113, is due to benzpyrene.

b.

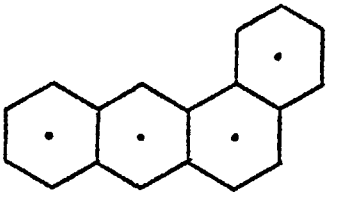


Benzo(c)phenanthrene

As might be expected, in view of the reported boiling point of 3,4-benzpyrene (860°F.), it has been found that the distillate refinery streams analyzed thus far, with true end boiling points less than 860°, contain relatively small amounts of this 5-ringed carcinogen. The available data from biological tests on fractions prepared from catalytically cracked oils suggest strongly that the important carcinogen in such cycle gas oils is a 4-ringed derivative of phenanthrene. Since the results further indicate that simple alkyl derivatives of pyrene and 1,2-benzanthracene



Pyrene



1,2-Benzanthracene

are not contributing significantly to the carcinogenicity of these oils, attention is being centered upon benzo(c)-phenanthrene. This is the hydrocarbon of lowest molecular weight which has been shown to be carcinogenic without the benefit of methylation.

Pure samples of benzphenanthrene and of each of its six monomethyl derivatives have been obtained. Their chemical and physical properties are being examined in the development of a direct method of analysis applicable to refinery streams.

2. Accelerating constituents.

It is of considerable interest that the number of carbon atoms (18) in the accelerator, dodecylbenzene, is the same as the number in the carcinogen, benzo(c)-phenanthrene. The known carcinogenic hydrocarbons have Carbon Numbers from 16 to 25. The approximate boiling range of branched-chain alkylbenzenes with 16-25 carbon atoms is 475-700°F., which is the very range that has been suspected of having accelerating activity from the results of biological tests on refinery streams and fractions thereof. It seems likely that we have here something more than just coincidence.

The problem of the identification of the important accelerators in refinery streams is being approached in two ways:

(1) Biological testing of certain synthetic liquid hydrocarbons as solvents for benzpyrene, to determine

which types have accelerating properties. The results obtained in the prosecution of this phase of the program will furnish a definite outline of the range of molecular weights and of the structural types of possible importance.

(2) Biological testing of fractions of certain catalytically cracked oils which have demonstrated (in tests at the 100 mg. level of dosage) potencies three to ten times as high as were expected on the basis of their content of four to six ringed aromatic hydrocarbons. These efforts are being concentrated on the components boiling below 700°F. which contain not more than two fused aromatic rings.

The foregoing phase (2) of this program has already led to the concentration of a colorless, liquid fraction from the TCC bottoms product, API-71, which possesses the specific irritant properties of dodecylbenzene. This fraction is being redistilled through an 80-plate column to prepare a number of well-defined cuts to be tested as possible accelerators of the carcinogenic action of benzpyrene.

In general, it is a much simpler matter to separate saturated hydrocarbons and monocyclic aromatics from oils and from each other than it is to fractionate any single class of polycyclic compounds from an oil. Furthermore, in the separation of compounds boiling in the range 500-650° at 760 mm.,

highly efficient distillations may be carried out at reduced pressure without fear of cracking. Hence there is little reason to doubt that systematic application of available techniques will lead to an adequate knowledge of the structural types of the accelerating constituents of refinery streams in a reasonable period of time. The step from that knowledge to a direct method of analysis for their effective concentration in any given stream should present no great difficulties.

3. Physicochemical methods for predicting the relative potencies of refinery streams.

During the last six months, the completion of the picture (Figure 1) of the interrelations between concentration of carcinogen, concentration of accelerator, dosage per application, and relative potency, P_{MC}, has brought with it a firm confidence that a reliable analytical tool will result from the further extension of this fundamental approach to the problem. The equation for which parameters are being determined is of the following type:

$$P_{MC} = f(c_a d)\,[K_5 c_5 + K_4 c_4] ,$$

where $f(c_a \cdot d)$ is a function of the amount of the accelerator component applied in each application of the whole oil, c_a being the effective concentration of accelerator in the oil, and d the total dosage of oil per application;

C_5 and C_4 are the concentrations of the 5-ringed benzpyrene and of the 4-ringed carcinogen respectively, while K_5 and K_4 are the respective potencies of benzpyrene and the 4-ringed compound based on methylcholanthrene.

Since the values for half of the factors in the equation for calculating P_{MC} are already known (d, K_5 and C_5), the remaining job is the determination of c_a, K_4C_4 and the breakpoints at B and C in the curve of Figure 1. These phases have been discussed in Sections B.2., C.1.b. and C.2.

ESTIMATED BUDGET OF THE KETTERING LABORATORY FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS OF THE PETROLEUM INDUSTRY ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

Salaries		
Direct Salaries	$ 30,000.00	
Indirect Salaries		
Histopathological Preparation	$ 2,000.00	
Other Services	$ 22,000.00	
		$ 54,000.00
Miscellaneous Expense		
Purchase of Animals	$ 1,500.00	
Special Laboratory Supplies	$ 5,500.00	
Travel	$ 4,000.00	
Overhead (Proportion of heat, gas, electricity, steam, telephone, general laboratory supplies, postage, annuities, pensions, maintenance, etc.)	$ 14,000.00	
		$ 25,000.00
Total		$ 79,000.00

ESTIMATED BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS

OF THE PETROLEUM INDUSTRY

ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS

IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

I. Further development of semi-quantitative biological testing methods for measuring the relative carcinogenic potencies of petroleum products and fractions thereof	$ 12,000.00
II. Determination of the relationships between the rapidity of induction of benign and malignant tumors in experimental animals and various exposure factors such as frequency of application, dosage per application, area of exposure, number of applications, special irritant or toxic properties of the oil applied, etc.	$ 14,500.00
III. Development of rapid analytical methods for estimating the relative carcinogenic potency of any given refinery intermediate or product	
A. Isolation and identification of compounds responsible for observed potency of various types of oils and determination of pertinent physical and chemical properties of these compounds	$ 30,500.00
B. Development of semi-empirical methods of estimation of carcinogenic potencies of oils based on the chemical or physical properties of known or suspected carcinogens and accelerators	$ 4,500.00
IV. Epidemiological Program Collection and correlation of data on cases of cancer among employees of the petroleum industry including any special investigations in particular plants of the industry	$ 17,500.00
Total	$ 79,000.00

FIGURE 1 - 1007* CASE REPORTS FROM 13 COMPANIES RECEIVED BY THE CENTRAL REGISTRY ACCORDING TO SEX, RACE AND MALIGNANCY

SEX	RACE	MALIGNANT	BENIGN	TOTAL
MALE	White	745	23	768
	Colored	26	-	26
	Not Given	114	38	152
	TOTAL	885	61	946
FEMALE	White	33	1	34
	Not Given	9	5	14
	TOTAL	42	6	48
NOT GIVEN		4	-	4
TOTAL BOTH SEXES		931	67	998

* Nine reports could not be used, Six were not tumors; one of these was Boeck's Sarcoid. Three gave only the occupational history.

FIGURE 2 - MALIGNANT TUMORS IN MALES AS REPORTED ACCORDING TO TYPE OF TUMOR AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90--	Total
Buccal Cavity 00-09	11	64		1				1			77
Digest. Sys. and Perit. 10-19	247	24		4				7		3	285
Respiratory System 20-29	28	91						1	2	3	125
Breast 30-39	1	1									2
Genital Organs 40-49	42	16							11		69
Urinary System 50-59	21	21						1	1		44
Skin and Soft Tissue 60-69		170			2			4	2	3	181
Bones 70-75	6	3		1				2	1		13
Brain 76-79		2			3	1				13	19
Lymph. and Hem. System 80-89			12	17							29
Other Sites 90---	8	27		1				1		4	41
Total	364	419	12	24	5	1		17	17	26	885

FIGURE 3 - MALIGNANT TUMORS IN FEMALES AS REPORTED ACCORDING TO TYPE OF TUMOR AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90---	Total
Buccal Cavity 00-09		1									1
Digest. Sys. and Perit. 10-19	8										8
Respiratory System 20-29	1	1									2
Breast 30-39	14	1									15
Genital Organs 40-49	2	3									5
Urinary System 50-59		1									1
Skin and Soft Tissue 60-69	1	6									7
Bones 70-75								1			1
Brain 76-79											
Lymph. and Hem. System 80-89											
Other Sites 90---		1	1								2
Total	26	14	1					1			42

FIGURE 4 - MALIGNANT TUMORS AS REPORTED BY SEX AND PRIMARY SITE COMPARED WITH U.S.A. MORBIDITY AND MORTALITY ESTIMATES

SEX	MALES				FEMALES				BOTH SEXES		
Site	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.** Per Cent Cancer Deaths
Buccal Cavity	77	8.7	10.0	4.7	1	2.4	2.0	1.2	78	8.4	2.9
Digestive System and Peritoneum	285	32.2	36.0	47.7	8	19.0	23.0	38.7	293	31.6	43.2
Respiratory System	125	14.1	8.0	15.4	2	4.8	2.0	3.9	127	13.7	9.6
Breast	2	0.2		0.2	15	35.7		19.1	17	1.8	9.7
Genital Organs	69	7.8	12.0	13.0	5	11.9	51.0	23.5	74	8.0	18.3
Urinary System	44	5.0	7.0	6.6	1	2.4	3.0	3.4	45	4.9	5.0
Skin and Soft Tissue	181	20.5	17.0	2.2	7	16.7	11.0	1.5	188	20.3	1.8
Bones	13	1.5		1.3	1	2.4		1.1	14	1.5	0.1
Brain	19	2.1		2.4				1.5	19	2.0	2.0
Lymph, and Hematopoietic System	29	3.3							29	3.1	
Other Sites	41	4.6	10.0	6.5	2	4.8	8.0	6.2	43	4.6	7.4
TOTAL	885	100.0	100.0	100.0	42	100.0	100.0	100.0	927	100.0	100.0

* Primary site of development of cancer among white males and females according to Dorn, Harold F.: Illness from cancer in the United States. Reprint No. 2537, Public Health Reports. (Based upon morbidity records collected from ten large cities in the United States between 1937 and 1939.)

** Cancer deaths by site in the United States for 1948 as prepared by the Statistical Research Section, American Cancer Society, utiiizing statistics from the National Office of Vital Statistics.

Research Project Advisory Committee Meeting

January 16, 1953

1. Straight run naphthas from Oklahoma City and Kuwait just like benzene as diluents - reduce potency of L-4 by just 50% (at 20 mg. dosage) - as solvents for Methylcholanthrene gave latent periods essentially same as benzene.

2. Oklahoma O-3 showed two early papillomas which regressed - accelerator?

3. Summary of British work
   Sec. 1 Industry and raw materials

   * Lube oils for cotton spinning
   * Slack wax
   * Cutting oils in light engineering industry
     Solvent extracts as plasticizers during war

   * Cancer in workmen

   Sec. 2 Chemistry
   Isolated perylene from solvent extract
   No luck with cold conc. H_2SO_4 on extract
   Boiling ranges of K-4, L-4, and O-4 suggest that most of the carcinogens of the crudes were left in the residuum
   Does I.B.P. method IP 28/42 compare with ASTM distillation?

   Sec. 3 Biology
   Rabbit equals mouse at high dosage - rabbit would be a way out if toxicity prevented use of high dose on mice
   Reduced crudes gave no tumors
   Rabbit more sensitive than mouse (note API-80 and boiling ranges of distillates)
   Using 0.2 and 0.05 Methylcholanthrene and 9,10-Dimethylbenzanthracene in white oil as reference standards in new series of experiments.

   Memo with me page 5 of IV

4. Ask Mr. Landon about trip through Cleves Refinery

5. Ask Drs. Hine and Mithoff about San Francisco visit (March 11th to 15th.)

   13th March 12

FIFTH MEETING
RP(MC-1) ADVISORY COMMITTEE
KETTERING LABORATORY, UNIVERSITY OF CINCINNATI
January 16, 1953 9:30 A.M. E.S.T.

AGENDA

1. Approval of minutes of Fourth Meeting held 9/24/52
2. Progress report - Dr. A. W. Horton
3. Progress report on Epidemiological Survey- Dr. J. J. Phair
4. Research activities for the year beginning 7/1/53
   - Chemical and biological - Dr. A. W. Horton
   - Epidemiological - Dr. J. J. Phair
   - Budgetary allocations - Dr. R. A. Kehoe
5. Report of the Committee on the Carcinogenic action of Mineral Oils to the Medical Research Council (Great Britain) on their "First Three Years' Work"
6. Communications with Dr. Paul Kotin, University of Southern California
7. Other
8. Time and place of next meeting
   (MAC meets Hotel Shamrock - Houston 9/30/53)

M. N. NEWQUIST, M.D., CHAIRMAN

E. W. Adams
L. C. Beard, Jr.
Kieffer Davis, M.D.
R. E. Eckardt, M.D.
T. M. Frank, M.D.
C. H. Hine, M.D.
R. M. Landon
E. K. Linder, M.D.
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

D. V. Stroop (2)
R. A. Kehoe, M.D. (3)

meeting 9-24-52

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

December 19,1952

To Members,
Research Project Advisory Committee

E. W. Adams
L. C. Beard, Jr.
Kieffer Davis, M.D.
R. E. Eckardt, M.D.
T. M. Frank, M.D.
C. H. Hine, M.D.
R. M. Landon
E. K. Linder, M.D.
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

Gentlemen:

I am attaching the minutes of the Fourth meeting of the Research Project (MC-1) Advisory Committee which was held in Chicago, September 24, 1952. (report in report file)

The Research Project Advisory Committee will hold its next meeting at the Kettering Laboratory in Cincinnati, Friday, January 16, 1953, commencing at 9:30 A.M. Eastern Standard Time.

