PLAINTIFF'S EXHIBIT

API-139

API SUBCOMMITTEE ON CARCINOGENICITY
MEETINGS AND MINUTES 1948-1952

Meeting 10-25-55

October 27, 1955

Dr. Robert Eckardt
Medical Research Division
Esso Research and Engineering Company
P. O. Box 51
Linden, New Jersey

Dear Bob:

Further examination of the text of the Interim Report indicated a need for other changes in addition to those discussed at the meeting of the Subcommittee. We had about decided to retype the stencils but learned that Mr. Stroop had already made the general distribution. Hence, at his suggestion we have prepared the attached sheet showing the suggested changes with the understanding that Dave will distribute a copy of these errata along with the Summary Tables and covers for binding the whole works together.

Sincerely yours,

A. Wesley Horton

AWH:mjg
attachment

ERRATA

for

Interim Report
API Research Project MC-1
October 1, 1955

Page Number	Line Number	Suggested Change
1	4	Insert "scrotal and other" between "of" and "cutaneous"
1	5	Delete "especially scrotal"
3	3	Replace "satisfactory" with "one-to-one"
3	20	Add "in benzene." after "carcinogen"
6	19	Replace "II" with "VII"
7	18	Insert "(the contribution to potency due to accelerators)" between "M_a" and "may"
10	1	Delete "," after "far"
10	15	Replace "after each application failed to prevent the" with "accomplished a"
10	16	Delete "development of tumors. A"
10	17	Delete "could be accomplished"
11	21	Insert "(See Table X for experimental details)" after "applied"
11	24	Replace "III" with "IX"
12	2	Replace "indicated" with "suggested"

October 13, 1955

Dr. Robert E. Eckardt
Medical Research Division
Esso Research and Engineering Company
P. O. Box 51
Linden, New Jersey

Dear Bob:

Attached is a copy of the text of our Interim Report together with the tables prepared by Dr. Phair. The tables covering the experimental program will be distributed as soon as they are ready or at the latest will be passed out at the meeting on the 25th.

Copies of the report are being sent directly to the other seven members of the Subcommittee to give them full opportunity to review the material before the meeting. 100 copies and the multilith mats are being sent to Mr. David Stroop for the Medical Advisory Committee and for any further distribution you and he may deem desirable.

I shall be looking forward to seeing you on the 25th.

Sincerely yours,

A. Wesley Horton

AWH:mjg
CC: Mr. David V. Stroop

October 12, 1955

Dr. Robert E. Eckardt
Director, Medical Research Division
Esso Research and Engineering Company
P.O. Box 51
Linden, New Jersey

Dear Bob:

In response to your letter of October 3, I will be happy to review our studies with Dr. Bennison the morning of October 25. I will be most appreciative of any help that he can give me in setting up our tables.

We are sending by air parcel post 24 copies of the report for the Subcommittee. My part is complete with tables, but Dr. Horton has only his text ready at this time. The completed report should be ready by the end of October, and we can arrange for the mechanics of its distribution during the Subcommittee meeting.

I will be in New York City the nights of the 18th and 19th, attending the celebration of the Sloan-Kettering Institute. If I don't see you at the dinner, I will give you a call sometime Wednesday.

With very best personal regards, I am

Sincerely yours,

Sgd.

John J. Phair, M.D.

cc: Dr. Horton ✓

September 26, 1953

E. W. Adams
L. C. Beard, Jr.
M. M. Marisic
C. N. Hinz
E. K. Linder
R. C. Mithoff
M. N. Rosquist

Gentlemen:

The vote of the Subcommittee is now in and the tally appears as follows:

October 25	- 6
October 24	- 3
October 26	- 2
October 27	- 1
October 28	- 1
October 21	- 1

It thus appears that October 25 has the vote for the meeting of the Subcommittee. The total number of votes cast, naturally totals more than the members of the Subcommittee since several members indicated several different dates. The plan, therefore, will be for the Subcommittee to meet in my room at the Terrace Plaza Hotel at 9 A.M. On the morning of the 25th, when our business is completed at the hotel which should be at about 10:30 A.M., we will go to the Kettering Laboratory to meet with the Kettering Laboratory group. It is anticipated that the meeting at the Laboratory will begin at about 11 A.M. No meeting of the Subcommittee is planned for the San Francisco meeting. I shall look forward to seeing all of you on the 25th.

Sincerely yours,

R. R. BOCKEMU, M. D.

RRB:ovm
cc: E. A. Mahne
A. W. Morton
J. J. Blair
D. V. Strong

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 121, 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

September 15, 1955

E. W. Adams
L. C. Beard, Jr.
C. H. Hine
E. K. Linder
M. M. Mariaic
R. C. Mitkoff
M. N. Neuquist

Gentlemen:

It now appears that several members of the Subcommittee will not be able to attend the meeting in San Francisco in November. In view of this I am, therefore, proposing that the Subcommittee meet some time during the week of October 24th at the Kettering Laboratory in Cincinnati. I personally would propose that the Subcommittee meet on the 25th with the usual meeting in my hotel room beginning about 9:00 followed by a meeting at the Kettering Laboratory to begin about 10:30 or 11:00. However, I would be willing to meet on another date of this week that is convenient to the Subcommittee. I would greatly appreciate it if each of you would let me know by return mail whether this plan would be more convenient to you in order that we can proceed with the planning for this meeting. Since time is getting short, a quick answer would be greatly appreciated.

It is my understanding that the Kettering Laboratory group plans to have their report in our hands by the middle of October which would then give us a week to review the report prior to the meeting of the Subcommittee. In addition, it would give us an opportunity to prepare the Subcommittee report well in advance of the Medical Advisory Committee Meeting in San Francisco so that we could circulate our Subcommittee report to the Medical Advisory Committee in advance of their meeting. I hope that this arrangement will be satisfactory for each of you and also for the Kettering Laboratory.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:mak

cc: R. A. Kehoe
A. W. Horton
J. J. Phair

ESSO RESEARCH AND ENGINEERING COMPANY

MEDICAL RESEARCH DIVISION

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

August 29, 1955

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

Gentlemen:

On Tuesday, August 23, I met briefly with Dr. Phair of the Kettering Laboratory. This reminded me that the next meeting of the Subcommittee on Carcinogenicity has been tentatively scheduled to precede the meeting of the Medical Advisory Committee in San Francisco. I believe that the tentative date of Thursday, November 10, has been agreed upon by the members of the Subcommittee. However, since Dr. Phair must be in attendance at meetings of the American Public Health Association in Kansas City on the 11th of November, he has asked that I pole each of you and ask whether or not the 9th would be just as convenient for you for the meeting of the Subcommittee on Carcinogenicity. Although he can make the meeting on the 10th, it will mean that he must leave San Francisco at 11:30 that night and travel all night by plane in order to get to Kansas City in time for a morning meeting on the 11th. I would very greatly appreciate it therefore if you would all let me know whether you could attend a meeting of the Subcommittee scheduled for Wednesday, November 9th, or whether you would still prefer to have it on Thursday, November 10th. I will be perfectly happy, and Dr. Phair also indicated that he would be perfectly willing, to abide by the wishes of the majority of the Subcommittee.

In addition, Dr. Phair will be distributing to each of us within the next few days a copy of the new code which he is using for the recording of the carcinogenic data on IBM cards. He told me that the transfer of the data on the some 1900 cases of cancer which have been reported to him onto the IBM cards is almost complete. He has requested that I ask each of you to let him know if there is any particular breakdown of this data which would be of value to you so that he may prepare it for the meeting in November.

At this time, I would also like to request each of you to send me items which you feel should be included on the agenda of the next meeting of the Subcommittee. It is my understanding that the Kettering Laboratory is making an attempt to have the reports for the Subcommittee finished on or about October 1 so that we may be getting them about the middle of October. You will remember that the subcommittee has requested that this year's report be a summary of all work done to date on this problem. This will then give us approximately a month to review the report in advance of the Subcommittee meeting. I would urge each of you to review in detail the report when you receive it and make notes of questions and comments which you wish to bring up before the Subcommittee. I am sure that this will expedite our meeting a great deal.

I trust each of you have had a very pleasant summer.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:evn

cc: D. V. Stroop
R. A. Kehoe
A. W. Horton
J. J. Phair

Date September 13, 1956

To Mr. D. V. Stroop Received 9-21-56 DVS

From: DR. R. E. ECKARDT

Possibly you might wish to distribute this to the members of the MAC.

R.E.E.

R. E. E. cjh

REE:cjh
Attach.

Copy From D. V. Stroop For Information Of Members Of MEDICAL ADVISORY COMMITTEE & TECHNICAL ADVISORS 9/21/56

DVSTRUCT

MINUTES OF THE MEETING OF THE SUBCOMMITTEE ON CARCINOGENICITY
Held in the Conrad Hilton Hotel in Chicago
Thursday, September 6, 1956

On Thursday, September 6, 1956, the Subcommittee on Carcinogenicity met at the Conrad Hilton Hotel in Chicago. In attendance were the following:

R. E. Eckardt, M. D. - Chairman
C. H. Hine, M. D.
P. Halley - (representing E. W. Adams)
E. K. Linder, M. D.
R. C. Mithoff
M. B. Newquist, M. D.

Representing the Kettering Laboratory were:

J. J. Phair, M. D.
R. A. Kehoe, M. D.
A. W. Horton

Two guests, namely, T. M. Frank, M. D. and Lamson Blaney, M. D., attended the meeting.

The Kettering Laboratory representatives joined the meeting at approximately 10:00 A. M.

After approval of the report of the Subcommittee to the Medical Advisory Committee at its April meeting, the meeting was turned over to Dr. Horton. Dr. Horton reviewed the slides which he intends to use for his talk in Atlantic City before the American Chemical Society. The manuscript for this talk has already been approved by the MAC and the Medical and Health Committee of the Board.

Dr. Horton then submitted to the group the abstract entitled, "Relationships Between the Composition and Carcinogenic Properties of Various Refinery Streams." At the request of the American Chemical Society, this abstract was prepared for distribution to reporters at the ACS meeting. The Subcommittee had certain suggestions concerning the abstract and these will be incorporated in subsequent revisions of the abstract by the Kettering Laboratory.

Dr. Horton next presented a table of his more recent data which is developing scientific support for his equation $P_{mc} = M_a(C_1 + C_2 + C_3)$. It will be remembered that this equation has been qualitatively formulated by the Kettering Laboratory to express the carcinogenicity of any complex mixture.

In the formula, M_a represents a multiplication factor which is determined by the accelerators. C_1, C_2 and C_3 represent contributions from the carcinogens in the mixture; it being supposed that there are at least three classes of carcinogens. In the table submitted by Dr. Horton, the experiments with API NUMBER 89, suggest that at a 100 mg. dosage the P_{mc} is 0.3. This mixture was then chromatographed and separated into saturates through alkyl naphthalenes and total polycyclics. Biological testing of the

of the polycyclics yielded a P_{mc} of 0.04. This data suggested that M_a in the above formula is somewhere between 7 and 8. The polycyclics would resprsent the $C_1 + C_2 + C_3$ in the above equation. Next, Dr. Horton treated API NUMBER 89 with maleic anhydride. It will be remembered that such treatment yields an adduct with anthracene-type compound It is not believed that two or three ring maleic anhydride adducts are carcinogenic, but it is believed that the 4+ rings, which react with maleic anhydride, contain the carcinogens of a benzanthracene type. Biological testing of this 4+ ring material yielded a P_{mc} of 0.012. Thus, this type of compound contributes about 1/3 of the carcinogenicity of the polycyclics. Conceivably, this figure, 0.012, might be taken to represent C_1 in the above equation. $C_2 + C_3$ would represent the difference between 0.04 and 0.012, a would represent the contribution of other classes of carcinogens, such as cyclopentano phenanthrene.

In the case of the API NUMBER 65, the P_{mc} of 0.11X is probably all contributed to by the polycyclics and of these, approximately 1/4 are by the benzanthracene-type compounds Thus, a thermal tar has little, if any, accelerators and M_a in the above equation would be one. The rest of the data in the table is incomplete at the present time, but is bei evaluated by Dr. Horton in the above fashion, in an attempt to determine the contributio of each of these constituents, to the over-all carcinogenicity of the mixture. It is Dr. Horton's hope that this work will permit a chemical quantitative estimation of the carcinogenicity of complex mixtures.