I would greatly appreciate receiving promptly from the members suggested items to be included on the agenda which will be circularized prior to the meeting.

Very truly yours,

M. N. Newquist

M. N. NEWQUIST, M.D.
Chairman, Research Project
Advisory Committee

MNN:RMS
Enclosure

mc: Members and Associates
Subcommittee on Carcinogenicity
Members and Associates
Medical Advisory Committee
Dr. Robert A. Kehoe
Dr. A. W. Horton
Dr. J. J. Phair
Mr. D. V. Stroop

Fourth Meeting
R. P. A. COMMITTEE (MC-1)

Chicago, Illinois - Sept. 24, 1952, 10:00 a.m. D.S.T.
Conrad Hilton Hotel Room 523

AGENDA

1. Consideration of the various items listed in the report to be made on 9-25-52 by the Subcommittee on Carcinogenicity to the Medical Advisory Committee, including progress reports by Dr. R. A. Kehoe, Dr. A. W. Horton, and Dr. J. J. Phair.

   (Copies of the reports have been circularized by Mr. Stroop.)

2. For information and any action that may be indicated.

   (a) Letter of August 26, 1952, from Mr. G. G. Rumberger to Mr. Elmer O. Mattocks.

   (b) Letter of August 13, 1952, to Col. S.J. M. Auld from Dr. M. N. Newquist.

   (c) Letter of September 10, 1952, from Dr. R. E. Eckardt to Dr. M. N. Newquist.

3. Other

4. Time and place of next meeting.

Respectfully submitted,

M. N. NEWQUIST, Chairman

E. W. Adams
L. C. Beard, Jr.
Kieffer Davis, M.D.
R. E. Eckardt, M.D.
T. M. Frank, M.D.
C. H. Hine, M.D.
R. M. Landon
E. K. Linder, M.D.
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

D. V. Stroop (2)
R. A. Kehoe, M.D. (3)

For Information Only - Not For Publication

REPORT ON FOURTH MEETING

Research Project MC-1 Advisory Committee
September 24, 1952
Conrad Hilton Hotel
Chicago, Illinois

MEMBERS PRESENT

M. N. Newquist, M.D. - Chairman
R. E. Eckardt, M.D. - Acting Sec'y.
E. W. Adams
L. C. Beard, Jr.
Kieffer Davis, M.D.
T. M. Frank, M.D.
R. M. Landon
E. K. Linder, M.D.
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

MEMBERS ABSENT AND NOT REPRESENTED

C. M. Hine, M.D.

OTHERS PRESENT

R. D. Bent	-	Atlantic Refining Company
R. C. Cole	-	Phillips Petroleum Company
H. W. Gerarde, M.D.	-	Standard Oil Development Company
A. W. Horton	-	University of Cincinnati
R. A. Kehoe, M.D.	-	University of Cincinnati
E. O. Mattocks	-	American Petroleum Institute
A. C. Pabst	-	Socony-Vacuum Oil Company, Inc.
J. J. Phair, M.D.	-	University of Cincinnati

The attached agenda of the meeting, which had been distributed by Dr. Newquist prior to the meeting, was used as the program.

ITEM 1

The report of the Subcommittee on Carcinogenicity to be presented to the Medical Advisory Committee on September 25, 1952, was reviewed. This report, which had been sent to members of the subcommittee on September 11, 1952, had received approval by the subcommittee.

The final tabulation of the voting on epidemiological studies of cancer among employes of customers was as follows:

Do you recommend that Kettering Laboratory, University of Cincinnati, make epidemiological studies of cancer among employes of customers?

Yes 12 No 12 Not voting 1

If yes, what is your opinion of the following points?

a. Random selection of plants for survey.
Yes 3 No 6 Not voting 3

b. Limit surveys to plants where cancer cases are allegedly due to petroleum products.
Yes 6 No 0 Not voting 6

c. Maintain a cancer registry wherein only cancer cases proven to be due to exposure to petroleum products would be recorded.
Yes 5 No 2 Not voting 5

DR. HORTON'S REPORT

Dr. Horton used as the basis for his discussion the memorandum from Kettering Laboratory, dated September 24, 1952, which had been distributed to members of the Medical Advisory Committee. Perhaps the most important feature stressed by Dr. Horton was the observation that there are non-carcinogenic oils which are not white oils; that is to say that apparently it is not necessary to carry out such an extreme degree of refining as to produce a white oil in order to eliminate the carcinogenicity of an oil. In support, Dr. Horton stressed the results obtained with API-100 and API-99. There was considerable discussion by the associates on just what the nature of API-100 and API-99 might be since many of them did not feel that the specific gravity and viscosity indicated that these represented a type of oil which

might ordinarily be found on the market. It was emphasized, however, by Dr. Horton that these oils were taken out of cans and were used presumably in certain test engines.

Dr. Horton suggested that because of the negative results obtained when white oils are painted on mice, it might be advisable to test such materials on rabbits since the English are placing so much emphasis on the importance of rabbits in skin cancer testing work.

There was next a considerable amount of discussion on the experiments which have indicated that dodecyl benzene has a specific irritant action on the skin of the mouse which seems to enhance the carcinogenicity of truly carcinogenic compounds. These experiments were summarized on page 29 of the tabular summary of current and completed biological experiments dated September 1, 1952. They indicate that dodecyl benzene can sensitize the skin to carcinogens even if it is applied prior to the application of the carcinogen. These results are indicated in experiments designated 221, 9, 9, 221-9, 221-9 (the first 5 samples listed in Table III, page 29). These experiments indicate that if the skin is sensitized with dodecyl benzene prior to the application of API-9, the average latent period of tumor induction is approximately 1/2 of what it is when this sensitization process is not carried out. It is from an accumulating body of data of this nature that Dr. Horton is developing the concept that certain materials contain accelerators to the carcinogens. It is believed by Dr. Horton that these accelerators are particularly important in what he designates as side streams and are of considerably less importance in residua. Thus he has found that an oil which has been prepared by distillation which has no benzpyrene, or essentially none, still has a considerable activity. The laboratory is attempting to find out the class or classes of compounds which are responsible for this activity.

Dr. Horton's laboratory has developed a very rapid method for quantitatively determining the amount of benzpyrene in an oil sample. This discussion led to the suggestion that Dr. Horton should consider performing an experiment in which a batchwise solvent extraction of a typical lube stock base (for instance API-56, API-79, or API-105) with subsequent testing of the extract(s) and raffinate(s) would be performed. It is felt that such an experiment might essentially remove 4 and 5 ring aromatic compounds, leaving the 1, 2, and 3 ring materials for testing.

Experiments are now underway to determine the effect on PMC of painting once, twice or three times a week. In addition, experiments on the effects of varying the amount of material applied at a given application (i.e. from 5-100 mg.) are also being conducted. Preliminary, it is beginning to appear that the amount of material applied each time may be significant in materials which have a considerable amount of the accelerators in them but probably is not important in those materials in which these accelerators are minimal or absent. Thus, when the potency of a material

seems to correlate with its benzpyrene content, the amount of material applied per application seems not to have any effect on this potency determination; but when a material seems to have a higher potency than its benzpyrene content would suggest it should have, the mount of material applied at each application may have a considerable effect on the potency determined.

In addition to the presence of accelerators, Dr. Horton has some evidence to indicate that there may be inhibitors in certain petroleum products, and that these inhibitors are present in the residua of distillation processes but are absent in the side streams. This fact, correlated with certain other observations, has given some suggestive evidence, although certainly not conclusively demonstrated, that the inhibitors may be heavy metals or may be compounds associated with the heavy metals. Dr. Horton believes that these inhibitors probably account for the reason why crude oils are essentially non-carcinogenic, while gas oils prepared from such crudes may exhibit some carcinogenicity. It is Dr. Horton's belief that crude oils contain sufficient benzpyrene and other related carcinogens to demonstrate a significant degree of carcinogenicity, whereas, animal and human data indicate that they do not. It was Dr. Horton's intent not to pursue inhibitors very strenuously. Certain members of the committee, however, believe that the pursuit of such inhibitors might have very important practical considerations to the petroleum industry and suggested that they not be abandoned lightly.

Because of the great complexity of carcinogenesis in petroleum products, which now appears to be a summation of the concentration of carcinogens, the presence of accelerators, and the presence of inhibitors, many of the members of the committee felt that the development of a simple analytical tool to test for carcinogenicity would be considerably more difficult, if not impossible, than originally believed. Thus, it was felt that carcinogenicity is not the result of a single class of compounds but rather the summation of three separate and distinct types of activity, and that, therefore, the development of an analytical tool has been considerably complicated.

DR. PHAIR'S REPORT

Dr. Phair discussed the memorandum from the Kettering Laboratory API Research Project on Carcinogenicity Epidemiological Studies, dated September 24, 1952. This memorandum had been previously distributed to members of the Medical Advisory Committee. There was some discussion of the significance of the figures presented in Figure 4, page 6 of this memorandum. Dr. Phair emphasized the importance of not drawing any conclusions from this table at the present time since the number of cases is so small. He emphasized again the necessity of collecting a large number of cases for analysis before any statistically significant differences can be demonstrated. Premature conclusions from data of this type will be detrimental and should not be done. Dr. Phair asked for

the criticisms of each of the members of this committee and of the Medical Advisory Committee of the coding system which he is using on the cas record cards. Dr. Kehoe and Dr. Phair reported that the Kettering Laboratory would be willing to undertake a critical review with abstracts of the literature on cancer as related to petroleum and that the annual cost of such bibliographic service would be $4,430. The Chairman of the RPA Committee then further emphasized the necessity of medical directors of petroleum companies, who have membership on the Medical Advisory Committee, submitting their cancer cases to Dr. Phair if his work is to have any significance. If they are unwilling to submit their records, then this should be brought out in the open and the epidemiological side of these studies dropped now rather than attempting to continue when the lack of sufficient cases doom the project to failure before it starts.

ITEM 2a

The inquiry from Mr. G. G. Rumberger, Marathon Corporation, dated August 26, 1952, to Mr. E. O. Mattocks concerning possible carcinogenicity of petroleum waxes and Mr. D. V. Stroop's reply were presented for information with the verbal comment that contributors to the API Fundamental Research Project are not thereby entitled to reports on other API research projects. Copies of this correspondence were sent to members of the Medical Advisory Committee.

ITEM 2b

Dr. Newquist's letter of August 13, 1952, to Col. S. J. M. Auld concerning possible reporting in England of the research work at Kettering Laboratory was presented for information. A copy of this letter was sent to each member of the Medical Advisory Committee.

ITEM 2c

Dr. R. E. Eckardt's letter of September 10, 1952, to Dr. Newquist commenting on the research activities of Dr. Paul Kotin of the University of Southern California on the matter of cancer and smog was discussed. It was the consensus of the R.P.A. Committee that Dr. Eckardt and any other interested members of the committee might, as individuals, meet informally with Dr. Kotin at the time of the Industrial Health Conference in Los Angeles in April 1953 if they so desired.

ITEM 3 - BUDGET FOR YEAR JULY 1, 1953 - JUNE 30, 1954

Dr. R. A. Kehoe submitted a proposed budget totalling $104,073 for support of research project MC-1 for the next fiscal year, a copy of which is attached. In executive session, the

R.P.A. Committee recommended a reduction of $25,790, making a proposed budget of $78,283 for fiscal 1953-1954. The following recommendations were made with respect to Dr. Kehoe's budget:

I - Delete	
II and III to be combined	$25,720
IV - Reduce the total amount by $10,000 and apply the balance to items A & B as deemed best.	33,130
V - Delete items B & C and increase item A by $6,263.00.	19,433
	$78,283

Any change in research activities necessitated by this reduction in the budget would be discussed by the R.P.A. Committee with Dr. Kehoe and Dr. Horton at the next R.P.A. Committee meeting.

ITEM 4

The next meeting of the R.P.A. Committee was set tentatively for January 16, 1953 at the Kettering Laboratory in Cincinnati.