Following Dr. Horton's presentation the chair was turned over to Dr. Fhair, who describe what they hoped to accomplish with the epidemiological data thus far collected. It is his hope that among the 2,000+ cases thus far collected, they will at least be able to provide us with some figures on relative frequencies of different types of cancer within the petroleum industry. Dr. Fhair emphasized that he did not believe the epidemiological work had been a total failure, since he believes that secondary benefits, such as making medical directors think in terms of disease reporting and the collecting of disease statistics, had been accomplished by the abortive attempt to collect epidemiological data. It is possible that this attempt within the petroleum industry was just 10 years ahead of its time.

Subsequent to these discussions, the Subcommittee discussed the present situation concerning milk carton wax which had been precipitated by a recent article in THE NEW YORK TIMES. It was the general consensus that the following represented a fair estimate of what we should do at the present time.

1) No public statement should be made by the API at the present time.
2) The Chairman of the Subcommittee should distribute to all members of the MAC, a memorandum summarizing presently available information on the carcinogenicity of milk carton wax. Such distribution will be dependent upon his being able to obtain clearance from his management.

3) The chairman of the Subcommittee, after receiving Dr. Hueper's Rome manuscript and the resolutions of the Rome symposium, should write a letter to the Surgeon-General, with a carbon copy to Dr. Hueper, asking for clarification of the statements which appeared in THE NEW YORK TIMES. This should be done on AFI letterhead and the tenor of the letter should be dependent upon the text of Dr. Hueper's manuscript and the resolutions adopted in Rome. The letter will be circulated to the Subcommittee prior to being forwarded to the Surgeon-General.

4) It was the general consensus that insufficient data is presently available to permit adequate evaluation of the carcinogenicity of dairy waxes. The Kettering Laboratory was asked whether they would be interested in conducting the research necessary to clarify and establish the status of dairy waxes in regard to their carcinogenicity. The Kettering Laboratory expressed interest in this research program and promised to prepare definite proposals for such research with budget estimates as to the cost for a subsequent meeting of the Subcommittee, to be held in Chicago on October 20, 1956. Tentatively, the place of this meeting will be at the Drake Hotel, providing the chairman of the Subcommittee can obtain adequate accommodations for a meeting room for the Subcommittee on that date. At this time, the Kettering Laboratory will have specific proposals with, more or less, specific budgetary estimates for the research necessary to clarify this situation. In the meantime, the chairman of the Subcommittee will provide to Dr. Kehoe, a copy of the memorandum which is to be distributed under item #2 above.

Dr. Kehoe was reminded, just before the meeting adjourned, that there would be a meeting of the Subcommittee about the time of the IMA meeting in April and at this time, he would be expected to present budgetary figures for the year July 1, 1958 to June 30, 195

R. E. ECKARDT, M. D./cjh
Chairman, Subcommittee on Carcinogenicity
September 10, 1956

Attach. - ABSTRACT RELATIONSHIPS BETWEEN THE COMPOSITION AND CARCINOGENIC PROPERTIES OF VARIOUS REFINERY STREAMS. A. Wesley Horton, et al.
cc - D. V. Stroop
R. A. Kehoe

REE 4
LCM
BEB
4HG

ABSTRACT

RELATIONSHIPS BETWEEN THE COMPOSITION AND CARCINOGENIC PROPERTIES OF VARIOUS REFINERY STREAMS

by

A. Wesley Horton, Russell Tye and Mary Jane Graf

Kettering Laboratory, University of Cincinnati

Various high-boiling mixtures derived from fossil fuels have the capacity to produce tumors when applied repeatedly upon the skin of certain experimental animals for long periods of time. An extensive program of testing of such materials encountered in petroleum refining operations has been undertaken (at the request of this industry).

A technique of analysis for benzopyrenes in such oils has been developed. Application of this method to a wide variety of oils has shown that knowledge of the concentration of this carcinogen alone is not sufficient for reliable estimation of the carcinogenic potency of a particular oil.

Further research indicated that very important contributions to the potencies of certain oils are made by classes of hydrocarbons which are completely non-carcinogenic when separated and tested by themselves. The exact mechanism of their action in mixtures with polycyclics such as benzopyrene is unknown, but their effect is to shorten the latent period before the development of tumors.

Work is also in progress to identify the important carcinogens of certain active oils which are essentially free of benzopyrenes. The techniques of chromatography, distillation, solvent extraction, and the formation of Diels-Alder adducts have been used to produce relatively simple mixtures. Some biological testing of these fractions has been made and additional testing is under way. The approximate composition of these fractions has been determined by absorption and mass spectrometry. A strong likelihood is indicated that the unknown carcinogens are 4-ringed hydrocarbons, but different in structure from the classical benzanthracenes and chrysenes.

API NUMBER	DESCRIPTION	100 mg. P_{MC}	CHROMATOGRAPHIC FRACTIONATION		CONTRIBUTION OF POLYCYCLICS TO P_{MC}	FRACTION EXTRACTED BY MALEIC ANHYDRIDE		
			Saturates thru Alkylnaphthalenes (%)	Polycyclics (%)		% Yields		Contribution of 4+ Ring Fraction to P_{MC}
						2-3 rings	4+ rings	
89	FCC Sidestream	0.3						
89-1						1.64		-
89-2							0.2	0.012
89-3				19	0.04			
89-4			81*					
65	Thermal tar	0.11X						
65-1				60	0.12			
65-2						(0.9)	1.1	0.03
120	Straight run distillate	0.07 (50 mg.)						
120-1						(1.2)	0.4	<0.01
120-2				33	inc.			
33	Coker gas oil	0.4						
33-3						(2.1)	2.2	inc.
33-4				33	inc.			
105	Straight run distillate	0.11						
115	Straight run distillate	0.03						

* A direct test of this fraction has produced 1 benign papilloma in 28 weeks.

Meeting 9-10-54

UNIVERSITY OF CINCINNATI
Department of Preventive Medicine and Industrial Health

The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

March 1, 1955

Dr. Robert E. Eckardt
Medical Research Division
Esso Research and Engineering Company
P. O. Box 51
Linden, New Jersey

Dear Doctor Eckardt:

As suggested in your letter of February 25, we are distributing copies of the corrections to the minutes of the last subcommittee meeting in Chicago. Extra copies are being sent to each of the members of the Medical Advisory Committee for any further distribution within their companies they may wish to make.

Sincerely yours,

A. Wesley Horton

AWH:mjg
enc:

Corrections to Minutes

Meeting of Subcommittee on Carcinogenicity

September 10, 1954

Page 2, paragraph 1

Item 2. Normal decane is the compound of lowest molecular weight thus far shown to be an active accelerator. Normal octane is definitely not. Isooctane probably does not accelerate, but further work will be required for certainty.

Item 3. The cholanthrene-type molecule may contribute most to the potency of the mixture extracted from cracked oils by maleic anhydride (Diels-Alder reaction). No data is available yet on a comparable extract from straight run distillates.

Item 4. Samples of certain crude residua have been collected for future study of the question of naturally-occurring inhibitors.

Item 5. Washing experiments are being planned to obtain further information on the apparent accelerated development of tumors previously observed when a white oil of low viscosity was used as a rinse prior to washing with detergent (Experiments 306 vs. 307).

For Information Only - Not for Publication

AMERICAN PETROLEUM INSTITUTE

SUBCOMMITTEE ON CARCINOGENICITY

Minutes of Meeting
September 10, 1954
Conrad Hilton Hotel
Chicago, Illinois

Members Present or Represented:

C. H. Hine, M. D. - Acting Chairman
E. W. Adams (by C. M. Loane)
L. C. Beard Jr.
Allan E. Dooley
F. D. Gassaway, M. D.
L. M. Henderson
E. K. Linder, M. D.
R. C. Mithoff
M. N. Newquist, M. D.
J. W. Osborn, M. D.
F. J. Sanders (by W. E. Scovill)

Member Absent:

R. E. Eckardt, M. D.

Others Present:

T. W. Albin	Shell Development
J. W. Crookshank, M. D.	Cities Service
T. M. Frank, M. D.	Pan American Refinery
Paul D. Halley	Standard Oil, Indiana
A. W. Horton	Kettering Laboratory
R. M. Landon	Gulf Oil
M. M. Marisic	Pure Oil
Clark R. Miller, M. D.	Tidewater Assoc. Oil
A. C. Pabst	Socony-Vacuum
J. J. Phair, M. D.	Kettering Laboratory
B. B. Reeve, M. D.	Standard Oil, Indiana
J. G. Ruddock, M. D.	Richfield Oil

The minutes of the Subcommittee meeting of June 19, 1954 were approved as circulated.

It was the consensus of the Subcommittee that the last sentence of third paragraph in Section 1, (Chemical and Biological Work) of Dr. Eckardt's report of June 21, 1954 to the Medical Advisory Committee should read "Selected portions of these investigations will undoubtedly be prepared as a manuscript for publication."

Dr. Horton discussed his progress report, dated September 1, 1954 copies of which he had mailed to the Subcommittee at the end of August. In Dr. Horton's discussion he has brought out the following points:

1. Future work will be directed toward solidifying the qualitative findings into a good analytical tool.

2. With respect to accelerating materials, octane has been found to be a good accelerator; normal octane is not an accelerator; it appears that a C_{18} chain length is about the upper limit of accelerators.

3. In uncracked oils (paraffin distillates 650°-725°) the carcinogen has not been identified but it is not benzpyrene. The cholanthrene molecule may be important in low-boiling carcinogens.

4. No work is being done on inhibitors.

5. No washing experiments are being done; Dr. Horton believing that nothing more is needed in this phase of the study.

6. Six or seven oil company laboratories which are testing the analytical method for benz (a) pyrene developed by Tye, Graf and Horton have been obtaining satisfactory reproducibility.

It was voted to receive Dr. Horton's report.

Dr. Phair reported on the epidemiological phases of the research project and brought out the following points:

1. Case reporting is getting better, 289 case records, most of them current ones, having been received in the past year.

2. Fifteen companies are now participating with an additional one to start shortly.

3. More detailed population figures will be needed and Dr. Phair will write to the various medical directors advising them in detail what figures are needed.

Dr. Phair stated that one oil company had made records of skin examinations of all its employes and that a second company had key-punched all its periodic physical examination findings for the past 10 years. He stated that an analysis of these records might be worhtwhile and asked approval of the Subcommittee to go ahead. This analysis would require hiring a clerk for a few weeks to copy the records of the first company. The cost involved in the second company's records would be much less; merely the cost of having IBM punch a duplicate set of cards. Dr. Phair stated that it would not require any additional funds; he could handle the costs within his present budget. After a thorough discussion, the Subcommittee concluded that it could see no objection to Dr. Phair's obtaining the epidemiological information from these two companies within his present budget.

Dr. Horton commented on the statement in the Subcommittee's report of June 21, 1954 which says that "expenditures (for the chemical-biological work) - - - - should stabilize at levels not in excess of $25,000 after June 30, 1956." Dr. Horton felt that this is too great a cut since the 1955-1956 budget allotted $52,250 for these phases of the research project. After considerable discussion the Subcommittee, in executive session voted that "It is the sense of the Subcommittee that it is their intent at this time that the budget be reduced in the order of 10 per cent annually for the next few years."

It was also voted that the next meeting of the Subcommittee would be in Buffalo, New York, 12 April 1955, one day prior to the meeting of the Medical Advisory Committee.

SHELL DEVELOPMENT COMPANY

EMERYVILLE, CALIFORNIA

TELEPHONE OLYMPIC 5-2100

August 9, 1954

Messrs. E. W. Adams
L. C. Beard, Jr.
Allan E. Dooley
F. D. Gassaway
L. M. Henderson
E. K. Linder
R. C. Mithoff
M. N. Newquist
J. W. Osborn
F. J. Sanders

Gentlemen:

In accordance with Dr. Eckardt's letter of June 25, a meeting of the Subcommittee on Carcinogenicity is to be held in Chicago at the Conrad Hilton Hotel, in private dining room No. 9 at 9:30 A.M. on September 10. The following is a tentative agenda for this subcommittee meeting:

1. Approval of minutes of the last meeting.
2. Progress report by Dr. A. W. Horton.
3. Progress report by Dr. J. J. Phair.
4. New items of business.
5. Time and place of the next meeting.

If any of the members of the subcommittee have additional items which they would like to include in the agenda, they may submit them prior to the meeting and I will see that they are scheduled.