R. E. Eckardt, M. D.,
Acting Secretary

M. N. Newquist, M. D.,
Chairman

BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF THE POTENTIAL CANCER HAZARD OF THE

PETROLEUM INDUSTRY

SPONSORED BY THE MEDICAL ADVISORY COMMITTEE

of the

AMERICAN PETROLEUM INSTITUTE

July 1, 1953 - June 30, 1954

I. Determination of the location and extent of the cancer hazard from refinery intermediate and product streams

Direct Salaries	$ 4,000.00	
Indirect Salaries	3,500.00	
Miscellaneous Expense	2,000.00	
Overhead	1,860.00	
		$ 11,360.00

II. Development of semi-quantitative biological testing methods for measuring the relative carcinogenic potencies of petroleum products

Direct Salaries	$ 3,500.00	
Indirect Salaries	4,200.00	
Miscellaneous Expense	2,300.00	
Overhead	1,630.00	
		$ 11,630.00

III. Determination of the relationships between the rapidity of induction of benign and malignant tumors in experimental animals and various exposure factors such as frequency of application, dosage per application, area of exposure, number of applications, special irritant or toxic properties of the oil applied, etc.

Direct Salaries	$ 4,500.00	
Indirect Salaries	5,200.00	
Miscellaneous Expense	2,300.00	
Overhead	2,090.00	
		$ 14,090.00

.....

Indirect Salaries include Histopathological Preparation and other services.

Miscellaneous Expense includes purchase of animals, special laboratory supplies, and travel.

IV. Development of rapid analytical methods for estimating the relative carcinogenic potency of any given refinery intermediate or product

A. Isolation and identification of compounds responsible for observed potency of various types of oils and determination of physical and chemical properties of these compounds which could be used in the development of a widely applicable analytical tool (including associated animal testing)

Direct Salaries	$12,000.00
Indirect Salaries	10,200.00
Miscellaneous Expense	3,050.00
Overhead	5,500.00
	$ 30,750.00

B. Semi-empirical correlations with carcinogenic potencies based on the chemical or physical properties of known or suspected carcinogens in the oils (including associated aniamal testing)

Direct Salaries	$ 5,000.00
Indirect Salaries	3,700.00
Miscellaneous Expense	1,350.00
Overhead	2,330.00
	$ 12,380.00

V. Epidemiological Program

A. Collection and correlation of data on cases of cancer among employees of the petroleum industry

Direct Salaries	$ 5,000.00
Indirect Salaries	3,500.00
Miscellaneous Expense	2,350.00
Overhead	2,320.00
	$ 13,170.00

B. Special investigations of cases of cancer in particular plants in the industry or among customers of the industry

Direct Salaries	$ 2,500.00
Indirect Salaries	1,750.00
Miscellaneous Expense	850.00
Overhead	1,163.00
	$ 6,263.00

C. Survey of pertinent literature on cases of cancer occurring among workers exposed to tar or oil in their occupation

Direct Salaries	$ 2,000.00
Indirect Salaries	1,400.00
Miscellaneous Expense	100.00
Overhead	930.00
	$ 4,430.00

Meeting 7-10-5

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

August 22, 1952

To Members and Associates
Subcommittee on Carcinogenicity

Gentlemen:

I am enclosing a copy of the minutes of the meeting of the Research Project Advisory Committee which was held at Kettering Laboratory, Cincinnati, Ohio, July 10, 1952.

Will you kindly indicate your approval or disapproval of the actions and decisions of the R.P.A. Committee and your decision on questions 2, 3 and 4 listed on the enclosed letter ballot and return it to me. Negative votes should be accompanied by an explanation.

I will also appreciate receiving any comments and suggestions you may have concerning the research project at Kettering Laboratory.

Very truly yours,

M. N. Newquist

M. N. NEWQUIST, M. D.
Chairman, Subcommittee on
Carcinogenicity

MNN:RMS
Enclosures

mc: Members and Associates
Medical Advisory Committee

Dr. R. A. Kehoe (2)
(Without letter ballot)

AGENDA

Research Project (MC-1) Advisory Committee Meeting
Kettering Laboratory, Cincinnati, Ohio

July 10, 1952, 9:30 a.m. to 4:00p.m. EST

1 - Summary of April 1952 Progress Report	Dr. A. W. Horton
2 - Comments on the Progress Report	Dr. R. E. Eckhardt et al.
3 - Progress of studies since April 1952 and future plans	Dr. A. W. Horton
4 - Effect of viscosity on potency and the use of embodying agents to modify viscosity	R. M. Shepardson L. C. Beard, Jr.
5 - (a) Need for additional studies on straight-run, uncracked distillates and residua	
(b) Appraisal of British literture and the magnitude of the hazard in Great Britain	L. C. Beard, Jr.
6 - Plans of the Sub-panel on Lubricants and Process Products Hygiene of the API Lubrication Committee	R. M. Landon K. G. Mackenzie L. C. Beard, Jr.
7 - Report on mid-year meeting, General Committee, Division of Refining, May 1952, with respect to the RPA Committee's report of April 30, 1952, to Mr. T. J. Sullivan	R. M. Landon
8 - Epidemiological Surveys (a) Among employes of petroleum companies	Dr. J. J. Phair Dr. E. K. Linder
(b) Among employes of customers	Dr. M. N. Newquist
9 - Other business	
10 - Date and place of next meetings of (a) Subcommittee on Carcinogenicity (b) RPA Committee	

For Information Only - Not For Publication

REPORT ON THIRD MEETING

Research Project MC-1 Advisory Committee
July 10, 1952
Kettering Laboratory
Cincinnati, Ohio

.....

MEMBERS PRESENT OR REPRESENTED

M. N. Newquist, M.D. - Chairman
R. E. Eckardt, M.D. - Acting Sec'y.
L. C. Beard, Jr.
Kieffer Davis, M.D.
C. M. Doane (For E. W. Adams)
T. M. Frank, M.D.
R. M. Landon
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

MEMBERS ABSENT AND NOT REPRESENTED

C. M. Hine, M.D.
E. K. Linder, M.D.

OTHERS PRESENT

F. F. Heyroth, M.D. - University of Cincinnati
A. W. Horton - University of Cincinnati
Arthur Pabst (Socony-Vacuum Oil Co., Inc.)
J. J. Phair, M.D. University of Cincinnati

The attached agenda of the meeting, which had been distributed by Dr. Newquist prior to the meeting, was used as the program.

ITEMS 1 AND 3

Dr. Horton presented to each of the members the attached "Memorandum from the Kettering Laboratory, Third Meeting of the Advisory Committee, API Research Project MC-1". Dr. Horton followed the outline presented in this memorandum with additional comments, as follows:

a. The year 1951 in terms of the health of the experimental animals did not satisfy the laboratory as well as the year 1950 and, therefore, the laboratory has considerable reservations concerning the accuracy of mouse test data determined in 1951. This has led to the adoption of correction factors for the determination of the P_{MC} values of the various materials tested. One source of this difficulty was discovered in infestation of the animals with mites. These mites presumably caused an eye disease in the mice, which was thought to be due to the scratching by the animals in an attempt to rid themselves of the mites. The mites have now been controlled by using a dusting powder consisting of a low concentration of Chlordane plus pyrenones.

b. Criteria used by the laboratory for determination of what is considered a good animal test include 85% survival of the animals for at least 6 months, or until 50% of the animals have tumors.

c. Experiments are designed so that the average latent period will be not less than 100 days or more than 280 days. If the average latent period is less than 100 days or more than 280 days, it is believed that the accuracies of the P_{MC} determination will be considerably reduced.

d. The desirability of weighing the animals once a week is now recognized and attempts to weigh them at this frequency will be made in order that no breaks in the weight curves will be present in the data sheets presented to the group.

ITEM 2

In the discussion that followed on Dr. Horton's comments it was brought out by Dr. Beard that he had heard of some data from England which indicated that in straight run distillates maximum-carcinogenicity is observed in the 300-400°C. cut. Dr. Horton then emphasized that the nature of the distillation must be fully understood before the significance of this observation could be accepted, since in distillations in which poor fractionation occurs a material presumably cut between 300 and 400°C. could contain considerable amounts of material boiling below 300°C. and boiling above 400°C.

Later, Dr. Beard placed on the board the following 9 variables which may affect the quantitative nature of mouse tests and their extrapolation to human significance:

1. The amount of carcinogen per unit of area.
2. The dilution of the carcinogen.
3. The frequency of application.
4. The effect of the physical state, i.e., viscosity and surface tension.
5. The health of the animals.
6. The psychic state of the animals as concerns eating.
7. The effect of area of application.
8. The persistence of carcinogenesis if applications are stopped.
9. The variability of susceptibility of human skin, i.e., black versus whites.

Mr. Shepardson then brought up the possibility that the work which Dr. Horton has done indicates that there may be several types of response to carcinogenic agents. Thus, with fuel oils and methycholanthrene it would appear that the activity of a given oil does not increase with the increase in dosage. This conclusion was reached as a result of the experiments using 20 and 100 mg. of

material per application with solutions of methycholanthrene and with API No. 8. In the latter case activity seemed to increase with dosage. Dr. Eckhardt then commented that this variation in activity might be both a function of the dosage per application and the dosage per week (frequency).

A considerable amount of discussion followed, the outgrowth of which seemed to be that a great deal more additional work will have to be done in order to develop all of the various variables which seem to influence the quantitative nature of the mouse test. There were many who expressed the opinion that to think that we could begin tapering off on the amount of effort in this program in 2 years' time is an extremely optimistic outlook. Rather, it was their feeling that this type of research will have to continue for a considerably longer period than 2 years at the present level of effort. Dr. Eckardt introduced the concept that perhaps we have the practical answers which we need at the present time to control this problem and that these various refinements of the technique, although of extreme interest, would not contribute appreciably to the development of any practical solutions. He compared to a degree the establishment of MAC values in which a considerable safety factor is always allowed, and where the MAC value is exceeded certain medical supervision is carried out. From the strictly medical standpoint, this is the type of approach which most medical departments and industrial hygiene departments will require. Whether this approach will provide the answers needed by the refiners is a question that can only be answered by the refiners.

ITEM 4

Dr. Beard brought with him a sample of alkylated polystyrene which had been shown to increase the viscosity of a catalytically cracked recycle oil from about 84 to about 1100 when 5% of the material was added to the oil. It was suggested as a possible agent to use in increasing the viscosity of carcinogenic oils without appreciably changing their chemical composition. Reference was made to a letter submitted by Mr. Shepardson which indicated that Vistanex and polypropylenes would apparently not satisfy the requirement of increasing the viscosity sufficiently with a sufficiently small addition of the agent.

ACTION Dr. Horton will test on mice some petroleum fractions of known potencies but those viscosities have been altered by the addition of alkylated polystyrenes (using Dr. Beard's sample) in order to evaluate the effect of viscosity on potency.

ITEM 5a

Dr. Beard indicated that experience thus far has shown that most occupational cancers allegedly due to petroleum products had resulted from prolonged contact with uncracked distillates and residua. For this reason it is his belief that additional studies should be carried out on this type of material in order to help us develop the answers to the problems of this type of material.

ACTION Dr. Horton feels that the samples he already has on hand including the fractions of the three crudes (Oklahoma, Kuwait, La Gunillas) presently being studied in Great Britain would suffice for the time being.

ITEM 5b

Dr. Beard suggested that it probably would be helpful if Dr. Phair could or would review critically the literature on cancer as related to petroleum with particular emphasis on keeping the members of the committee informed of any new articles which are appearing in the literature on this subject by circulating to the members of the committee a critical abstract of each of these articles. Dr. Phair felt that this could well be done by himself and is presumably planning to undertake such a critical abstracting of current literature for the committee.

ACTION While Dr. Phair is favorable to such an undertaking he hesitated to commit Kettering Laboratory in the absence of Dr. Kehoe. Therefore, this matter awaits official clearance from Kettering Laboratory.

ITEM 6

Dr. Beard told the group of the activities of the Sub-Panel on Lubricants and Process Products Hygiene of the API Lubrication Committee. A small subcommittee has been formed to discuss the advisability of labelling petroleum products in order to warn customers of potential hazards. Solvents prepared from petroleum should probably bear labels which are in conformity with those recommended by the Manufacturing Chemists' Association. Other materials, such as lube and cutting oils, should probably bear a simple label which indicates that the oil may cause skin irritation, that it should be kept off of the skin and that if it cannot be kept off of the skin, it should be washed off as soon after contact

as practicable. Mr. Mackenzie emphasized the need of making such washings practicable so that workers would not be spending half of their day washing things off of their hands.

ACTION None taken

ITEM 7

Dr. Landon reported that a verbal summary of the report of the RPA Committee was given to the General Committee, Division of Refining, in May of 1952. As a result, the General Committee, Division of Refining, addressed a letter to the chairman of the Medical Advisory Committee asking that the Committee recommend minimum standards for medical care, qualifications of medical directors and minimum standards for adequate medical records. This letter will presumably be presented to the Medical Advisory Committee at its next meeting. It was the feeling of the RPA Committee that the General Committee, Division of Refining, recognizes the importance of the carcinogenic problem to the petroleum industry and the general recommendations of Dr. Kehoe that the petroleum industry must develop the adequate medical and industrial hygiene measures to control this problem. However, the General Committee, Division of Refining, went further than the simple problem of carcinogenesis and included, presumably, all of the medical problems of the petroleum industry in their request.

ACTION None taken

ITEM 8a

Dr. Phair indicated that he has now received about 900 historical records. Apparently he is receiving very few current

records and asked the cooperation of the Committee to stimulate the various medical directors to send in their current records of cancer cases. He indicated that since April, only 35 or 36 records have been sent to him. He stated that up until the present time there has been no real call on his services in a consultation capacity. Discussion by the Committee indicated that Dr. Newquist would provide the stimulus to the various medical directors to send in their current cancer cases, and that following the action of the Medical Advisory Committee, on the request of the General Committee, Division of Refining, much of the work of Dr. Phair may be implemented because some of the companies which do not now have adequate medical records may begin to develop them on the recommendation of the API as to what constitutes adequate medical service, adequate medical personnel and adequate medical records.

ACTION The Chairman of the Subcommittee on Carcinogenicity will aid the epidemiological studies by stimulating the various medical directors in the petroleum companies to submit the data requested by Dr. Phair.

ITEM 8b

Dr. Newquist mentioned the need for epidemiological studies among the employes of customers of petroleum products since most of the cases are apparently occurring among users rather than among manufacturers. He indicated, however, that the collection of such data would require great tact. Dr. Phair felt that the University of Cincinnati could probably make such studies at the proper time and in a proper manner.

ACTION It was the consenus of the RPA

Committee that the University of Cincinnati should undertake epidemiological studies among customers at an appropriate time. This matter is subject to further action by the Subcommittee on Carcinogenicity.

ITEM 9

Under item 9 on the agenda Mr. Shepardson presented a table of data collected by the Standard Oil Development Company and New York University which indicated that there are at present 4 methods which will predict tumor potency within what it is believed to be a useful range of accuracy. These 4 methods involve: (1) ultraviolet absorption at 360 μ of a 650-1000°F. cut of the oil, (2) polarographic determinations which depend upon the diffusion current at two voltages, (3) the caffein number which depends upon the ultraviolet absorption at two wave lengths of caffein extract of the oil, and (4) the high aromatics characterization which is a more complicated method and was not discussed in detail. He indicated that the Development Company is in the process of checking these four methods in three different laboratories in order to determine their reproducibility from laboratory to laboratory. He urged that the University of Cincinnati give serious consideration to checking these methods also since they have been found to be so useful by the Development Company. He indicated willingness to provide to the University of Cincinnati the details of each of the methods as soon as it had been determined that they were reproducible from laboratory to laboratory.

ACTION Dr. Horton has already been in communication with Mr. Shepardson on the above subject and he will give it further study in connection with Kettering's effort to develop an analytical tool.

ITEM 10

The Committee adjourned at 4:30 p.m., after agreeing that the next RPA Committee meeting should be held September 24th, at the Conrad Hilton Hotel in Chicago, one day prior to the meeting of the Medical Advisory Committee which is to be on September 25th. It was felt by most members of the RPA Committee that a meeting of the Subcommittee on Carcinogenicity prior to the date of the September Medical Advisory Committee meeting would not be necessary if the Subcommittee could handle its interim work by mail. Considerable duplication of presentation and discussion can be eliminated by having the Subcommittee make its report, including Dr. Horton's report, to the Medical Advisory Committee as a whole on September 25th.

NOTE: During the meeting Dr. Horton distributed a sheaf of data sheets (copies mailed to MAC Members 7-16-52) on various mouse experiments which are to be included in the available data thus far submitted. Dr. Horton indicated that he would present a series of data tables for the consideration of the full Committee at its meeting in Chicago.

R. E. Eckardt, M.D.
Acting Secretary

M. N. Newquist, M.D.,
Chariman

COPY

SOCONY-VACUUM LABORATORIES
26 Broadway, New York 4, N. Y.

See pages 7, 8, 9, + 10 of 4-52 report
page 4 of 10-51 report

June 5, 1952

M. N. Newquist, M.D.
Medical Department
The Texas Company
135 East 42nd Street
New York 17, N. Y.

pages 10, 11 of 4-51 report

Dear Dr. Newquist:

In reply to your letter of June 3, 1952, I advise that I plan to attend the meeting of the subject committee commencing at 9:30 a.m. at the Kettering Laboratory in Cincinnati. You may wish to clarify to members whether this be Daylight Saving Time or Eastern Standard Time.

As an item for your agenda, I suggest a realistic discussion of the hazards of straight run, uncracked distillates and residua. I feel this is an aspect of our work that must be squarely faced.

The large majority of cases of cancer of the skin from contact with petroleum products that have come to our attention have a history of contact with relatively non-viscous lubricating oil distillates. To name them:

1) Mule skinners cancer in Great Britain - while there was an early history of use of shale oils, yet such have not been used for many years;

2) Cancers of the scrotum in wax pressmen - these were confirmed by tests at Kettering to be due to the pressed distillates;

3) Cutting oils containing 94% of 100" pale paraffin oil - experiments at NYU on such oil from two different manufacturers both operating on Mid-Continent crude produced cancers in mice;

4) An increasing volume of British literature of which the recent paper by Cruickshank and Goureveitch is an example;

5) Rumors of more cases of cancer of the skin from cutting oil on the Pacific Coast - our Pacific Coast representative may be able to elaborate.

While we have proven as concerns mice that high boiling catalytically cracked products are much more carcinogenic, yet we must face the fact that the cancers in men we now know of come instead from straight-run products of the character indicated.

1. Analytical techniques to estimate the order of potency of any given stream from any of the processes listed above.
2. Epidemiological appraisal of the incidence of cancer among employees of the petroleum industry.
3. Hygienic measures to reduce hazard to employees of the petroleum industry.
4. Dilution of carcinogenic oils as a means of reducing potential hazards to employees of industrial consumers of various petroleum products containing these oils.

Plans for Investigative Work for 1952

A. Process Samples for Animal Tests.

1. Cracked residua from thermal cracking of virgin gas oils (samples to be collected). 2 f.o. from Jersey
2. Sidestreams and residua from other cracking processes to be tested on a limited basis to improve analytical methods of estimating potency and further to test the validity of these methods (these samples already collected, analyzed spectrophotometrically, and held in reserve in the laboratories of twenty-one of the participating companies). lowest priority
3. Untreated lube stocks from straight run distillation now being screened by analytical methods. Samples to be selected for animal testing on the basis of a comparison of their physical properties (including absorption spectra) with those of virgin distillates already tested. British

4. Scottish shale oil and fractions thereof. To gain further analogies between potencies to mice and potential hazards to exposed humans, two or three fractions of shale oil comparable to those employed as spindle lubricants in the British cotton industry to be tested. (Samples already collected and held at Kettering Laboratory).

B. Reference Standards.

For control purposes and improvement of biological methods it is contemplated that tests on known concentrations of standard carcinogens in standard solvents will be carried out with about 9 percent of the animals received.

C. Analytical Techniques for Estimating Carcinogenic Potencies of Petroleum Products.

Chemical research will continue on the two main approaches to this goal, the empirical and the fundamental. Animal testing of fractions which can furnish useful information for this purpose will, as in the past, be given priority over tests on process samples. At the same time, it is recognized that an analytical tool has very limited significance when based on an inadequate number of biological tests of samples of materials to which it is to be applied.

Tests on non-carcinogenic fractions of various oils will be conducted to determine the effects of variations in the composition of these fractions upon the total effective potency of the oils. It is obvious that if fractions which do not contain polycyclic carcinogens are markedly affecting

the rate of induction of tumors in the test animals, then any tool based purely on the concentration of polycyclics will be seriously limited in general applicability.

D. Epidemiological Studies.

Efforts to expedite the collection of case records and other pertinent information on an industry-wide basis will be continued. At the present rate of reporting, there should be sufficient accumulation of information by the time of the spring meeting in 1952 to permit a preliminary tabulation of the data.

E. Experimental Study of Efficacy of Various Cleansing Agents and Skin Creams.

As soon as the current tests which employ rinsing with white oil and washing with detergent solution have been completed, new experiments will be started to compare hydrocarbon solvents, such as technical white oil, with the viscous medicinal white oil currently employed as a rinsing material.

Part of B

Further tests with other skin creams will be designed on the basis of the results of the current tests with Verex.

F. Dilution of Carcinogenic Oils.

Sixteen of the participating companies have already started or completed collection of representative production blends containing carcinogenic streams from catalytic cracking or recycle coking, together with data on the composition of these blends. The majority of the members

Use synthetic blends of samples already tested

of the committee have evidenced their desire for an analytical tool applicable to these complex mixtures. Since it is obvious that no such tool could be developed without knowing the biological potency of at least a few of the blends, a selected group of these materials, on which detailed information is available, should be subjected to animal testing.

November 26, 1951

Brain
Type
Hrtm

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR
NATHAN V. HENDRICKS, CH E
HEAD INDUSTRIAL HYGIENIST
HORACE W. GERARDE, PH D., M.D.
HEAD TOXICOLOGIST
BERTRAND E. BENNISON, M.D.
CHIEF CLINICAL RESEARCH PHYSICIAN

November 2, 1955

Mr. D. V. Stroop
American Petroleum Industry
50 W. 50th Street
New York 20, N. Y.

Dear Mr. Stroop:

I am attaching some information recently received from Dr. Newquist who received it from our British associates in the field of petroleum cancer studies. I believe that the members of the Medical Advisory Committee as well as those at the Kettering Laboratory would be interested in reviewing the Progress Report by Dr. Carruthers and Dr. Cook, and also Progress Report by Dr. Woodhouse and Dr. Squire. I would appreciate it if you would have these reports duplicated for these individuals. I do not believe that the rest of the attached information would be worthwhile duplicating since it concerns only the agenda and minor changes in the nomenclature.

Very truly yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:evn

Encs.
MRC.55/830
MRC.55/815
MRC.55/814
MRC.55/804

Copy From D. V. Stroop For Information
of Members of Medical Advisory Committee
11/4/55

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.55/830
CMO. Ag.19

Committee on the Carcinogenic Action of Mineral Oils

AGENDA

for the Nineteenth Meeting to be held at
26, Old Queen Street, Westminster, London, S.W.1.,
on Tuesday, 25th October, 1955, at 11.15 a.m.

1. Minutes of the previous meeting (MRC.55/510, CMO. Min.18 - already circulated)

2. Amendments to nomenclature of oil fractions.
A memorandum (MRC.55/815, CMO.55/8) (Enclosure A)

3. Expenses grant to Dr. William E. Smith for testing oil fractions (Minute 155)

4. Progress Reports

   (i) Chemical - by W. Carruthers and J.J. Cook (MRC.55/814, CMO.55/9 - (Enclosure B)

   (ii) Biological - by D.L. Woodhouse and J.R. Squire.
   Progress Report No. XV (MRC.55/804, CMO.55/7 - (Enclosure C)

5. Future Plans

6. Any other business

7. Date of next meeting

MEDICAL RESEARCH COUNCIL

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MRC.55/815
CMO.55/8

Committee on the Carcinogenic Action of Mineral Oils

Nomenclature of Oil Fractions

It will be recalled that, at the Eighteenth Meeting of the Committee, the standardisation of the nomenclature of the various oil fractions was discussed (Minute 152) and it was agreed that Professor Squire and Professor Morton should consider this in the light of coding symbols already agreed (Minute 136).

Professor Squire and Professor Morton now propose the following amendment to Minute 136.

paragraph 4, line 7:

DELETE "..... were split into aromatic (A) and raffinate (R) portions."
SUBSTITUTE "..... were split into aromatic (A) and paraffin raffinate (P) portions."

This amendment and the previous confusion of symbols call for amendments in the following documents as shown:

CMO.55/2 and CMO 55/6: for R read P
CMO.54/16; CMO.55/3 and CMO.55/4; for M, P and R read m, p and r.

MEDICAL RESEARCH COUNCIL

"Unclassified"
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MRC.55/814
CAMO.55/9

Committee on the Carcinogenic Action of Mineral Oils

Progress Report
by
W. Carruthers and J.W. Cook

The 1955-56 series of animal experiments with the Kuwait fractions are to be carried out with fractions obtained from the active non-picrate-forming material by chromatography and fractional distillation. For this purpose, the five non-picrate-forming fractions K_4S_6bir, K_4S_7air, K_4S_7bir, K_4S_8air, and K_4S_8bir have been separated into three main fractions by chromatography on alumina by the general method outlined in the last Report. The oil fractions, in batches of about 200 g., were adsorbed on 2 Kg. of freshly activated alumina and successively eluted with petroleum ether, benzene and methanol. Elution with each solvent was continued until no more material was recovered, and three fairly well defined fractions obtained. Corresponding eluates from all the chromatograms were combined, and the three composite fractions sent to Professor Morton for fractional distillation. The total quantities of these fractions obtained were as follows:-

(i) petroleum ether eluate; 1977 g. (77%) yellow oil,

(ii) benzene eluate; 349 g. (13.5%) orange-yellow oil,

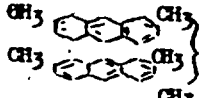
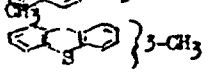
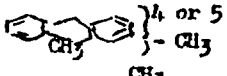
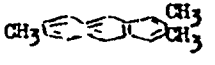
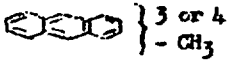
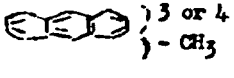
(iii) methanol eluate; 244 g. (9.5%) black viscous gum with a strong unpleasant smell.