Very truly yours,

C. H. Hine, M.D., Acting Chairman
Subcommittee on Carcinogenicity

CHH/jck
cc: A. W. Horton ← THIS COPY FOR
J. J. Phair
G. W. Saunders
D. V. Stroop

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

June 25, 1954

Messrs. E. W. Adams
L. C. Beard, Jr.
Allan E. Dooley
F. D. Gassaway
L. M. Henderson
C. H. Hine
E. K. Linder
R. C. Mithoff
M. M. Newquist
James W. Osborn
F. J. Sanders

Gentlemen:

I have just today talked with Dr. Saunders and he informs me that the Medical Advisory Committee will hold a one-day meeting in Chicago at the Conrad Hilton Hotel on Thursday, September 9, 1954. In view of this, I am calling a meeting of the Subcommittee on Carcinogenicity to be held in Chicago at the Conrad Hilton Hotel on Friday, September 10th. This meeting will be a closed meeting of the Subcommittee members and the Kettering Laboratory representatives. As an unofficial member of the Subcommittee, naturally Dr. Saunders has an invitation to attend. I believe it is the expressed opinion of all of the members of the Subcommittee that we will be able to accomplish work only if we keep the meeting small and confined to the members of the Subcommittee, and it is for this reason that I am calling this as a closed meeting.

Since I will be out of the United States on this date, I am making Dr. Hine Acting Chairman of the Subcommittee, and he will carry on from now with any further arrangements that may be necessary for the proper conduct of this Subcommittee meeting.

By carbon copy of this letter to Mr. Stroop, I am asking that he reserve a room in the Conrad Hilton Hotel for our Subcommittee for this date. By carbon copy of this letter to Dr. Morton I am requesting that he set aside this date on his calendar in order to attend this meeting with us, as well as Dr. Fhair to attend the meeting with us, and give us a progress report of the studies at the Kettering Laboratory, along with a prospectus of the future work for the next succeeding months after September 10th.

Very truly yours,

R. E. ECKARDT, M. D.

REE:ilk

cc: Messrs. A. W. Morton
J. J. Fhair
G. M. Saunders
D. V. Stroop

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

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

July 1, 1954

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

Dear Dr. Eckardt:

In response to a request made in your letter of June 25, 1954, arrangements have been made for the Subcommittee on Carcinogenicity to hold its meeting on Friday, September 10, 1954, in Private Dining Room 9, Third Floor, Conrad Hilton Hotel, Chicago, Illinois.

Very truly yours,

DVS:jm
cc: E. W. Adams
L. C. Beard, Jr.
Allan E. Dooley
F. D. Gaggeney
L. M. Henderson
C. E. Kline
A. W. Horton
E. K. Linder
R. C. Mithoff
M. M. Newquist
J. W. Osborn
J. J. Phair
F. J. Sanders
G. M. Saunders
Lacey Walker

August 11, 1954

Dr. Robert E. Eckardt
Medical Research Division
Standard Oil Development Company
P. O. Box 51
Linden, New Jersey

COPY

Dear Doctor Eckardt:

I am sending to you herewith, the necessary number of copies (for the Subcommittee) of the paper by Dr. Horton and Mrs. Denman in a form which may be presumed to be final, so far as we are concerned. As I have forewarned you in a copy of my letter to Dr. Wade, it has seemed wise to take account of certain objections to the original form of the first paragraph of the paper by preparing an alternative first paragraph. This I have done, and, for the sake of expedience and convenience, we have prepared an alternate to the entire first page of the paper, so that by common choice or consent the first original page can be removed and this substituted for it. This procedure may or may not be acceptable to you, and I leave the matter entirely to you and your associates, in such a manner, I hope, that no source of confusion or delay will have been created.

No doubt you will wish to issue a note or letter to accompany the copies of the article to their several destinations. If there is anything else which we should do, I should appreciate your letting me know.

Cordially yours,

Robert A. Kehoe, M.D.

RAK:mjg
CC: Mr. D. V. Stroop

August 7, 1954

Dr. Leo Wade, Medical Director
Esso Standard Oil Company
15 West 51st Street
New York 19, New York

Dear Doctor Wade:

I have a copy of your letter of July 20 to Dr. Eckardt, re the "Proposed publication by the Kettering Laborator(y) of 'Carcinogenesis of the Skin. I'," and it seems to me a matter of both wisdom and courtesy to write to you directly about it.

Let me say, first of all, that I had not known about your objections to the first paragraph of the paper. If I had I should have been prepared to meet them, at least in part. It now appears to me, perhaps incorrectly, that any significant change which I may make may delay the circulation of the paper at this time, and since time is short, I doubt the wisdom of so doing. I think you should know, however, that I shall not raise any objections to such further change, if the consensus of opinion runs in that direction. I should certainly not wish you to feel that we would hold to a manner of expression to which you and others take serious exception, especially in the purely introductory part of the paper, out of pride or insistence upon our own perogatives. On the other hand, I shall not disguise the fact that I find it difficult to agree with your objection to the first paragraph of this paper, and more specifically to the first sentence.

The first sentence of the paper, whether necessary or not, is, I think, a realistic expression of our purpose in carrying out our entire investigation, which has included other means than that of animal experimentation. The animal experiments with the products of a number of the petroleum companies, the methods of which are the subject of this paper, were not a series of academic observations made in the atmosphere of theoretical cancer research, but were, in fact, an attempt on our part to acquire useful knowledge of the potential hazards which might reasonably be expected to be associated with the handling of these products. The word <u>potential</u> takes the sting off of the direct implications of the method of investigation, while our concern with the specific response of mice to these products is no more or no less relevant to the "potential" response of man, than is the physiological response of experimental animals to the toxic products of the chemical industry as evidence of the potential hazards to which industrial employees are subjected. This is simply a method, albeit a somewhat faulty method, in both instances, of determining what we may expect.

If we deny our primary purpose in performing such experiments, we become somewhat precious, just as we become mentally lax, with respect to sound critique, when we attempt to make direct inferences from the behavior of experimental animals to that of man. I could elaborate on this thesis at some length and in some detail, with specific reference to the applicability of the response of mice to that of man, but I think I have made my point without laboring it. However we say it, therefore, and we could have said it in a simpler manner, or we might have left it unsaid without impairing the paper, the essential purpose of the entire experimental program is to assess the potential hazards of the industries involved, so as to alert physicians not only to the general, but to the specific and localized (i.e. to specific processes and products) potential hazards which it is their rôle to appraise in actual terms.

I do not believe you will find in the article, beyond this controversial paragraph, that any unjustified implications have been "read into the data."

The second, third and fourth sentences, when combined with the last, are, I think open, to some extent, to the criticism which you have made. The transition from the laboratory to the industrial environment and to the behavior of exposed personnel (personal hygiene) is a bit abrupt, and it may be thought of as conveying the implication that the two situations are different representations of the same thing, although I had not thought of this when I read it. I thought merely of the ultimate goal back of experimental method, as did the original author, and I, as editor, do not like to do violence to an author's train of thought and expression unless I believe it to be incorrect and misleading, or at least open to misinterpretation. I did not so believe in this case, but perhaps I had not given it sufficient thought.

The objection to the last sentence of the paragraph is not unreasonable, particularly, since this sentence follows immediately upon a reference, which, perhaps, is too casual, to personal and industrial hygiene. I am disposed to agree that it should state the truth of the experimental method - i.e. that the measurement of the first variable concerns itself solely with the response of mice.

Despite what I have said about changes at this time, I shall rephrase a first paragraph on a separate sheet, this to be attached to the copies to be circulated, if in Dr. Eckardt's and Mr. Stroop's opinion this will not delay unduly the completion of the clearing of this paper for publication.

If I have failed to appreciate the full significance of your comments, I should be glad to have you write to me further.

With kindest regards.

Sincerely yours,

Robert A. Kehoe, M.D.

RAK:vr
cc: Dr. R.E. Eckardt, Dr. A.W. Horton

ESSO STANDARD OIL COMPANY

15 West 51th St. N.Y.,19, N.Y.

July 20, 1954

Re: Proposed publication by the Kettering Laboratories of "Carcinogenesis of the Skin. I

Dr. R. E. Eckardt
Medical Research Division
Standard Oil Development Company
Post Office Box 51
Linden, New Jersey

Dear Dr. Eckardt:

Please forgive me if I seem overly persistent in objecting to the opening paragraph of the above paper. The opening sentence " The investigation of skin cancer in this Laboratory has been concerned with the estimation of the extent of the potential hazard of this disease in certain industries" is simply not in keeping with established facts and contributes nothing to the meaning of the paper other than possibly abetting some already established misconceptions. The statement is erroneous in the sense that only doctors dealing with human beings exposed to the substances in question under existing working conditions can determine whether or not an actual hazard exists. I believe Mr. Horton and Miss Denman would be well advised not to read into their data more than is justified by the facts which they have established. To my way of thinking, this detracts nothing from the importance of the fine job they have done.

It would be my suggestion that the first sentence be replaced by the following: "A number of chemical substances have been suspected of being etiological agents for cancer of the skin." In addition, I would insist the the final sentence read " ..... methods of determining the first variable for mice, the level of activity ....." If it is firmly established at some time in the future that the mouse data are directly transferrable to humans, there is no reason to doubt that this publication will have proved any less useful.

Sincerely yours,

LEO WADE, M.D.

LW:HH

cc Dr. G. M. Saunders
Mr. D. V. Stroop
Dr. R. A. Kehoe

A-313-A

STANDARD OIL COMPANY
(INDIANA)

RESEARCH DEPARTMENT
WHITING RESEARCH LABORATORY
P. O. BOX 431, WHITING, INDIANA

E. W. ADAMS
ASSOCIATE DIRECTOR OF RESEARCH

June 3, 1954

Sub-committee on Carcinogenicity
Meeting of June 18-19, 1954

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

Dear Dr. Eckardt:

I regret I shall be unable to attend the meeting of the sub-committee on carcinogenicity at Cincinnati on June 18 and 19. I shall be tied up in other activities at that time. I could have participated on June 7 since I am scheduled to be nearby in Columbus the latter part of that same week.

As to our budget for 1955-1956, I feel we should proceed on about the same basis as currently. I make this statement on the presumption that there are no new developments which indicate we should extend the current program. In the latter case, I would not be unalterably opposed, but feel any such proposed expansion must be extremely well justified.

Over-all, I feel the manuscript, "Carcinogenisis of the Skin, I", is in excellent shape. I do have a few minor comments, largely of an editorial nature, which I am tabulating below:

1. Page 3, lines 5 and 6:

The sentence, "The same trouble has been experienced in recent experiments with Swiss males, although the females seem to be more congenial.", seems a bit humorous when taken out of context. I recommend this sentence be modified.

2. Page 4, lines 5 and 6:

The phrase, "a small camel's hair brush ——," would be better stated as, "a small camel-hair brush ——." This is to avoid the inference that the hair is from a small camel.

3. Page 9, last line:

The words "--- following Table:" presumably refer to Table I, which is not mentioned as such in the text. I recommend that "--- Table I:" be substituted for "--- the following Table:". If not, then the Table should not be labelled "Table I" and the other tables should be renumbered accordingly.

4. Page 16, 3rd line from the bottom:

"--- ascertaining ---" is misspelled.

5. Page 23, 3rd line from the bottom:

I suggest the term, "--- i.e., ---," be changed to, "--- e.g., ---". The statement now infers that 20 and 100 are specific and required whereas, I believe, they are cited only by way of example.

6. Page 24, paragraph 2, line 11:

Start the sentence with the phrase, "On the other hand, 7,12-Dimethylbens [a] anthracene ---".

7. Page 26, line 4:

I suggest the example cited in the sentence beginning, "Thus, since 0.345 per cent ---" be keyed back to experiment 214, as has been done later on the same page.

8. Page 26, paragraph 2:

Some attention should be given to the sentence beginning the paragraph where Experiments 244, 252, and 282 are cited to give the relative potency of benzopyrene on this scale as a range of 57-65. The data do not support the range quoted. My calculations from Table III are as follows:

Experiment 244	58 and 52
Experiment 252	56, 34 and 40
Experiment 282	No data in Table III

Based on data from the Table, the range is thus 34-58 and not 57-65 as given in the text. The Table and the discussion in the text should be revised to be in agreement.

9. There are a few instances where sentences contain in the range of 60 to 70 words. This tends to be a bit cumbersome for the average reader and is to be avoided, if at all possible. Robert Gunning, writing counselor, refers to such sentences in terms of "high-fog index."