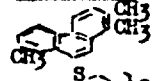
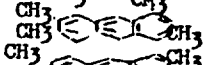
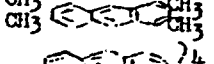
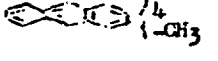
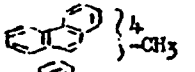
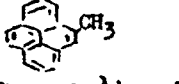
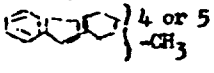
The ultra-violet absorption spectra of the chromatogram fractions K_4S_7Ar i, ii and iii, and K_4S_7bir i, ii and iii, indicate that fractions i and ii are still complex mixtures of different ring systems. In each case there is general absorption with a fall of intensity toward the long wavelength. The spectra of the petroleum ether eluates (i) however, show two well defined maxima at 234 and 326 mμ which possibly indicate the presence of considerable amounts of dibenzothiophen derivatives in these fractions. Experiments are in progress which may lead to a decision on this point. In contrast to these, the spectra of the methanol eluates (iii) exhibited well defined maxima at 243, 292 and 318-355 mμ, (log $E^{1\%}_{1cm}$; 4.9, 4.3, 3.9, and 5.0, 4.5, 4.9) attributable to the presence of carbazole derivatives. This is quite in keeping with the difficulty of removing this material from the chromatogram. It is of interest in this connection that at least one carbazole

homologue has been isolated from a corresponding fraction in the picrate-forming series.

We are continuing our work with the picrate-forming fractions (p). These have also been subdivided by large-scale chromatography, and we have isolated two other compounds from them. One of these, from $K_4S_{2}ap(i)$ had m.p. 84-86° and was shown by its elementary analysis and ultra-violet absorption spectrum to be a trimethyldibenzothiophen $C_{15}H_{14}S$ or its equivalent. Attempts to desulphurise this compound with Raney nickel in boiling ethanol were unsuccessful. In tetrahydrofurfuryl alcohol desulphurisation was achieved but was accompanied by hydrogenation with formation of a more or less completely hydrogenated diphenyl derivative which has not yet been identified. The second compound, isolated from $K_4S_{7}ap(i)$ had m.p. 100° and was shown to be a derivative of phenanthrene by its ultra-violet absorption spectrum. Elementary analyses of the substance and its s-trinitrobenzene complex (m.p. 205-206°) indicated the molecular formula $C_{18}H_{18}$ for the parent hydrocarbon. The melting points of these two compounds, however, do not correspond to those recorded for any known $C_{18}H_{18}$ phenanthrene hydrocarbon or its trinitrobenzene complex.

In response to a request by the Committee the following Table has been drawn up delineating the compounds which have so far been isolated from the Kuwait oil.

Compound isolated	Molecular Formula	Molecular Weight	Structural Formula	Fraction from which isolated
Eutectic of 2:6- and 2:7-dimethylanthracene	$C_{16}H_{14}$	206		K_4S_1aAm, K_4S_1bAm, K_4S_2aAm.
2:6-Dimethylanthracene	$C_{16}H_{14}$	206		K_4S_2aAm.
2:7-Dimethylanthracene	$C_{16}H_{14}$	206		K_4S_2bAm.
1:8-Dimethylphenanthrene	$C_{16}H_{14}$	206		K_4S_2bAp.
Unknown trimethyldibenzthiophen (or equivalent) (m.p. 84-86°).	$C_{15}H_{14}S$	226	 3-CH_3	K_4S_2bAp.
Unknown tetra- or pentamethyl-fluorene (or equivalent) (m.p. 198-199°)	$C_{17}H_{18}$ or $C_{18}H_{20}$	222 or 236	 4 or 5 - CH_3	K_4S_2bAp.
2:3:6-Trimethylanthracene	$C_{17}H_{16}$	220		K_4S_3aAm, K_4S_4aAm, K_4S_3bAm, K_4S_5bAm, K_4S_6aAm, K_4S_5bAm.
Unknown tri- or tetramethyl-anthracene (m.p. 108-110°).	$C_{17}H_{16}$ or $C_{18}H_{18}$	220 or 234	 3 or 4 - CH_3	K_4S_3bAm.
Unknown tri- or tetramethyl-anthracene (m.p. 224-225°)	$C_{17}H_{16}$ or $C_{18}H_{18}$	220 or 234	 3 or 4 - CH_3	K_4S_5bAm, K_4S_6bAm.
Unknown tri- or tetramethyl-anthracene (m.p. 169-170°)	$C_{17}H_{16}$ or $C_{18}H_{18}$	220 or 234	 3 or 4 - CH_3	K_4S_6bAm

Compound isolated	Molecular Formula	Molecular Weight	Structural Formula	Fraction from which isolated.
1:2:8-Trimethylphenanthrene	$C_{17}H_{16}$	220		$K_4S_6bAp.$
Unknown trimethyl-6:7-benzothionaphthen	$C_{15}H_{14}S$	226	 3-CH_3	$K_4S_6bAp.$
1:3:5:7-Tetramethylanthracene	$C_{18}H_{18}$	234		$K_4S_7aAn.$, $K_4S_7bAn.$
1:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$	234		$K_4S_8aAn.$, $K_4S_8bAn.$
2:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$	234		$K_4S_8aAn.$, $K_4S_8bAn.$
Unknown tetramethylanthracene (m.p. 67-69°)	$C_{16}H_{13}$	234	 4 -CH_3	$K_4S_7bAn.$, $K_4S_8aAn.$
Unknown tetramethylphenanthrene (m.p. 103°)	$C_{16}H_{18}$	234	 4 -CH_3	$K_4S_7aAp.$
1-Methylpyrene	$C_{17}H_{12}$	216		$K_4S_7aAp.$
Unknown tetra- or penta-methylcarbazole (m.p. 184-185°) or	$C_{16}H_{17}N$ or $C_{17}H_{19}N$	223 or 237	 4 or 5 -CH_3	$K_4S_7aAp.$

10th October, 1955.

MEDICAL RESEARCH COUNCIL

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MRC.55/804
CAMO. 55/7

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Progress Report No.XV (Sept, 1955)

From D.L. Woodhouse and J.R. Squire, Cancer Research Laboratories, and Department of Pathology, University of Birmingham, Medical School.

Tests carried out by D.L. Woodhouse (1954-55)

The fractions have been applied to the rabbits for 45 weeks and to the mice for 40 weeks. The rabbit tumours are given in Table I.

TABLE I

Rabbit tumours at 45 weeks

Fraction		tumours	Fraction		tumours	Fraction		tumours
$K_4S_4A_m$	(j)	0	$K_4S_4A_p$	(t)	1	$K_4S_4A_r$	(p)	4
$K_4S_5A_m$	(n)	0	$K_4S_5A_p$	(d)	2	$K_4S_5A_r$	(r)	2
$K_4S_6A_am$	(f)	0	$K_4S_6A_ap$	(g)	8	$K_4S_6A_ar$	(b)	5
$K_4S_6A_bm$	(m)	1	$K_4S_6A_bp$	(c)	1	$K_4S_6A_br$	(c)	7
$K_4S_7A_m$	(o)	1	$K_4S_7A_p$	(h)	2	$K_4S_7A_r$	(k)	4
$K_4S_8A_m$	(a)	0	$K_4S_8A_p$	(q)	2	$K_4S_8A_r$	(s)	3
Total		2			16			25
K_4S_9	(l)	8	D(2)	(u)	15	D($\frac{1}{2}$)	(i)	7

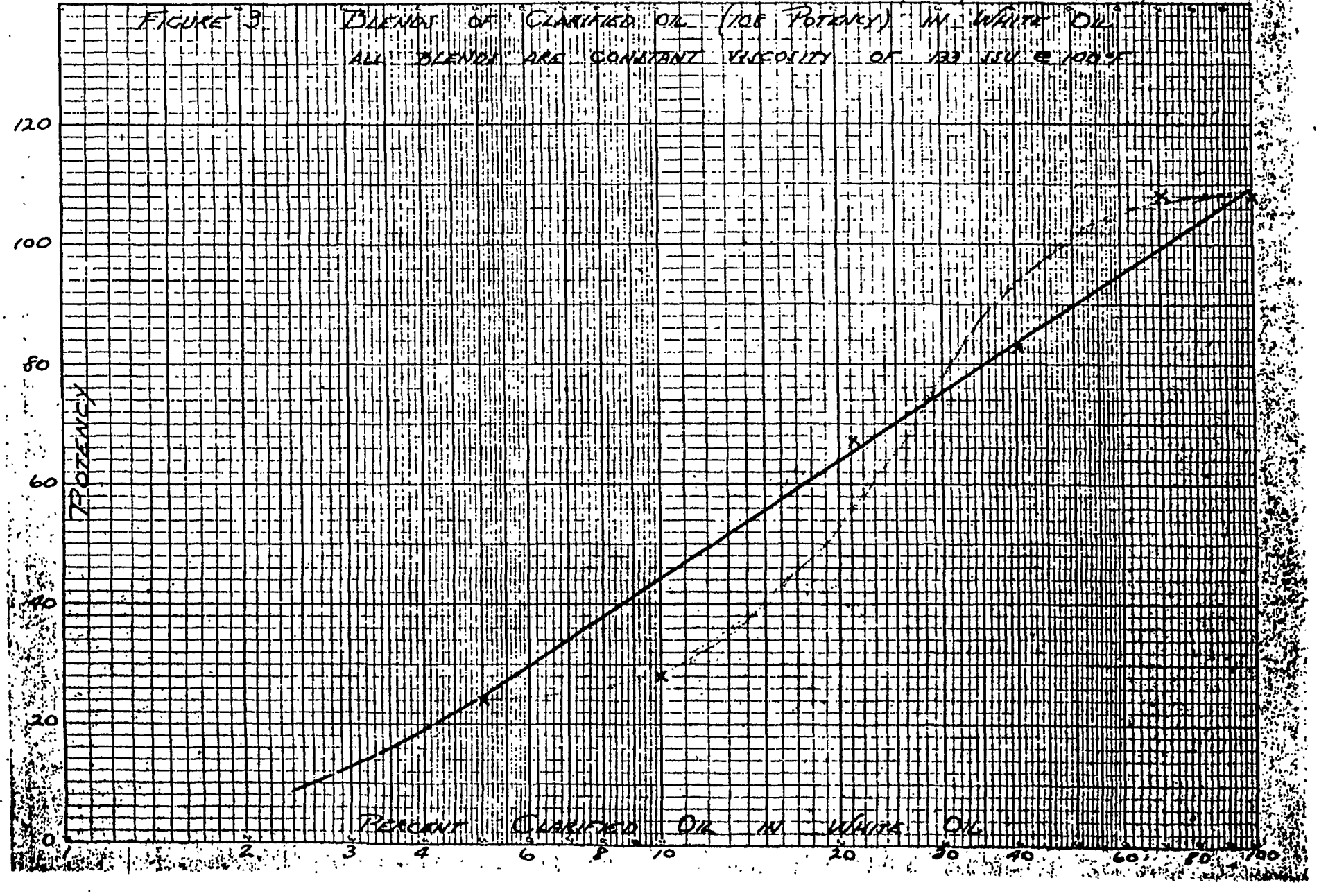
Mouse tumours have appeared in the following mineral oil fractions. b (1); c (1); k (1); l (2); m (1); p (1):