I shall look forward to receipt of a copy of the minutes of the meeting and I am sincerely sorry I cannot attend.

Very truly yours,

E. W. ADAMS

EWA:eb

cc: Mr. A. Wesley Horton

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

June 4, 1954

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

Dear Dr. Horton:

The other day when I was talking to you on the telephone, you suggested that I send you some preliminary comments concerning the manuscript on "Carcinogenesis of the Skin, I". I am listing below the comments which have been collected from various interested people in our affiliates, as well as the Development Company, along with some of our own comments from this Division concerning the paper.

It has been suggested that the title of the paper be changed to read "Experimental Carcinogenesis of the Skin, I" . . . since the paper deals with experimental carcinogenesis in mice and not with the clinical aspects of carcinogenesis.

It is suggested that the first paragraph of the first page be rewritten, since the Kettering Laboratory's work thus far on this problem has not really been concerned with the estimation of the extent of a potential hazard but only in determining the relative carcinogenicity of various petroleum oils and fractions. I believe it is the feeling of the members of the Subcommittee, as I can assure you it is mine, that the determination of the relative carcinogenicity is information which will then be interpreted in terms of hazard by the medical men of the Medical Advisory Committee of the American Petroleum Institute. This is due to the fact that these medical directors are in a position to determine the nature and extent of the exposure, and hence the degree of the hazard.

In the first sentence of the second paragraph, I believe it would be wise to indicate that mice were chosen as experimental animals for reasons in addition to the one given; for instance, because guinea pigs are unsuitable, rabbits develop mainly papillomas rather than cancers, and monkeys take too long. It even occurs to me here that some reference to previous work on experimental carcinogenesis, in which it was decided that mice made the most suitable animal, might be indicated.

In the second sentence of this paragraph, it is suggested that the certain specific materials be identified since it may be concluded by some people that these materials are high boiling catalytically cracked oils. You may wish to refer to slack waxes, cutting oils and shale oils, as well as coal tars, in this sentence, and I would suggest that references be given for each of these.

In the first paragraph of page 2, the 6th line, I believe it is unfair to previous investigators to say that they met their problems only by increasing the number of animals on test. This is assuredly not true and might be misleading to those who are unfamiliar with this type of work. It also occurs to me here that you might give some credit to Dr. Smith and his work on this subject since it was available to you at the time that you began your investigations and you were therefore in a position to benefit by the experience which he had already accummulated.

On page 6, first paragraph, first sentence, we believe this should be changed to read as follows: "The date of which each typical papilloma reached the arbitrary minimum size of approximately 1 mm. in diameter . . ." since the size of the tumor is estimated at examination times rather than accurately measured, and on occasion tumors greater than the minimum may have appeared between periods of observation.

In the 3rd line from the bottom on page 6, it is suggested that the sentence "The method of relating this variable frequency of application to standard methylcholanthrene curves which are independent of frequency of application will be discussed in a later section." be inserted immediately following the sentence ending in "12 weeks". It is believed that such an explanatory sentence is essential here since the immediate question which comes to my mind without it is: How can the potencies of different materials be compared if the severity is varied?

On page 8, the following comment is made concerning the calculation of the mean time of appearance of tumors:

A straight line is fitted to the points by the method of least squares, using <u>all</u> the points for computation (at least nothing is said about excluding points). This is, of course, the best way to get the "best straight line" when all points have comparable apriori reliabilities. However, it is well known that this condition does not usually hold for probit plots; that is, points lying either under about 16% cumulative frequency, or above about 84% cumulative frequency, are generally excluded during construction of the probit line. In the language of statistics, "the permissible magnitude of random deviations from the theoretical line is considerably larger for probability values close to 0 and 100% than for values in the neighborhood of 50%". This means that when determining the straight line which gives the graphical estimate of the theoretical straight line, the extreme points are less important than the mid-points (Ref. - Hald, "Statistical Theory", pp. 138-9).

In the S.O.D. work this was taken into account by visually plotting the line to give the best fit to the intermediate points, and attaching little or no weight to the points under about 20% or over about 80%. This unsophisticated method of constructing the line through the probit plot is, in fact, recommended by the leading authority on the subject (Finney, "Probit Analysis") for the statistical reason stated above. In other words, we feel that it is just as valid to plot the lines visually as to go through a series of complicated calculations which statisticians do not feel are justified.

In the 3rd sentence in the first paragraph on page 8, is it not true that if tumor response varies linearly with dosage, it will also vary linearly with the logarithm of dosage?

We believe that the last sentence of the first paragraph of page 8 is irrelevant to the paper and can be omitted.

It is suggested that in Table I, a column giving the cumulative percentages of tumors be inserted for the benefit of those individuals not familiar with the probit techniques. This will give them a method of following the results which you are discussing more carefully.

On page 12, the first sentence of the second paragraph, it is believed that this would be less confusing if it were reworded as follows: "Not infrequently, as the animals recover from such disturbances, a large proportion of the animals develop tumors of a measurable size in a relatively short time." As it reads now, it implies a relationship between the size of tumors and the frequency of response, and I am sure that you do not wish to imply this.

In the 3rd sentence of this paragraph, it would be helpful if you defined what you mean by the normal standard deviation of the mean time of appearance of tumors. It is further suggested that the following sentence be inserted at the end of this paragraph: "This is an example where statistical analysis of biological data may lead the experimenter to a false sense of security concerning the validity of his results if he ignores or is not aware of other biological variables which force him to reject certain experiments as unsatisfactory."

On page 13, the 7th line, it is not felt that Figure 3 illustrates too clearly the point being made. It is suggested that another example be substituted for Figure 3 and that preferably a methylcholanthrene standard be used since this paper is not concerned with the tests on oils but only with the variables of methylcholanthrene standards. If this example must be used, then it would be advisable to identify the oil completely as to its source, that is, operation from which produced, the charge stock to the unit, and its physical properties. I do not mean to imply that the company furnishing the sample be identified, but only that the oil be identified sufficiently so that one could understand what type of an oil is being talked about.

In the next sentence following the above, the reference to size of tumors is again confusing and it is suggested that this be rewritten as follows: "Thus, in such experiments, the time of appearance for what meets our arbitrary specification for a tumor (a minimum size of approximately 1 mm. in diameter and 1 mm. in elevation) may be delayed, thereby lengthening the apparent average period of exposure required for the induction of tumors by the material under test."

On page 15, in the last 3 lines from the bottom, the terminology for the pure carcinogens follows the modern approved chemical terminology. Since this is to be published in a medical journal and, in general, the medical literature has continued to use the older terminology, it might be advisable to insert a footnote giving equivalents, or to use the older terminology even if it is felt to be chemically not as accurate. Thus, certain people who read this paper may believe that the 3-methylcholanthrene which you mention is actually something different from 20-methylcholanthrene.

On page 16 and in Table II, the determination of Class A, B or X experiments is not dependent upon the 5% fiducial limits but on an arbitrary evaluation of all the data by a competent biologist. Therefore, it is suggested that the fiducial limits be given either for all classes of experiments or for none. Otherwise it might be interpreted that the X experiments are so classified because of large fiducial limits. In other words, the last two columns of Table II are completely unrelated since the last column depends only upon an arbitrary subjective impression of the biological experimenter.

On page 16, in the last paragraph, are the results with the so-called "impure methylcholanthrene" included in the standard curve? In accordance with the data of Miller and Baumann (Cancer Research, 3:217, 1943), pure methylcholanthrene melts at 179.5-181°C instead of the 176-177°C recorded here. Therefore, it should have been recognized immediately that this was an impure sample of methylcholanthrene. If the amount of impurities indicated by this difference in melting points was due to impurities of similar structure (a plausible assumption), one would not expect to be able to detect it by UV absorption. In any event, one would not regard 177°C mp MC as very impure. Is it to be assumed that so-called "pure MC", which represents the "normal material", also had an mp of 176-177°C? If so, then one might conclude that all of the standard curves have been developed with an impure carcinogen and, therefore, all are inaccurate or incapable of reproduction by another investigator who purified his MC by the method of Miller and Baumann until it had a melting point of 179.5-181°C. If the above statements are true, then it is essential that a standard bio-assay for a standard methylcholanthrene be presented and that these standards be accurately defined. Any deviations from either the standard of purity of methylcholanthrene or the bio-assay obtained with this standard of reference for methylcholanthrene would be suggestive that other impurities are influencing the results. In essence, what this paragraph implies, if true, is that the Kettering Laboratory is setting itself up as an international standard of reference for the purity and biological action of methylcholanthrene against which all other methylcholanthrene standards must be checked. I am sure that you do not wish to undertake this responsibility.

On page 19, in the first line, the use of the word "dosage" is confusing without a complete understanding of the difference between a dosage applied and dosage per unit area of skin. It is suggested that the word "dosage" be used only when referring to dosage per unit area of skin, and that a word such as "quantity" or "amount" be used for all other purposes. Thus, this sentence should read ". . . variation in the quantity applied . . ." These comments also apply to page 4, lines 3, 4, 11 and the last line, where "quantity" might well be substituted for "dosage" or "dose".

On page 19, first paragraph, first sentence, it would be better if the following phrase were added to the end of this sentence: "if it can be assumed that a 20 mg. sample covers one-fifth of the area of skin covered by a 100 mg. sample". Since on page 4 it is stated that animals were shaven for the application of less than 100 mg. and were not shaven for 100 mg. applications, this assumption is extremely difficult to accept.

In the first sentence of the second paragraph on this page, it would be clearer to say: "The values in column 5, Table II were obtained by multiplying the concentration of methylcholanthrene in the solutions by the number of applications per week." The second sentence of this paragraph should read: ". . . variations in the concentration of the carcinogen in any one solvent did not affect . . ."

In the third sentence of this paragraph, this assumption is difficult to believe, as the animals were shaved for 20 mg. applications and not for 100 mg. applications.

In the formula given at the bottom of page 19, do all the changes in the formula in the first draft of the manuscript imply that as more data are obtained, this formula will be subject to constant revision? If so, then it should be clearly stated in the paper that this is a tentative formula derived from the presently available data, subject to change as more data are collected.

On page 20, lines 1-9, it is believed that this section should be left out since it seems to add confusion when inserted at this point.

In the second sentence of the first paragraph, page 20, where the data in Table III are discussed, this should read ". . . together with some data on a solution of methylcholanthrene in cotton seed oil." since this is the only methylcholanthrene solution included in the table.

On page 22, in the third sentence of the first paragraph, the implication is that the S.O.D. method of determining potency numbers is an adaptation of the Iball index. This is in fact not true and the Iball index was referred to along with several other methods in the publication by Blanding et al, reference 13.

Fifth sentence, same page, in addition to variations in experimental technique, there are countless other variations which may influence results and make comparison of data between laboratories difficult.

In the first sentence of the second paragraph, it has already been stated on page 20 that benzpyrene does not make a good standard of reference; therefore, it should be omitted from this sentence. The opening portion of the next sentence should therefore also be omitted at this particular point of the discussion and the term "methylcholanthrene" substituted for the term "former", and the rest of the sentence changed accordingly.

On page 23, first line, delete the phrase "supposed to be" since the reference cited already reported the isolation of a methyl chrysene and an isopropyl benzanthracene. These compounds either are present or the work cited is not true, if the term "supposed to be" is used.

On page 23, in the formula, the same comments made concerning the formula on page 19 apply also to the first draft of the formula given here.

On page 23, lines 2 and 3 from the bottom, substitute the term "quantity" for "dosage".

On page 24, lines 1-6, it would be clearer if the thoughts expressed in these 6 lines were presented immediately prior to the last sentence on page 23.

On page 24, the first sentence of the first paragraph should be modified with the phrase "other things being equal" added to it.

In the last sentence of this paragraph, it should be pointed out that the same precaution outlined for dimethyl benzanthracene applies to methylcholanthrene as well, since it can also oxidize, especially in light, to a non-carcinogenic oxidation product.

On page 25, first paragraph, first sentence, does this mean data collected at the Kettering Laboratory but as yet unpublished? If so, it should be so stated. The way this sentence now reads it is not clear whether these data were published by others or unpublished data of the Kettering Laboratory.

On page 25, line 6, how does the statement concerning 10 mg. of sample tie in with the statement made on page 4, last line, indicating that a quantity as low as 5 mg. per application was used?