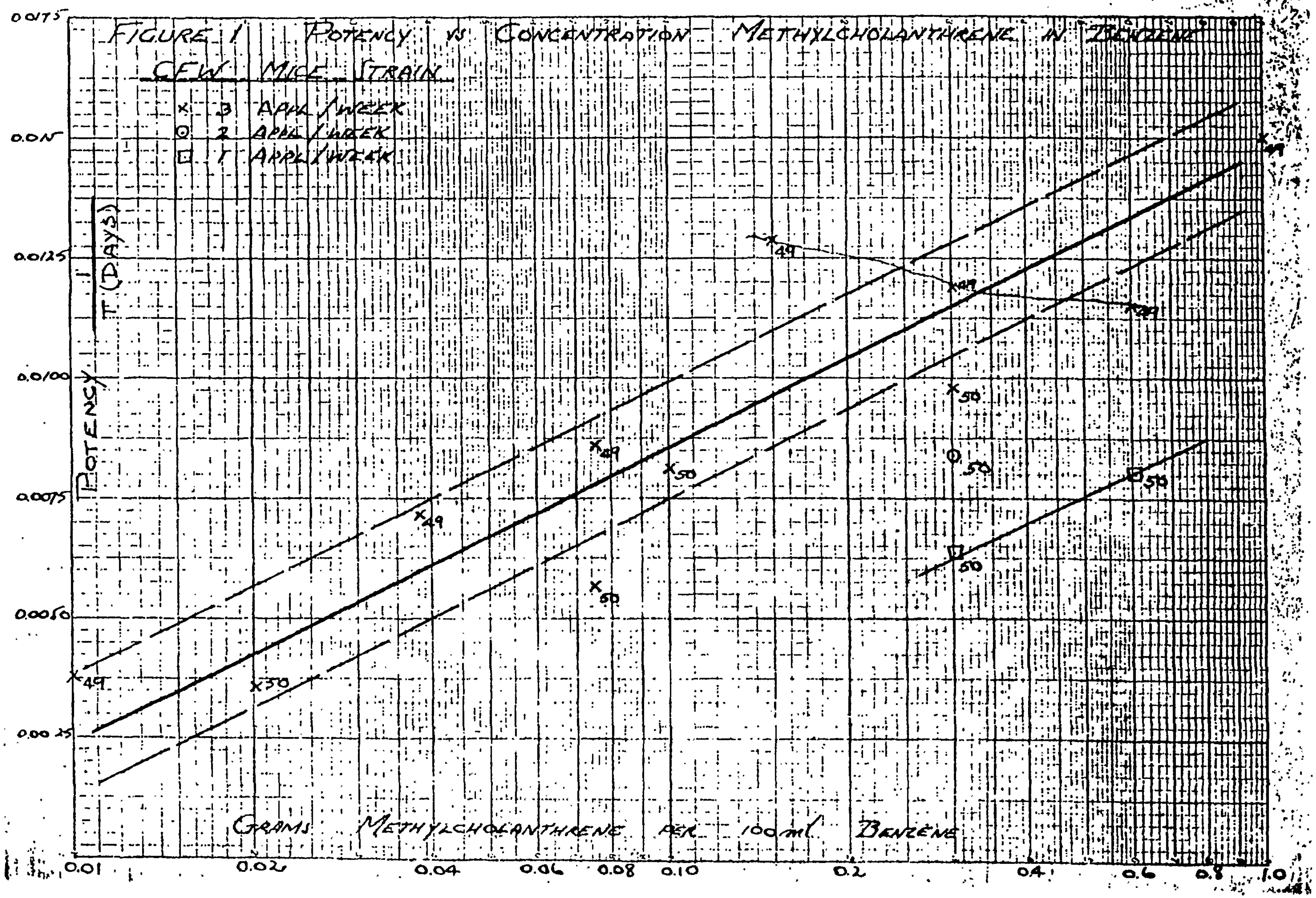
Mice treated with the weaker standard D($\frac{1}{2}$) had 100% incidence of tumours by the 28th week. The stronger standard D(2) had produced 100% of tumours at the end of 15 weeks.

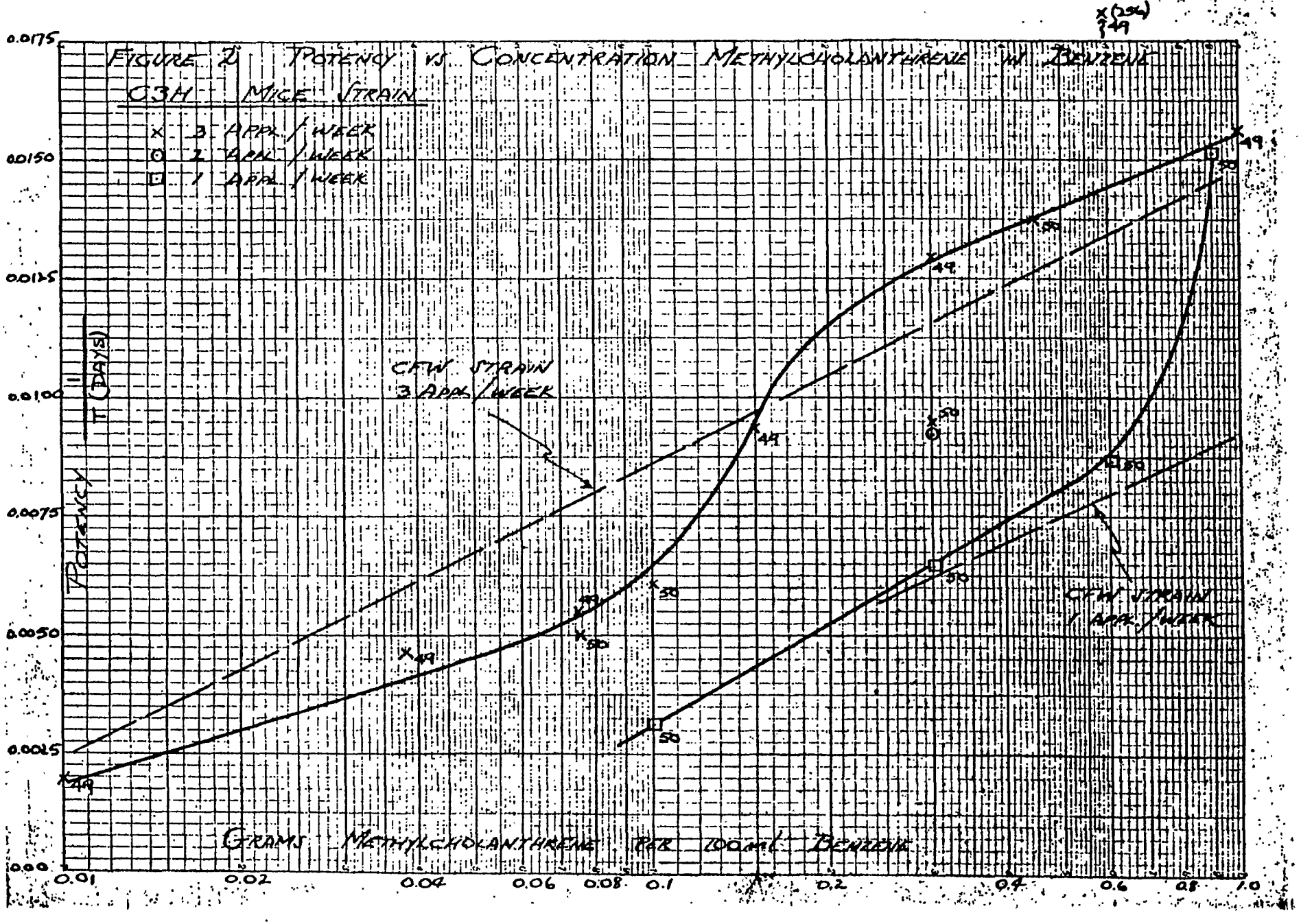
A complete return of all tumours with sites will be given on completion of the experiments, i.e. after 52 weeks.