On page 25, last line, and page 26, first line, the terms "relative carcinogenic potencies" or "relative potency" are used frequently, although here they have a different connotation than, for example, on page 23. It might be advisable here to refer to this as perhaps the "per cent of activity relative to methylcholanthrene", which is, in fact, what this really is.

On page 26, the second sentence of the first paragraph following the formula, in referring to the data from Experiment 252, how can one know that the same effect is not occurring with a complex oil mixture?

On page 27, first sentence after the formula, the concept of non-accelerating solvents and the specific area of 10 sq. mm. are not discussed in the text but are new concepts being introduced into the summary. It is our belief that these terms should either be discussed fully in the text or excluded from the summary.

In the second sentence after the formula, this should read ". . . good health of the mice, as measured by their growth and other factors . . ." since such factors as mortality, infestation with lice, biting, etc. have also proved essential factors in obtaining reproducible results.

The last paragraph of the summary should probably be omitted entirely since it implies more than is actually presented in the paper on the relative potencies of complex oils. We believe it would be advisable to completely rewrite the summary in order to give a better indication of the important points to be made in connection with the development of the reference standard rather than devoting so much time of the summary to discussing its application to complex oils. The following are some suggested points to be made:

(1) The potency of a sample is shown to be related not to the frequency of application but rather to the dosage, defined as the dosage per unit area of skin per week.

(2) The comparative potencies of 9, 10-dimethyl, 1, 2-benzanthracene and benzpyrene in terms of the methylcholanthrene standard were found to be 180 and 60 respectively.

(3) A standard curve relating dosage to mean time of appearance of tumors is presented for methylcholanthrene solutions in benzene.

(4) It is suggested that the standard curve will find application in expressing the relative potencies of complex oil mixtures.

(5) It is suggested that a standard of reference of this nature may make comparison of results obtained in different laboratories more simple.

(6) It was found that varying concentrations of a pure carcinogen in any one solvent spread over approximately the same area of skin etc., etc.

General comments concerning particularly Figure 1 and Table II:

(1) It is somewhat discouraging that only one A experiment is represented in the reference standards.

(2) Relatively few of the experiments on the reference standards meet the criterion 12-20 weeks for mean tumor induction.

(3) Wide differences in the mean tumor induction times corresponding to small differences in d and vice versa leave much to be desired for a standard reference curve.

(4) The table might be arranged in order of increasing dosage per unit area per week for ease of comparison.

(5) One of the data sheets included for a methylcholanthrene solution is not represented in the table. Is this an oversight, or have other experiments on methylcholanthrene been omitted?

(6) Inconsistencies between the data sheets presented and the table should be corrected. For instance, for Experiment 220, the mean time on the data sheet is 10.1 ± 1.6; in the table it is listed as 9.7 ± 1.6.

In spite of the above criticisms and comments concerning this manuscript, policy-wise I want you to understand that I have no objections to your publishing this paper as it now stands and disregarding any of our comments. My comments are all directed from the scientific viewpoint rather than from a policy standpoint, since the policy has already been clearly established in the contract which the API has with the University. I trust that you will take these comments and criticisms as being constructive ones which we feel would improve the quality of the paper to be issued from the Kettering Laboratory.

There is one additional general comment which I would like you to be thinking about which has concerned me considerably after reviewing your paper. If the mean time of any experiment is to be chosen such that the average latent period will be as close to 15 weeks as possible, then potency is a direct variable of frequency of application per week; and if only 3 frequencies of application are used, then only 3 degrees of potency are expressed, namely, that potency which occurs with applications once a week, that which occurs with applications twice a week, and that which occurs with applications three times a week. What your data show is that you can; with a greater degree of surety than previous investigators, place any particular material into one of these three categories and by increasing the number of applications per week to greater than three, or by decreasing them to less often than once a week it might be possible to expand the degrees

of carcinogenicity being demonstrated. This comment is particularly evident if you take the section of your standard curve between 12 and 20 weeks and blow it up on an expanded scale. What you then obtain is essentially a scatter of points around the 15 week interval which does not seem to follow any particular standard curve. In other words, the limits of your curve are defined by its tails, which you admit represent unsatisfactory conditions of animal testing, and the useful portion of the curve, namely, that centering around the 15-week average induction period, gives a broad scattering of points which do not seem to be related to the curve unless the tails also are visible. I am simply adding this final comment for you to think about prior to our meeting in Cincinnati and hope to have the opportunity of discussing this more fully with you when I see you. Personally, I do not think it detracts from the paper if this is so, but I am not sure that all readers would come to the same conclusion. In addition, some of the more critical readers might draw this conclusion from your paper and suggest that you were claiming more for the method than it was capable of determining.

I am looking forward to seeing you and the rest of the Kettering Laboratory staff on June 19th.

Sincerely yours,

R. E. Eckardt
I.L.K.

R. E. ECKARDT, M. D.

REE:ilk

Dictated but not read.

April 29, 1954

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

Dear Doctor Eckardt:

There was no opportunity to discuss the manuscript on carcinogenesis in any detail in Chicago with the subcommittee members. Dave Stroop suggested that I send him the stencils so that he could distribute copies to members of the subcommittee and perhaps also to the general committee. At any rate, I expect that you will have had a chance to judge from the copy sent to you whether a meeting will be needed to discuss the paper or if you can depend upon an adequate response by correspondence.

I believe any date in May except the period from May 11 to 20 would be OK at this end if you want to call a meeting.

Sincerely yours,

A. Wesley Horton

AWH:mjg
CC: Mr. David V. Stroop

April 13, 1954

Dr. Robert Eckardt
Medical Research Division
Esso Laboratories
P.O. Box 51
Linden, New Jersey

Dear Bob:

Enclosed are six copies of the final draft of our paper on benzpyrene for the meeting of the Medical Committee of the Board on April 21.

I believe we shall have our first draft of the initial paper on carcinogenesis ready for the April 27 meeting of the subcommittee. Has a definite time and place been set?

Sincerely yours,

A. Wesley Horton

AWH:mjg

Whiting, Indiana - February 19, 1954

Dr. B. B. Reeve
Chicago Office

Dear Sir:

This will acknowledge your note of February 10, transmitting the manuscript from Kettering Laboratory on the Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures.

As you probably know, I have had the opportunity of going over this in rough form at Cincinnati with the Projects Advisory Committee.

Over-all, we feel the paper is in good shape and a worth-while contribution to the literature. We do have a few minor editorial comments which, by copy of this letter, I am also passing on directly to Dr. Horton. These are as follows:

1. Page 11, paragraph 2, line 5, under Section B--The phrase "careful evaporation" should be amplified to indicate wherein care must be used in order to avoid sputtering or entrainment of droplets with the stream of nitrogen in order that the recovery can be quantitative.

2. Page 11, Section B, line 1--It may be preferable, rather than to specify exactly 100 mg., to insert the phrase "weighed to the nearest 0.1 mg.".

3. Page 16, under Section on Repeatability--The range of 0.0025 to 0.5 is outside the limits shown in the table at the bottom of the page. We believe the table should show the precision of the method for the extreme limits indicated. At least a sentence should be included to cover the precision at the extreme limits.

4. Page 17--It would be preferable if measurements could be shown on samples containing known amounts of "interferers". There is also the possibility of negative "interferers".

5. Page 20, paragraph 1--The statement of the size sample should again be made, i.e., the limit of sensitivity should be stated as 0.0001 µg. when using a 100 mg. sample.

I regret not having returned this to you sooner but have been out of town for several days.

Very truly yours,

E. W. ADAMS

EWA:cb
Encl
cc: Dr. A. W. Horton

Comment 10 - Who ?
3

Shell 7
Texas 10
Carey
Carey
Atlantic

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 5, 1954

Dr. A. Wesley Horton
The Kettering Laboratory
University of Cincinnati
School of Medicine
Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Horton:

To date I have received the following comments concerning your paper for publication:

1) It is apparent from the statement at the bottom of page 20 that the authors realize that the procedure is empirical. It is probably for this reason that no mention is made of possible reactions of iodine with substituted benzo [a] pyrenes and other benzo [a] pyrenes. The study of these possible reactions would entail a considerable amount of additional work.

Carey

The method is admittedly long and tedious. It would probably be improved and shortened by the use of a Carey ultraviolet spectrophotometer instead of point scanning. Furthermore, other possible shortcuts might be worked by the use of this instrument.

2) One thing I am wondering about, however, which probably is due to my ignorance, and that is - if the primary purpose of the paper is to describe an analytical method for determination of benzopyrene in complex mixtures, and if it is a fact that it has heretofore been published that benzopyrene is potentially carcinogenic, then might it not be possible to rewrite the paper, letting it deal exclusively with the analytical method and removing all comments with regard to carcinogenic properties, and have it just as effective for analytical purposes?

3) We have reviewed Dr. Horton's paper on "An Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures". We can see no objection to its publication from a general standpoint.

4) Several members of our technical staff and of our papers committee have reviewed it and their consensus, as well as my own belief, is that it represents technical work of high quality. It has, therefore, my unqualified approval as comprising suitable material for publication. Also, I think that it is worded in such a way that it would not be subject to criticism from the policy standpoint as a publication sponsored by the Medical Advisory Committee.

Members of our staff have pointed out that it may be quite difficult to find a suitable magazine for publication of the article in its present form. It contains a description both of a research project and of an analytical method, and the research on developing the analytical method also is described. This combination does not agree with the editorial policy of any technical magazines with which we are familiar. It may be found necessary to split it into two articles to be published separately. I assume that this is a problem that the Kettering Laboratory people will resolve.

4. 5) I have reviewed in some detail the manuscript of Dr. Horton's paper entitled "An Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures". I think that it is very well written and an excellent piece of work. I have no criticism nor suggestions to make regarding the publication of this paper.

5. 6) In regard the proposed publication of an article by Wesley Horton, we agree that it should be done.

6. 7) The manuscript by Dr. A. Wesley Horton and associates entitled "An Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures" was reviewed, and I have no criticism to make concerning its publication.

A review by technical people in our Spectroscopic Department led to the comment that it is an excellent paper and shows much ingenious thought.

7. 8) We have reviewed carefully the proposed publication entitled "An Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures".

We have no objection to the publication of this material in its present form.

8. 9) My technical advisor and I have just completed reviewing the copy of the manuscript which Dr. Horton wishes to submit to the Journal of Analytical Chemistry.

We feel that it will be permissible to have such a paper published; however, there are two minor changes that we feel should be made. On page 1, the first sentence of the Prefactory Summary we feel that the two words "a heavy" should be inserted after the word "in", in the second line, the sentence would then read as follows:

"This paper describes the isolation and identification of the polycyclic hydrocarbon, benzo (a) pyrene, in A HEAVY oil produced by catalytic cracking of petroleum,"

On page 20, we feel that two sentences should be deleted from the final paper, the change would be in the second paragraph on that page. The paragraph reads:

"The method was developed primarily for application to various heavy petroleum products resulting from refining operations." We feel the following should be deleted, "It has been applied to more than thirty such materials which have been subjected to biological testing for carcinogenic potency. All analytical data thus far obtained have been plausible in the light of the observed potencies and the known physical properties of the materials." The remainder of that paragraph is not questionable.

We feel that if this paper is being submitted as a chemical physical study for the determination of benzo pyrene, that is all the paper should refer to. We do not believe that biological testing for carcinogenicity should enter into the paper, as it may raise question in many minds as to just what we have done along the lines of cancer potency testing, and we do not feel that this should be for publication at this time.

10) We do not believe that it is necessary to call attention to a physiological property of a material in a paper describing a purely analytical procedure. For that reason we would suggest elimination of any reference to the carcinogenic properties of benzo [a] pyrene in the introduction (page 1) of the manuscript. Elimination of such reference will not weaken the paper or detract from its value in any way.

Dr. Horton's paper has also been reviewed by several of the people in our research laboratories from the purely analytical standpoint and their suggestions are attached hereto.

11) I have reviewed our copy of the paper entitled "An Analytical Method for Determination of Benzo [a] Pyrene in Complex Mixtures" which Dr. A. W. Horton wishes to submit to the Journal of Analytical Chemistry for publication.

I have also had this manuscript reviewed by our technical people who have offered the following comments which I wish to forward for Dr. Horton's information:

"1. On Page 6, I feel that the paragraph on molecular complexing with Lewis acids and fluorine acids is quite superfluous and could best be eliminated from the paper.

"2. On Page 16, I would suggest that the new section be headed "Repeatability", and that on Page 17, another new section be headed "Interferences". This would make the paper a little clearer.