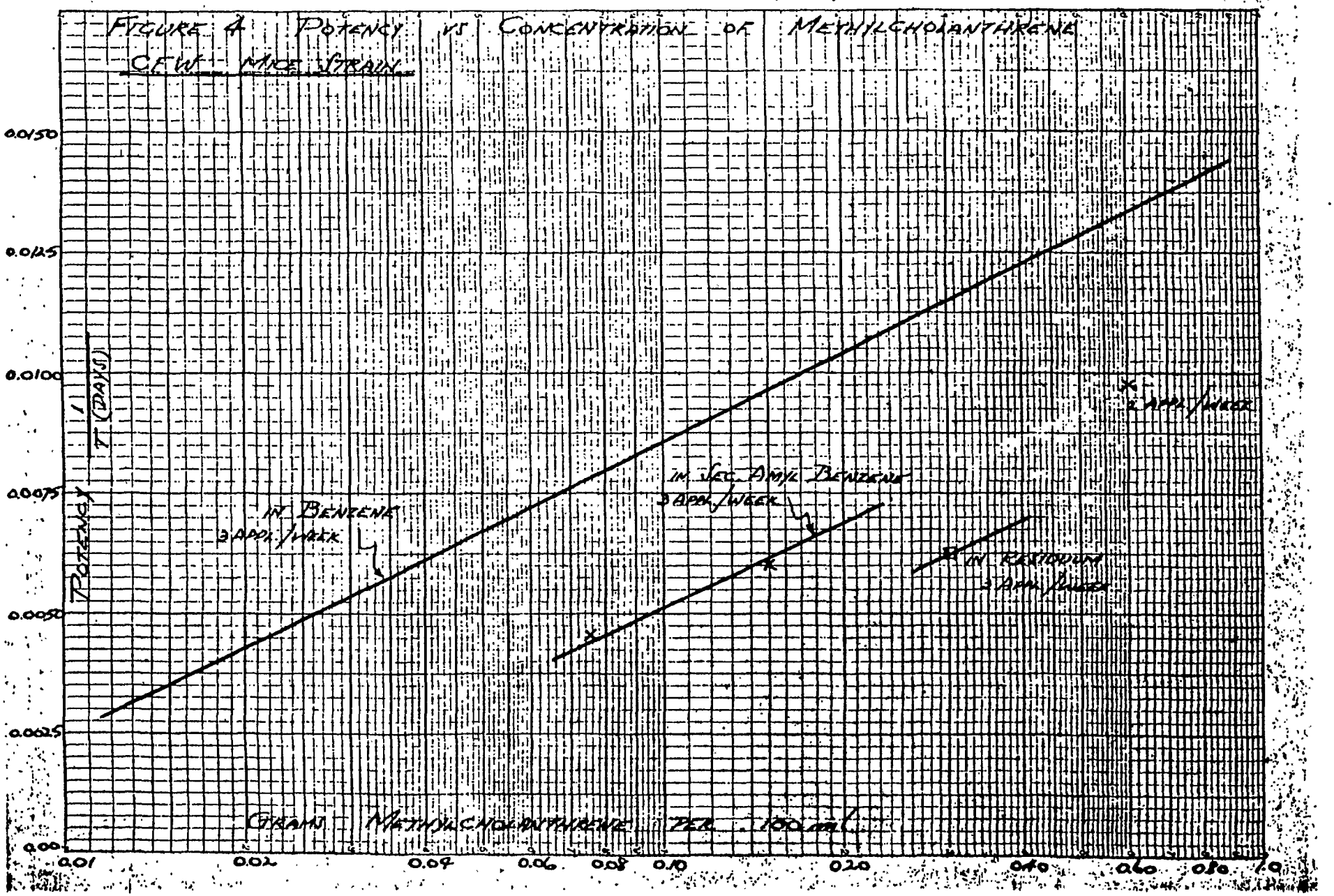
RPA Comm. - Shepard
11/26/51

FIGURE 3 BLENDS OF CLARIFIED OIL (FOR POTENCY) IN WHITE OIL
ALL BLENDS ARE CONSTANT VISCOSITY OF 133 SSU @ 100°F





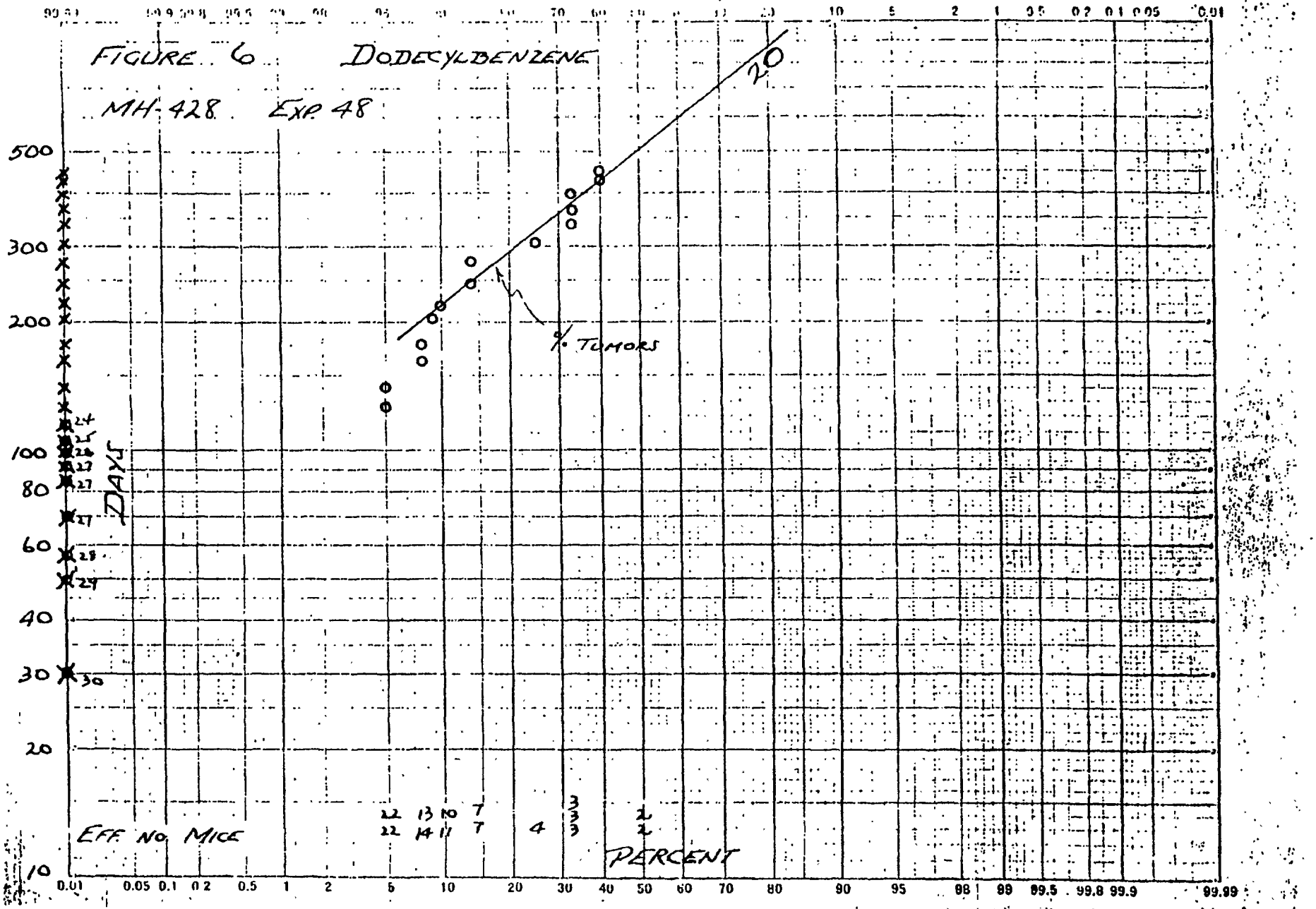




RPA Comm. - Slaughter
11-26-51

FIGURE 6 DODECYLBENZENE

MH-428 EXP 48



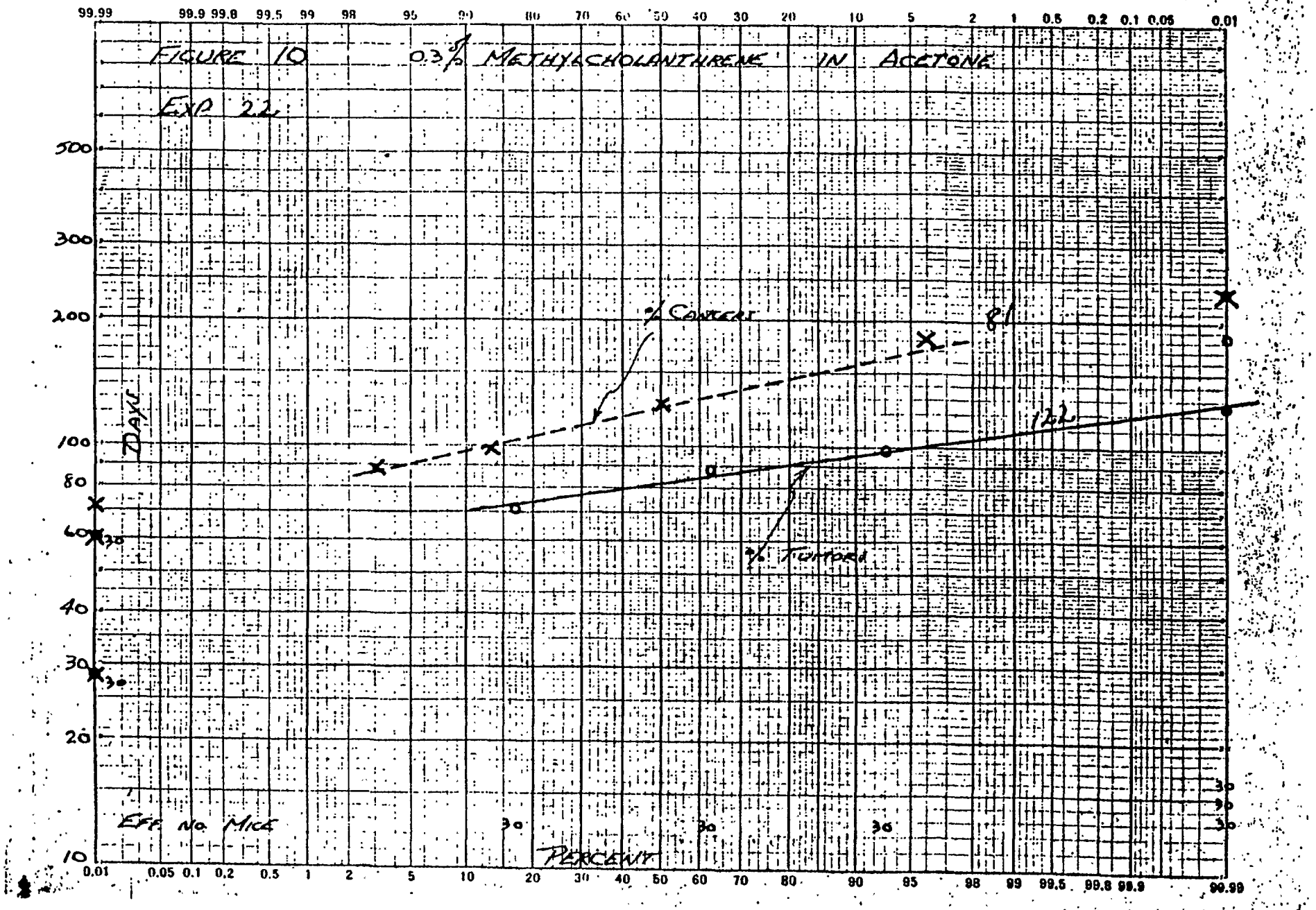
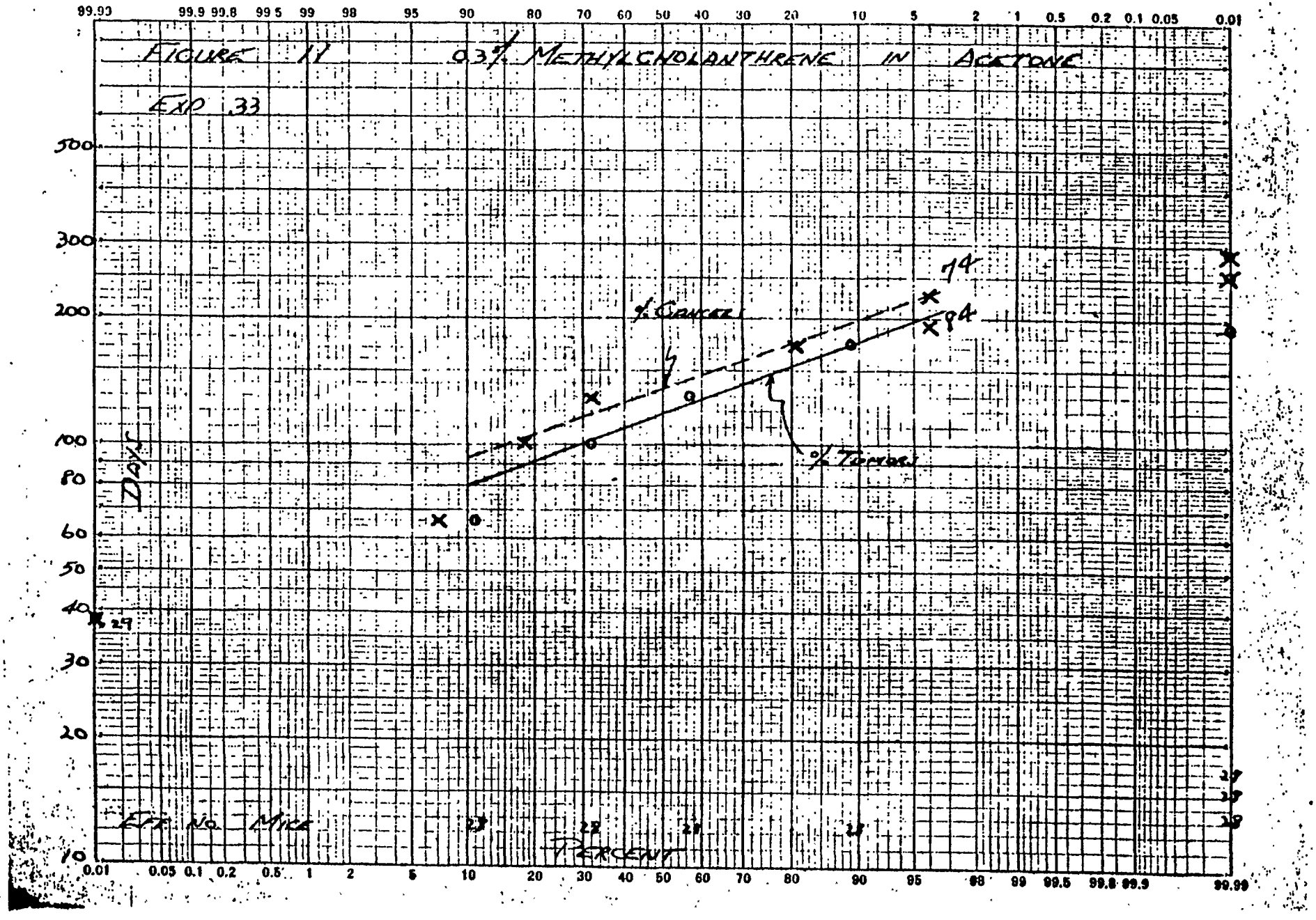


FIGURE 10
0.3% METHYLCHOLANTHRENE IN ACETONE
EXP 22
99.99 99.9 99.8 99.5 99 98 95 90 80 70 60 50 40 30 20 10 5 2 1 0.5 0.2 0.1 0.05 0.01
500
300
200
100
80
60
40
30
20
10
DAYS
% CANCER
81
122
% TUMORED
EFF NO MICE
PERCENT
0.01 0.05 0.1 0.2 0.5 1 2 5 10 20 30 40 50 60 70 80 90 95 98 99 99.5 99.8 99.9 99.99



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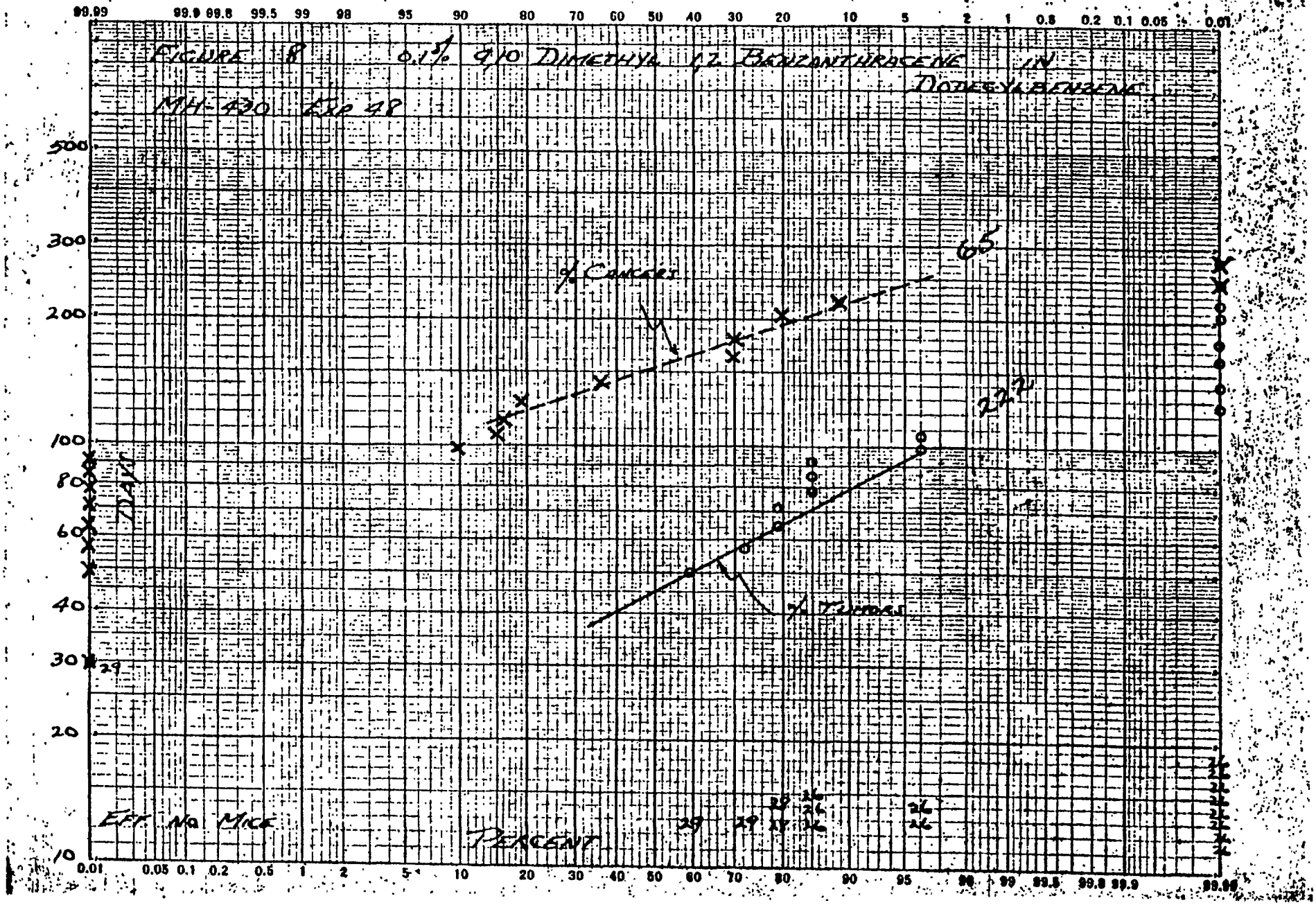

Copy From D. V. Stroop For Information Of Members of Medical Advisory Committee and Staff Members at Kettering Laboratory February 7, 1955

ESSO RESEARCH AND ENGINEERING COMPANY
P. O. Box 51, Linden, N. J.

February 3, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am attaching recent minutes of the Committee on the Carcinogenic Action of Mineral Oil of the Medical Research Council of Great Britain. I believe that these minutes would be of general interest to the members of the Medical Advisory Committee of the API and would appreciate it if you would have them duplicated for such distribution, and also to the members of the Kettering Laboratory.

Sincerely yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Encl. - MRC.55/53
CAMO.Min.17

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee Members)

MRC.55/ 52
CAMO.55/1

Committee on the Carcinogenic Action of Mineral Oils

The meeting of the above committee will be held at 2.30 p.m. on Monday, 2nd May, 1955, at 38, Old Queen Street, Westminster, London, S.W.1. The Agenda will be circulated in due course.

J.C.R. Hudson,
Secretary

20th January, 1955.

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee members)

MRC.55/53
CAMO.Min.17

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the Seventeenth Meeting, held at 38 Old Queen Street, London, S.W.1, on Friday, 17th December, 1954, at 2.30 p.m.

Present: Professor T. Ferguson (Chairman), Colonel S.J.M.Auld, Professor H. N. Green, Dr. T. Heiger, Dr. J.O. Irwin, Professor J.R. Squire, Dr. D.L. Woodhouse, and Mr. J.C.R. Hudson (Secretary).

Attended: Dr. W. Carruthers, (representing Dr. J.W. Cook) and Professor D. Hey.

Apologies for absence were received from: Dr. J.W. Cook and Professor F. Morton.

1. Minutes.

The minutes of the previous meeting were approved and signed.

2. Progress Reports

A. Progress Report No.XII by Dr. D. L. Woodhouse (MRC.54/854, CAMO.54/12).

It was pointed out that the standards, D and D½, were usually of about the same potency on rabbits as the fractions being tested, whereas they were more potent on mice than the oil fractions. It was therefore agreed that, in order that the standards should have approximately the same potency as the fractions under test, the standards used in future mice experiments should be D½ and a more dilute solution, say, D1/20.

B. Progress Report by Dr. W. Carruthers and Dr. J.W. Cook (MRC.54/875, CAMO.54/16).

Dr. Carruthers pointed out that the Di-methyl, tri-methyl and tetra-methyl anthracenes were being isolated from the lower medium and higher boiling fractions. This tended to confirm the effectiveness of the original distillations.

Many of the compounds which were being isolated from the various fractions were found in only milligram quantities. If, at a later stage, it was desired to test their carcinogenicity, it might be necessary to synthesise some of them in greater quantities. Professor Hey said that he already had comparatively large stocks of many of the synthetic methylated anthracenes and he would be willing to make these available if they were required.

It was pointed out that the percentage extraction of the M.P.R. subfraction given in Table I did not add up to 100%. This was due to losses in the process of separation and allowances for this had been made in calculating the blends given in Table II.

Colonel Auld asked if, in view of the spread of results amongst the fractions tested biologically, the chemists were satisfied that the methods being used could give sufficiently discreet separations. In this respect Professor Hey suggested that molecular distillation might give a better separation of small quantities.

C. Dr. Irwin's Report (MRC.54/887, CAMO.54/19).

Dr. Irwin pointed out that comparison of statistical results from year to year and between Birmingham and Leeds showed a reassuring reproducibility.

D. Professor Morton's Report.

It was noted that Lagunillas fractions were being prepared and would probably be available for biological testing to Professor Green when he was ready.

3. Possible Carcinogenicity of Diesel Exhaust Fumes (Minute 138).

The review of Research Group No.2 of the Institute of Petroleum was circulated (CAMO. 54/13).

The Secretary read a letter from Mr. E.T. Priddle offering the assistance of C.A.V. Limited in any investigation relating to Diesel exhaust fumes. In addition, Professor Hey said that a Diesel engine in the Engineering Department of King's College, London, could be made available similarly.

The Committee agreed:

(i) that in view of their own research commitments, which could be expected to last another 2 or 3 years, they could not undertake any research on this subject.

(ii) to recommend to the Council that, as the exaust fumes from internal combustion engines are particular components of atmospheric pollution, their study might be referred by the Council to the Committee concerned with that subject, or to an ad hoc Committee; the members of this Committee specially interested in Diesel fumes would be glad to cooperate in the work so far as possible. The Chairman undertook to write to the Secretary of the Council along these lines.

4. Future Work.

Professor Green said that his biological experiments on mice and rabbits would have run for 52 weeks at the end of a further 4 weeks and 6 weeks respectively.

(Professor Green left).

Dr. Woodhouse said that his biological experiments on mice and rabbits had been running for 6 weeks and 9 weeks respectively.

It was noted (see Minute 2, D above) that Lagunillas fractions, which Professor Morton had prepared, were ready for testing by Professor Green. It was pointed out, however, that the preliminary experiments had shown that the Lagunillas fractions were most potent above 390°C., which was beyond the limit of the Stedman still. Professor Squire undertook to ask Professor Morton to include in the batches which he sent to Professor Green a fraction or residue boiling above 390°C.

(Subsequent Note: Professor Morton proposes to obtain a Fraction 9, boiling above 390°C. by laboratory distillation of the Lagunillas residue. This will provide Professor Green with eight Lagunillas Stedman fractions and one more (L_4 S1-8A and L_4.9), another nine aromatic extracts of these L_4 S1-8 and L_4.9A), and the pooled rafinates (L_4 S.R.). With the two standard solutions of 9:10 dimethyl 1:2 benzanthracene, Professor Green will thus have 21 materials for his animal tests.)

5. Possible Carcinogenicity of Anti-Foaming Agents.

The memorandum (CAMO.54/15) was received and the Secretary added that further enquiries had elicited the following additional information from Shell Chemicals Limited:

(i) that the anti-foaming agent was to be added to the sewage in the proportion of 3 parts per million;

(ii) that there was no evidence of an oil film on the surface of the settling tanks and it was therefore thought that the majority of the anti-foaming agent was carried down with the sludge.

The Committee therefore agreed:

a) that those employed at sewage works might be exposed to some hazard in handling the anti-foaming agent and that this aspect of the question might be referred to the Occupational Health Committee; and

b) that it represented a negligible hazard as far as the general population was concerned.

6. Exhaust Filters on Internal Combustion Engines.

Professor Squire mentioned that in a television programme called "Panorama" a Mr. William Wyness had demonstrated a filter for attachment to the exhausts of internal combustion engines which, it was claimed, removed particulate matter from the exhaust. The Committee agreed that this fell outside their terms of reference.

7. Conference on Atmospheric Pollution.

Colonel Auld reported that the Institute of Fuel was proposing to hold a conference on Atmospheric Pollution at the Institute of Civil Engineering on the 20th January, 1955 under the Chairmanship of Dr. Foxwell. Professor Ferguson said that he would try to attend that Conference and it was suggested that representatives of other Committees, for example the Atmospheric Pollution Committee, might also wish to attend.

8. Date of Next Meeting.

In the absence of Professors Cook, Green and Morton, it was suggested that the next meeting might be held on Monday, 18th April, Thursday, 21st or Friday, 22nd April, 1955 at 12.30 p.m. The Secretary was to ask the absent members to indicate which dates they preferred.

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR
NATHAN V. HENDRICKS, CH.E
HEAD INDUSTRIAL HYGIENIST
HORACE W. GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST
BERTRAND E. BENNISON, M.D.
CHIEF CLINICAL RESEARCH PHYSICIAN

November 15, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

Enclosed is copy of the Minutes of the Meeting of Research No. 2 Committee of the Institute of Petroleum, and copy of the Progress Report of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council. Please have these duplicated for distribution to members of the Subcommittee on Carcinogenicity of the API, and to the interested individuals at the Kettering Laboratory.

Very truly yours,

R. E. Eckardt/mak

R. E. ECKARDT, M. D.

REE:mak

Encs. 2

Copy From D. V. Stroop For Information
Of Members Of Medical Advisory Committee
11/17/55

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.55/840
CIMO.55/10

Committee on the Carcinogenic Action of Mineral Oils

Progress Report
by
H.N. Green and M.J. Redcliffe
Department of Experimental Pathology and Cancer Research
School of Medicine, Leeds.

Mouse Experiment.

Fractions used:-

L_4S_2A = a

L_4S_6A = b

L_4S_1A = c

0.01% D.M.B. = d($^1/_{10}$)

L_4S_5A = e

0.05% D.M.B. = d($\frac{1}{2}$) = f

L_4SR = g

L_4S_4A = h

L_4S_7A = i

L_4S_3A = j

L_4S_8A = k

The experiment was begun on 7.6.55.

Tumours have been produced as follows:-

b (L_4S_6A) 3 tumours, at 9, 13 and 18 weeks.

c (L_4S_1A) 2 tumours, at 13 and 14 weeks

d($^1/_{10}$) (0.01% D.M.B.) 1 tumour at 14 weeks

f (0.05% D.M.B.) 9 tumours, 1 at 11 weeks, 2 at 14 weeks, 2 at 16 weeks and 4 at 18 weeks

i (L_4S_7A) 3 tumours, 1 at 17 weeks and 2 at 18 weeks

k (L_4S_8A) 1 tumour at 18 weeks.

Survivors at 18 weeks are as follows:-

a 45 b 32 c 39 d 35 e 20 f 44

g 29 h 29 i 21 j 19 k 17

Rabbit Experiment

This was begun on 23.8.55. The beginning of the experiment was delayed owing to an epidemic of pneumonia amongst the rabbits.

Five rabbits have died since the experiment began.

So far no tumours have been produced.

(The dilutions of D.M.B. for rabbits are 0.2% and 0.05%).

INSTITUTE OF PETROLEUM RES-2-15

RESEARCH NO 2 COMMITTEE

Minutes of Meeting No.15 held at 26 Portland Place On Tuesday,20-9-55

ATTENDANCE

IN THE CHAIR:	F.Morton.
GUEST:	P.H.S. Trasler
MEMBERS:	W.S. Ault J.N. Haresnape R.B. Killingsworth W. Pohl H.W. Stevenson
APOLOGIES FOR ABSENCE:	E.J. Boorman J.W. Cook E.J. Dunstan A. McLean
SECRETARY:	E. Herbert

1. MINUTES OF MEETING NO.12

These were signed as correct, subject to the addition of "Shell Petroleum, Co.," at the beginning of line 3 of the last paragraph of Minute 3 - I (Page 2)

2. MEMBERSHIP

The meeting accepted the resignation of Mr. W. Pohl with regret and desired to record its thanks to him for his valuable services. The nomination of Mr. H.W. Stevenson was approved by the Committee, who were glad to welcome him back as a Member.

3. WORK AT BIRMINGHAM UNIVERSITY

The Chairman reported on the progress of work at Birmingham University and drew attention to the paper "The Constitution of Petroleum Fractions; Structural Group Analysis of a Kuwait Heavy Gas Oil" which was presented at the recent World Petroleum Congress, and to various documents circulated by the MRC, in particular MRC 55/510 CAMO Minute 18 and CAMO 55/5

The Chairman distributed tables (dated September 20th 1955) of Analytical Data on Kuwait, Lagunillas and Oklahoma Crude Oils and mentioned that work in connection with Table 5, Sub-fractions from aromatic extracts, was now being carried out at Glasgow. The results indicated a very considerable potency concentrated in residues. There were small quantities of Kuwait Crude left over; it was proposed to blend fractions K4S2Aa/K4S5Ab and K4S6Aa/K4S8Ab and then redistil the blends for further test.

There would also be available some samples prepared from a Commercial Extract supplied by the Isle Grain Refinery. The Chairman mentioned that the Langunillas tests were a year behind owing to the withdrawal of the Chester Beatty Institute. This work was being carried on by Professor Green of Sheffield/Leeds University, but no medical school had been found to take an interest in the Oklahoma Crudes, which were therefore, being stored in their fractionated state.

Professor Morton added that he would prepare for publication in the IP journal a further paper in continuation of that presented at the World Petroleum Congress.

4. DIESEL GASES FUMES

The Chairman thanked Dr. Killingsworth for the material which he had provided for the report to the MRC and referred to a letter dated the 14th December 1954 from Mr. A. Fogg of MIRA in which, on behalf of the Diesel Engine Manufacturers, the IP were asked to draw attention of the major petroleum companies to the necessity to carry out investigations with the object of eliminating any exhaust smoke which might be attributable to fuel variations.

It was agreed that a general interest in the problem, which was separate from the medical aspect of smoke, was indicated but that it was a matter more for the Research Committee. Mr. Ault who promised to raise the subject at the meeting of MIRA which he was attending the next day was invited by Professor Morten to the next meeting of the Research Committee.

5. ANY OTHER BUSINESS

The Chairman intimated that he would shortly provide for circulation a copy of Mr. A.W.E. Poll's Thesis.

6. DATE OF NEXT MEETING

To be arranged by the Chairman.