"Otherwise, I find the paper would be an excellent contribution and strongly recommend its publication."

I concur in these comments and hope that they will add constructive criticism for Dr. Horton prior to the final draft of his paper before publication.

It is my intention to call you sometime next week after you have had an opportunity to review these comments in order to determine what your reaction to them has been.

Sincerely,

R. E. Eckardt
I.L.K.

R. E. ECKARDT, M. D.

REE:ilk

Attachment

Tepco

Attachment mentioned in comment No. 10.

a In the procedure used to isolate benzo (a) pyrene from a sample of oil, described on page 2, more details should be included concerning the chromatographic procedures used and the method of purification of the benzo (a) pyrene,

b so the isolation could be repeated if desired. It would be useful to further describe the process used to purify the 6-iodobenzo (a) pyrene.

The chromatographic procedure used in the analytical method itself could be followed without difficulty.

A section giving details on the calibration of the spectrophotometer should be added. The calibration absorptivity, $a = \frac{\Delta A_{BP}}{mg.}$

c should be obtained using several standard samples of varying concentrations.

a = calibration absorptivity. In the method this is 0.23.

ΔA_{BP} = base-line absorbance of the difference spectrum measured at 389 mμ.

mg. = milligrams of benzo (a) pyrene in the standard samples. Using this technique, non-linearity between ΔA_{BP} and concentration will be revealed. If none exists, as is assumed in the method, the calibration absorptivities, a, will be constant, within experimental error, and the final value is obtained by taking the average of several determinations on standard samples of varying concentrations.

If non-linearity exists between ΔA_{BP} and concentration, more accurate results will be obtained if an analytical curve is used plotting ΔA_{BP} versus concentration in the desired range.

Calculations can be clarified by reducing the first equation on page 15 to:

Per cent benzo (a) pyrene =

$$\frac{\frac{W_2}{W_1} \times \frac{\Delta A_{BP}}{a \approx 0.23}}{W_S} \times 100$$

where W_1 = weight of original eluate solution, grams

W_2 = weight of eluate after concentration or dilution, grams

W_S = weight of sample, mg.

ΔA_{BP} and a are defined above.

The fraction $\frac{W_2}{W_1}$ is adjusted to an equal value for Solutions I and II as described on page 13.

In case changes in volume are unnecessary then $W_2 = W_1$ and the equation is reduced essentially as it is on page 15:

Per cent benzo (a) pyrene = $\frac{\frac{\Delta A_{BP}}{a}}{W_S} \times 100$

January 25, 1954

Dr. Robert H. Eckardt
Medical Research Division
Esso Laboratories
P. O. Box 51
Linden, New Jersey

Dear Doctor Eckardt:

We have forwarded under separate cover ten completed copies of the manuscript, "An Analytical Method for Determination of Benzo[a]-pyrene in Complex Mixtures", for submission to the API board, and an additional one for your own use. We are assuming that pertinent comments and suggestions for recording will be received prior to April 1.

If you intend to pass the procedure along to Bob Shepardson or John Rehner, three minor changes should be made. On Fig. 2, page 9, the length of the upper section of activated alumina should be measured from the upper surface of the retaining disk, the indicated dimension, 1 1/8 in., being that obtained after gentle packing of the alumina (by tapping the column six times with a pencil).

The size of the glass tubing of which the column is constructed is 25 mm. O.D. (the actual inside diameter of the standard 25 mm. tubing attached to the Corning 39570 fritted disk is 22.6 mm).

In line with your suggestion, line 1 of Step 8 on page 11 has been changed to "Approximately 100 mg. (weighed to the nearest 0.1 mg.) of the material to be analyzed".

In the event that anyone wishes to use the copies of the procedure passed out at our meeting on January 21, it should be particularly noted that certain changes have been made on page 10. The volumes on line 13 now should read "120-150 ml.", that on line 18, "100 ml.", and the volume on line 21, "170 ml.".

Thanks very much for the additional information on the benzene and propylene tetramer used in the synthesis of Dodecylbenzene, tested as API-221.

With best personal regards,

Sincerely yours,

A. Healey Horton

AHH:mjg
CC: Dr. C. H. Hine
Dr. E. K. Linder
Dr. H. W. Newquist
Dr. R. W. Adams
Dr. L. C. Beard
Dr. L. K. Henderson
Dr. R. C. Mitkoff

meeting
6/19/54

ESSO LABORATORIES

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

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D.
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HEAD TOXICOLOGIST

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

July 13, 1954

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

Dear Dr. Saunders:

I am attaching the report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee of the API. This report summarizes briefly the work which has thus far been done, the expenditures thus far made, the anticipated future work to be done under the auspices of this Subcommittee, and the proposed budget for the period July 1, 1955-June 30, 1956. You will note that the Subcommittee suggests that funds in the amount of $65,000 be solicited for the continuation of the work of the Kettering Laboratory during the period July 1, 1955-June 30, 1956. This represents a reduction of approximately $7,250 in the amount already budgeted for the interval July 1, 1954-June 30, 1955.

It has been suggested by one of the Subcommittee members that this report should contain a statement which would describe the benefits which this study would accomplish for the oil industry. It is my belief that the benefits to be expected by the oil industry are contained in the brief outline of future work. However, if in your opinion this would not suffice, then I believe the following statement might be added to this report immediately following the section on future work and immediately preceding the estimated budget for July 1, 1955-June 30, 1956.

> "It is anticipated that this work will benefit the petroleum industry by providing basic information which will permit the petroleum industry to control its own potential carcinogenic hazards without governmental regulation."

As Chairman of the Subcommittee on Carcinogenicity, I respectfully submit this report of the Subcommittee.

Very truly yours,

R. E. ECKARDT, M. D.

REE:rlk
Attachment

cc: Messrs. J. L. Rhein
F. Healy Morton
R. A. Kehoe
D. W. Streep

THE REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY

TO THE MEDICAL ADVISORY COMMITTEE OF THE API

The Subcommittee on Carcinogenicity of the API Medical Advisory Committee, one of the first subcommittees created, was established early in 1945. It was formed after it became known that certain petroleum oils and fractions had been demonstrated to possess fluorescence similar to certain known carcinogens, and, when painted on mice, produced tumors and cancers.

Negotiations were then begun between this Subcommittee and Dr. Kehoe of the Kettering Laboratory which culminated, early in 1946, in an agreement between the API and the University of Cincinnati under which the Kettering Laboratory of Applied Physiology would "investigate the toxicity and mode of action of certain petroleum products".

The investigation began with the testing of 8 oils supplied by three participating companies, in addition to negative controls of water and white oil and positive controls of methylcholanthrene. Of the 8 oils tested, only 2 produced skin tumors in mice. One of these was an unflashed thermal residue, the other a clarified oil. These investigations were carried out at a cost of $6,000, and were reported in detail to the Subcommittee by the Kettering Laboratory on November 5, 1948.

However, when the results were becoming apparent early in 1948, the Medical Advisory Committee, on the advice of the Subcommittee on Carcinogenicity, forwarded to the members of the Safety Committee of the Board of Directors of the API a resolution dated April 5, 1948. This resolution called upon the Executive Committee of the Board of Directors "to establish a comprehensive research project for the development of fundamental facts, analytical techniques and related information pertaining to cancer-causing compounds which may occur in petroleum or be produced therefrom". This resolution called for the solicitation of contributions to a special research fund in the amount of $110,000 for the first year, of which $50,000 would be a non-recurring capital expenditure for construction of extraordinary experimental facilities at the Kettering Laboratory. This resolution was presumably approved by the Executive Committee and on July 1, 1948 a check in the amount of $65,000 was sent to the Kettering Laboratory, $40,000 of this amount as a grant for animal quarters.

With the expansion of this research project in 1948, A. W. Horton, Ph. D. was added to the staff of the Kettering Laboratory to supervise the chemical and biological work on petroleum and petroleum fractions, and the services of J. J. Phair, M. D., Professor of Preventive Medicine, University of Cincinnati, College of Medicine, were made available to the staff to develop and supervise an epidemiological survey of the incidence of cancer in the petroleum industry. From this point on, the research project can be divided into two phases, namely (1) the chemical and biological work, and (2) the epidemiology.

1. The Chemical and Biological Work

Under Dr. Horton's supervision, an expanded program of biological testing for carcinogenicity was begun on a variety of petroleum fractions selected and provided by the technical staffs of the participating petroleum companies. It soon became evident that in order to express the relative carcinogenicity of different petroleum fractions in a quantitative fashion, it would be necessary to develop standards of reference to which the petroleum fractions could be related. For this Dr. Horton began biological work with solutions of a recognized carcinogen, methylcholanthrene, in varying concentrations in various solvents. This work clearly showed that a biological assay for carcinogenesis was a highly complicated test which was affected by a great number of variables, such as the general health of the animals used in the test, the genetic strain of the mouse used for the test, the toxicity of the material applied in the test, the presence or absence of lice or mites on the animals, fighting among the experimental animals, etc. Therefore, steps were taken to control these variables insofar as possible, although it must be recognized that even after 4 or 5 years of research it has not been possible to eliminate or completely control these variables but only to minimize them. Where these variables were incapable of control, this early research did permit the biological experimenter to recognize their effects so that he could throw out as unsatisfactory those biological tests in which these variables have played too great a role in the final results. This biological research on the development of standards of reference is summarized in the report "Carcinogenesis of the Skin, I. Basic Methods Employed in Testing Complex Hydrocarbon-Type Tars and Oils, and the Development of a Quantitative Scale to Express Their Relative Potencies" by A. Wesley Horton and Dorothy T. Denham. This report has been proposed for publication in a cancer research journal.

The second achievement of this biological research has been the demonstration that solvents influence results obtained with pure carcinogens. At present two types have been recognized. The first type, represented by benzene, has no effect on the activity of pure carcinogenic hydrocarbons. This type of solvent has been designated a non-accelerating solvent. When the pure hydrocarbon, methylcholanthrene, is dissolved in this type of solvent, the carcinogenic activity in animals is directly related within limits to the concentration of the carcinogen in solution. The second type of solvent, represented by dodecyl benzene, has an additive or accelerating effect on the activity of pure carcinogenic hydrocarbons. This type of solvent has been designated an accelerating solvent. When the pure hydrocarbon, methylcholanthrene, is dissolved in this type of solvent, the carcinogenic activity in animals is not directly related to the concentration of the carcinogen in solution but rather appears to be more dependent on the amount of accelerating solvent applied with each application. The research work leading to this discovery is soon to be summarized in a paper which the laboratory will propose for publication, also in a cancer research journal.

In addition to the work on reference standards and solvents outlined above, the laboratory has tested biologically between 150 and 200 petroleum materials and fractions of these for their carcinogenic activity in mice. This work alone required some 4,000 mice for test purposes. A summary of the results of these investigations will undoubtedly be prepared as a manuscript for publication.

The laboratory has also investigated the effect of hygienic measures such as washing and protective creams on the carcinogenic activity to mice of several petroleum materials. It is anticipated that these results will be used in the framing of practical hygienic control measures.

The chemical work has encompassed the separation by distillation, chromatography, and chemical methods, of petroleum materials into various fractions in an attempt to define precisely the agents in petroleum responsible for this carcinogenic activity in mice. This work has already led to the submission of one manuscript entitled "The Use of Catalytic Iodination on Activated Alumina for the Determination of Benzo (a) Pyrene in Complex Mixtures". This manuscript was authored by R. Tye, M. J. Graf and A. W. Horton. It has been reviewed by the Subcommittee, the Medical Advisory Committee, and the Medical and Health Committee of the Board. No objections to publication were voiced and it has been submitted to the editors of the Journal of Analytical Chemistry for publication.

In addition, the following general information has come out of the combined chemical-biological studies:

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

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

c. Carcinogenic petroleum materials boiling between 725-800°F probably contain anthracene-like carcinogens, possibly cyclopenteno benzanthracene.

d. Carcinogenic petroleum materials boiling above 800°F probably contain benzo (a) pyrene.

2. Epidemiology

It was early recognized by the Subcommittee on Carcinogenicity that the chemical and biological work outlined above would give only a partial answer. It was expected that the epidemiological work would develop information on the following two questions.

a. Does work in the petroleum industry or at any specific job within the petroleum industry subject the worker to an increased risk of developing cancer?

b. Have newer refining processes, such as catalytic cracking, or increased severity of thermal cracking introduced any new risks of developing cancer to any segment of the petroleum workers? It is in general these newer processes which have been shown to produce materials which have a high degree of carcinogenicity to mice.

A central registry for the reporting of cancer cases occurring in the petroleum industry represented by the participating companies of the API was established at the Kettering Laboratory under the direction of Dr. Phair. In addition to reporting such cases, it was deemed essential that a complete occupational history for each case also be reported so that correlations with occupation could be made.

In the course of setting up this registry, it soon became apparent to Dr. Phair that the medical departments and medical records of some petroleum companies were inadequate to permit accurate reporting of cancer cases. Initially, therefore, Dr. Phair's major effort was in assisting medical directors, or refinery managers where medical directors were unavailable, in organizing their departments and/or records so that good case reports and occupational histories would be received in his office. Therefore, it has only been in the past year or two that an approach to effective reporting of all types of cancer cases and occupational histories has been achieved. Despite incomplete uniformity of reporting and participation, over 1,300 cancer cases have been reported to Dr. Phair from 15 companies, and are in the process of statistical analysis. It is believed that worthwhile statistical analysis of these cases will require maintenance of this registry for a minimum of 6 years. In the interim, Dr. Phair continues to act in an advisory capacity to the petroleum companies and their medical directors for the collection and reporting of these cases.

Expenditures of the Subcommittee on Carcinogenicity

1946	$ 6,000.00	
1947	0	
1948	65,000.00	(includes $40,000 grant for animal quarters)
1949	49,413.00	
1950	69,963.39	
1951	59,065.12	
to June 30, 1952	31,692.42	
July 1, 1952 to June 30, 1953	104,760.00	
July 1, 1953 to June 30, 1954	79,000.00	
	$484,893.93	
Budgeted July 1, 1954 to June 30, 1955	$ 72,250.00	

Future Work

As indicated in the above outline of expenditures, a peak of activity was reached in the period July 1, 1952 to June 30, 1953. Since that time there has been a gradual tapering off of expenditures for this research effort. The Subcommittee recommends that future work in the chemical-biological phases should be directed towards

1. Work on physico-chemical methods for assaying the carcinogenesis of petroleum materials. These methods will be validated by

    a. Determining the relative importance of carcinogens and mixtures of carcinogens and accelerators in the process of carcinogenesis.

    b. Determining the relative carcinogenicity of additional petroleum products and materials, not adequately covered to date.

    c. Isolating and identifying additional carcinogens and/or accelerators in petroleum materials.

d. Continuing work on the improvement of standard bio-assays for carcinogenesis.

2. Effective hygienic control measures for use by the petroleum industry.

3. Work on possible carcinogenic inhibitors.

In the Subcommittee's opinion, this type of research should continue until at least 1959. However, expenditures will continue to taper off during this interval and should stabilize at levels not in excess of $25,000 after June 30, 1956.

The epidemiology should be continued until at least 1959. The budget for this phase of the work will probably run between $15,000 and $20,000 per year. In the opinion of the Subcommittee, if full cooperation with Dr. Phair in the epidemiological work has not been achieved by June 30, 1955, the Subcommittee would recommend that epidemiology work be discontinued since it would be likely that full cooperation would not be expected to be achieved after this date. If cooperation has been achieved by this time, expenditures should stabilize at a somewhat lower level, since the work will consist principally of collecting and analyzing statistically those cases reported.

It is thus estimated that the anticipated annual expenditures for 1956-1959 will be in the vicinity of $40,000-$45,000.

Estimated Budget July 1, 1955 to June 30, 1956

The Subcommittee recommends that the Medical Advisory Committee request funds in the amount of $65,000 for the continuation of this work during the interval July 1, 1955-June 30, 1956. A brief breakdown of expenditures is approximately as follows:

Biological work	$20,000
Technical work	32,250
Epidemiological Work	12,750
	$65,000

Another breakdown of these figures can be given as follows:

Salaries

Direct	$22,000
Indirect	
Histopathology	2,000
Others	20,000
	$44,000

Salaries		$44,000
Miscellaneous Exp.		
Animals	$ 1,250	
Supplies	5,000	
Travel	4,000	
Overhead	10,750	
		21,000
		$65,000

Composition of Subcommittee

R. E. Eckardt, M. D., Chairman
Standard Oil Development Company

E. W. Adams
Standard Oil Company (Indiana)

L. C. Beard, Jr.
Socony-Vacuum Oil Company, Inc.

Allan E. Dooley
The Texas Company

F. D. Gassaway, M. D.
Gulf Oil Corporation

L. M. Henderson
The Pure Oil Company

C. H. Hine, M. D.
Shell Development Company

E. K. Linder, M. D.
The Atlantic Refining Company

R. C. Mithoff
California Research Corporation

M. N. Newquist, M. D.
The Texas Company

James W. Osborn, M. D.
Standard Oil Company (Ohio)

F. J. Sanders
Standard Oil Company (Ohio)

REE:ilk

June 21, 1954

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

May 26, 1954

Messrs. E. W. Adams
L. C. Beard, Jr.
Allen K. Dooley
F. D. Hennessey
L. M. Henderson
C. M. Hine
K. K. Linder
R. C. Mitkoff
M. H. Newquist
James W. Osborn
F. J. Sanders

Gentlemen:

It now appears that a suitable date for the meeting with the Kettering Laboratory will be June 19, 1954. This date has been arrived at by much communication between each of us and it appears to be the only satisfactory date available to the majority of the committee members, unless we postpone the meeting until after the summer, which does not seem possible in view of the request that a report of the committee and budgetary estimates be submitted to Dr. Saunders by July 15th. Therefore, I am calling a meeting of the Subcommittee on Carcinogenicity for June 18th, in my hotel room at the Terrace Plaza Hotel. I shall plan by that time to have prepared a rough draft of the report of the committee to Dr. Saunders, which can then be supplemented with Dr. Kehoe's budgetary estimates which he will give to us on the 19th. The remainder of the 18th will be spent in discussing the manuscript among ourselves so that we can expedite the discussion of the manuscript with Dr. Horton when we meet with his group at the Kettering Laboratory on the morning of the 19th.

Several of you have already indicated that you would be unable to attend a meeting on the 19th and have already forwarded to me your comments concerning the manuscript and budgetary considerations. I would suggest that any of you who will be unable to attend the meeting on the 18th and 19th forward to me your comments on the manuscript and on budgetary considerations for the period 1955-1956 so that we may include your views in the discussions which the committee will have on the 18th and 19th.

I regret very much having to be somewhat arbitrary about setting this date for the meeting, but it has appeared almost insurmountable to find a date suitable to both the committee and the Kettering Laboratory in order that the maximum number could attend. It may well be that we should discuss at the committee meeting what we plan for future situations like the one we have just been through. It appears to me that a better solution than the one we are now working under could be arrived at so that the committee could meet and discuss things in a more orderly fashion. I trust that we will be able to have a good representation of the committee, even though I am already aware that some of you will not be able to be there.

Sincerely yours,

RER:ilk

R. E. ECKARDT, M. D.

cc: Messrs. A. Wesley Horton, K. A. Kehoe, E. V. Stroup

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

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

September 2, 1953

To Members and Associates
Medical Advisory Committee

Gentlemen:

Pursuant to the action taken at its Sixteenth Meeting, the Medical Advisory Committee will hold its Seventeenth Meeting on:

Wednesday, September 30th, 1953 at 9:00 A. M., Central Standard Time, in the Castilian Room of The Shamrock Hotel, Houston, Texas.

On the preceding day, Tuesday, September 29th, subcommittee meetings will be held in the Castilian Room as follows:

9:30 A. M. Subcommittee on Carcinogenicity
Kieffer Davis M.D., Chairman

2:00 P. M. Subcommittee on Cutting Fluids
Leo Wade M.D., Chairman

---ooOoo---

Anyone desiring to present matters of new business for consideration at the Sixteenth Meeting is requested to communicate with me so that his subject may be included in the agenda which will be issued with such subcommittee reports as may be available on or before September 21st.

If you have not done so, please make your personal guest room reservations directly with the hotel.

Very truly yours,

W Stroop

DVS:js

Visits to European Laboratories - May 26 - Aug 5, 1953

Stockholm - Physical Chemistry Congress, Dr. Mackor - "Colloidal Dispersions in Non-polar Media Stabilized by Adsorption of Elongated Molecules such as dodecylbenzenes and Alkylnaphthalenes".

Britain

Health - Courthauld work on folic acid antagonists
No attention given by Hieger or Squires
at Britain, L-4 (100 mg.# - 3 tumors in 50 mice
50% mortality in 6 months.
at K.L., L-4 (20 mg.) - essentially 100% tumors,
good growth curves.

Lubricants for cotton mules - White Oil being written into legislatio
Improvement in bearing design has essentially eliminated exposur
Floors still impregnated with oil.

Cutting fluids real problem in Britain automatic machine operation.

Cleaverson FCC unit - 4 of 8 showing same oil folliculitis as Scott described in shale oil refinery, but latent period much shorter.

Personal Hygiene - ~~order be Navy officers.~~

Lung cancer from fumes in gas (from coal) industry - 5 year statistical study started by Medical Research Council
Irwin and Doll.

~~1909 Netherland~~

Col. Auld Mr. Herbert	IP Committee	Prof. Lacassagne Dr. Rudali	Institut du Radium (U. of Paris (U. of Brussels)
Prof. Cook Dr. Carruthers	Glasgow	Dr. Pullman Dr. Daudel	
Prof. Morton Prof Squires Prof. Orr Dr. Cruikshank Dr. Woodhouse	Birmingham	Prof. Martin Sir Ernest Kennaway, Sir Harold Hinsworth	ex. RCH, now St.Ba MRC
Dr. Irwin Dr. Doll	London School of Hygiene	Dr. Merewether Dr. Murray	Med. Inspector of Factories
Prof. Haddow Dr. Hieger Dr. Boyland	Chester Beatty	Dr. Hill	Shirley Institute, Manchester
Prof. Dodds Dr. Dickens	Courthauld Middlesex	Dr. Iversen Dr. Goldblatt	Copenhagen, London I.C.I.

L E T T E R B A L L O T

Subcommittee on Carcinogenicity
Medical Advisory Committee, American Petroleum Institute

. . . . . .

PLEASE MARK AND RETURN TO:

Dr. M. N. Newquist, Chairman
Subcommittee on Carcinogenicity
c/o The Texas Company
135 East 42nd St., New York 17, N. Y.

. . . . . .

1. Shall the actions and decisions of the Research Project Advisory Committee, as shown in the minutes of the July 10, 1952, Meeting at Kettering Laboratory, Cincinnati, Ohio, be approved by the Subcommittee?

Yes 25 No 0 Not voting 0

2. 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 on 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

3. Do you approve of continuing Research Project MC-1 at approximately its present scope and cost ($100,000 per year) for the year beginning July 1, 1953?

Yes 18 No 2 Not voting 5

4. Do you concur with the opinion of the RPA Committee that a meeting of the Subcommittee prior to September 25, 1952, is not necessary?

Yes 23 No 1 Not voting 1

It is requested that any negative vote be accompanied by an explanation.

_____
Name

_____
Company

Copy from D. V. Stroop for Information of Members and Associates of Medical Advisory Committee.

9-11-52

REPORT OF SUBCOMMITTEE ON CARCINOGENICITY
TO THE
MEDICAL ADVISORY COMMITTEE, API - SEPTEMBER 25, 1952

1 - The Subcommittee on Carcinogenicity has held no stated meeting since its last meeting in Cincinnati April 18, 1952, which action has been approved by letter ballot.

2 - The R.P.A. Committee held its third meeting at Kettering Laboratory on July 10, 1952, the minutes of which have been circularized to all members and associates of the Medical Advisory Committee and which minutes have been approved by the subcommittee by letter ballot.

3 - The research project (MC-1) has been continued on about the same scope as it has been during the past two years but with better results from the standpoint of quantitative mouse testing. Data sheets on various mouse experiments were mailed by Dr. Horton on July 16, 1952, to members of the Medical Advisory Committee, who also have received from Dr. Horton prior to this meeting a tabular summary of the current and completed biological experiments.

4 - Dr. Horton will present an interim progress report as part of this report.

5 - The subcommittee recommends that the various medical directors on the Medical Advisory Committee cooperate more fully by submitting the data requested by Dr. Phair in connection with the epidemiological survey and particularly the data concerning current cases.

6 - Dr. J. J. Phair will present as part of this report:

a. A progress report on the epidemiological studies.

b. Dr. Kehoe's decision as to whether or not Kettering Laboratory would be willing to undertake a critical review, with abstracts, of the literature on cancer as related to petroleum and his estimate of the additional cost if undertaken.

7 - With respect to the epidemiological survey (See Exhibit A) among employees of customers, the letter ballots of tho members of the subcommittee showed sufficient differences of opinion to warrant referral of this subject back to the subcommittee for further consideration. (Some letter ballots not received as of 9/10/52, but final tally will be available for the Chicago meeting.)

8 - The subcommittee by letter ballot approved of continuing Research Project MC-1 at approximately its present scope and cost ($100,000 per year) for the year beginning July 1, 1953. However, a few members recommended that the general level of research activity and the budget be decreased.

Dr. Kehoe will submit for this meeting an estimate of the budgetary requirements subdivided insofar as possible in terms of scientific objectives.

9 - Recommendations, if any, eventuating from the meeting of the Research Project Advisory Committee to be held on September 24, 1952.

Respectfully submitted,

M. N. Newquist, Chairman.

EXHIBIT A

API - MEDICAL ADVISORY COMMITTEE

ACTIONS WITH RESPECT TO CANCER REGISTRY

Fifth Meeting - April 28, 1947 - Buffalo, New York

Page 2 of Minutes, Item D, Report of Subcommittee on Carcinogenicity

"Establish a registry of malignancies to report to the Subcommittee on Carcinogenicity. This registry would collect data on all malignancies incident in employees of the petroleum industry. It would set up its own procedures, forms, extent of data, follow-ups, pathology, treatment, outcome, autopsy reports, etc. after consultations with existing registries."

Seventh Meeting - April 2, 1948 - Boston, Massachusetts

Page 3 of Minutes, Item 3, Report of Subcommittee on Carcinogenicity

"The committee recommended that Dr. Robert A. Kehoe and his associates collaborate with the Chairman of the Subcommittee on Carcinogenicity and as many members as is necessary in the preparation of a plan of collecting statistical medical information on cancer in the petroleum industry versus the country at large; and if possible versus other industries. The committee also recommended that a definite proposal be made for implementing the collection and coalition of such information (every effort should be made to separate any cancers caused by contact with known products from those arising from other causes)."

Eighth Meeting - November 12, 1948 - Chicago, Illinois

Page 2 of Minutes, Item 5-d, Report of Subcommittee on Carcinogenicity

The carcinogenic program -- at the University of Cincinnati should include: "Epidemiological studies of this problem in the industry."

Tenth Meeting - November 11, 1949 - Chicago, Illinois

Appendix A, 3rd paragraph, Report of Subcommittee on Carcinogenicity

"Dr. J. J. Phair, Professor of Preventive Medicine, University of Cincinnati, discussed the epidemiological aspects of this problem. He proposed the establishment of a cancer register at the University of Cincinnati to serve the petroleum industry and submitted a draft of a form to be used in obtaining the necessary morbidity information. It was agreed that legal advice should be obtained as to whether reporting such cancer cases to the University of Cincinnati would be an invasion of the patient's rights."

Meeting - Subcommittee on Carcinogenicity - August 26, 1947 - New York, New York

Page 2 of Minutes, Item 6-(a)

"It is desirable to assemble data regarding (1) nature, (2) frequency and (3) duration of exposure of employees and customers to intermediate or commercial products containing as a constituent heavy catalytic distillates or residua which contain fractions boiling above 700° F. Also, to obtain the number of (1) employees and (2) customers so exposed. In order to obtain uniformity, Dr. Woody will outline the procedure for survey and approach the companies to conduct the above survey."

for API meeting files

THE TEXAS COMPANY
135 EAST 42ND STREET
NEW YORK 17, N.Y.

M. N. NEWQUIST, M. D.
MEDICAL DIRECTOR

September 10, 1952

Dr. A. W. Horton
Kettering Laboratory
University of Cincinnati
Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Horton:

You will note from the attached copy of the report of the Subcommittee on Carcinogenicity to be submitted to the Medical Advisory Committee of the A.P.I. on September 25, 1952, that we are asking you under Item 4 to give an interim progress report as part of the subcommittee's report.

Since much of the data which you have compiled will have been sent to the members of the Medical Advisory Committee in advance of the meeting, your progress report should be in summary form and it will have to be limited to twenty minutes, with a few minutes allowed for discussion. Kindly be prepared to limit your presentation because we will be pressed for time. If you could have your summary typewritten it would facilitate the inclusion of your remarks in our report.

Looking forward with pleasure to seeing you in Chicago, I am

Very truly yours,

M. N. NEWQUIST, M. D.

MNN:RMS
ENC.

REPORT OF SUBCOMMITTEE ON CARCINOGENICITY
TO THE
MEDICAL ADVISORY COMMITTEE, A.P.I., - SEPTEMBER 25, 1952

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7 - With respect to the epidemiological survey (See Exhibit A)

among employes of customers, the letter ballots of the members of the subcommittee showed sufficient differences of opinion to warrant referral of this subject back to the subcommittee for further consideration. (Some letter ballots not received as of 9/10/52, but final tally will be available for the Chicago meeting).

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Respectfully submitted,

M. N. Newquist, Chairman.

API - Medical Advisory Committee

ACTIONS WITH RESPECT TO CANCER REGISTRY

Fifth Meeting - April 28, 1947 - Buffalo, New York

Page 2 of Minutes, Item D, Report of Subcommittee on Carcinogenicity

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Tenth Meeting - November 11, 1949 - Chicago, Illinois

Appendix A, 3rd paragraph, Report of Subcommittee on Carcinogenicity

"Dr. J. J. Phair, Professor of Preventive Medicine, University of Cincinnati, discussed the epidemiological aspects of this problem. He proposed the establishment of a cancer register at the University of Cincinnati to serve the petroleum industry and submitted a draft of a form to be used in obtaining the necessary morbidity information. It was agreed that legal advice should be obtained as to whether reporting such cancer cases to the University of Cincinnati would be an invasion of the patient's rights."

Meeting - Subcommittee on Carcinogenicity - August 26, 1947 - New York, N.Y.

Page 2 of Minutes, Item 6-(a)

"It is desirable to assemble data regarding (1) nature, (2) frequency and (3) duration of exposure of employees and customers to intermediate or commercial products containing as a constituent heavy, catalytic distillates or residua which contain fractions boiling above 700°F. Also, to obtain the number of (1) employees and (2) customers so exposed. In order to obtain uniformity, Dr. Woody will outline the procedure for survey and approach the companies to conduct the above survey

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

C
O
P
Y

April 30, 1952

Mr. T. J. Sullivan, Vice President
Gulf Oil Corporation
P.O. Box 1166
Pittsburgh 30, Pennsylvania

Epidemiological Survey
Subcommittee on Carcinogenicity
Medical Advisory Committee
API

Dear Mr. Sullivan:

I am enclosing a progress report of the activities of the Subcommittees on Carcinogenicity of the Medical Advisory Committee, API.

Inasmuch as Mr. G. A. Davidson plans to present the report to the General Committee of the Division of Refining in your absence, I am taking the liberty of sending 65 mimeographed copies directly to Mr. Davidson.

In connection with the study of the carcinogenicity of petroleum and petroleum products, our subcommittee considered originally that an epidemiological study should consist of two parts: (1) the study of the incidence of cancer among employees of the petroleum industry and, (2) the study of cases of cancer (mostly skin cancers) among employees of customers where the cancer was allegedly due to exposure to petroleum products. Item one is already underway. Item two is so involved that we have done nothing about it. We have, of course, been alerted by recent verbal reports of alleged skin cancer cases occurring among customer employees but we believe this situation should have the careful consideration of the Divisions of API which would be concerned. Your advice in this connection would be greatly appreciated by our Subcommittee.

Very truly yours,

/s/ M. N. Newquist
M. N. NEWQUIST, Chairman
Subcommittee on Carcinogenicity

MNN:RMS
Copies:
Mr. G. A. Davidson - Standard Oil of California
Mr. H. W. Ferguson - Humble Oil and Refining Company
Mr. J. P. Langfitt - The Pure Oil Company
Mr. W. T. Gunn - API
Members and Associates, Medical Advisory Committee, API

COPY

135 E. 42nd Street
New York 17, N. Y.

April 30, 1952

Mr. T. J. Sullivan
Vice President
Gulf Oil Corporation
Pittsburgh 30, Pennsylvania

Subcommittee on Carcinogenicity
Medical Advisory Committee
API

Dear Sir:

This resume prepared by the Research Project (MC-1) Advisory Committee in accordance with your request of February 13, 1952, summarizes the activities of the Subcommittee on Carcinogenicity of the Medical Advisory Committee API.

Experimental evidence on mice was developed about 1943 by Dr. E. V. Cowdry at the Barnard Hospital, St. Louis, attributing carcinogenic properties to residua from catalytic cracking. Late in 1944 Dr. R. E. Wilson called attention to the desirability of investigating any possible cancer hazards which might arise from newer refining processes. These were the chief factors leading to the organization in 1945 of the API Medical Advisory Committee. At its first meeting in May 1945, this committee, among other things, recommended a study of the possible carcinogenic properties of petroleum and petroleum products. This recommendation was approved by the Executive Committee of the Board of Directors of the API and a fund of $25,000 was authorized to initiate this and other medical studies.

After careful consideration Kettering Laboratory, University of Cincinnati, was selected to make an initial study of the problem. A grant of $6,000 was made February 1, 1946, to conduct a limited amount of animal testing on eight samples of high boiling fractions selected by the Subcommittee on Carcinogenicity. The results of this study completed in 1948 showed that high boiling gas oils from catalytic cracking produced skin cancers on repeated application to mice. This finding led to the formulation of a

comprehensive program of research at Kettering Laboratory. This program necessitated a capital grant to Kettering Laboratory of $40,000 for the construction of animal quarters. (See attached list of expenditures.) The expanded research program got under way late in 1949.

OBJECTIVES - The research program includes the following primary objectives:

1. The determination of which refinery streams and products are carcinogenic and to identify if possible the causative agents in such streams and products.
2. Development of reliable analytical techniques for quick and inexpensive determination of the carcinogenic potency of any stream or product.
3. Investigation of protective measures which might be applicable to man.
4. Epidemiological studies to determine the incidence of cancer among employees of the petroleum industry as compared to the general population.

PROGRESS TOWARDS ACCOMPLISHING THE OBJECTIVES -

1. Identification of carcinogenic streams or products and causative agents. To date 110 different petroleum fractions from representative processes have been tested on mice. Fractions of four different crudes are also being studied. Products of catalytic cracking and thermal cracking of catalytic gas oils have been sampled fairly completely. Vacuum distillates including lube stocks are also under study. A sufficient variety of samples is on hand to consummate this phase of the program.

It has been demonstrated that some carcinogens exist in the original crude oils and that certain refinery processing of oils concentrates and/or synthesizes carcinogenic materials. High boiling gas oils from catalytic

cracking have continued to show relatively high carcinogenic potency to mice. Thermal cracking of high potency catalytically cracked residua does not reduce the potency. Furthermore, high boiling gas oils produced in severe thermal cracking of straight run residua have demonstrated high potency. Untreated lube distillates show low to moderate carcinogenicity to mice.

Polycylic aromatics which fall into the general classes of benzo(c) phenanthrene, benzpyrene and benzanthracene have been identified chemically in carcinogenic oils. Certain compounds in these classes have been known for years to be carcinogenic to mice. The ratios of these classes of compounds or of individual carcinogens vary in oils depending upon their source and subsequent processing. Complicating the picture is the presence of materials which in themselves are not carcinogenic, but which have the ability to enhance the potency of carcinogens in these oils.

2. Analytical Tool - Many of the pure polycyclic compounds with known carcinogenic activity have an identifiable absorption spectrum in certain parts of the ultra-violet and visible range. This knowledge has been used as the basis for developing an analytical tool. Empiric correlations of biological data with absorption spectra have not thus far been entirely satisfactory, in part due to the non-quantitative nature of the biological tests and in part due to compounds whose chemical or physical properties influence carcinogenicity, but do not exhibit a characteristic absorption spectrum.

The first of these factors has necessitated a program adjustment to study the basic fundamentals which lead to a quantitative biological test. The second factor has led to a study of those chemical and physical properties which influence the carcinogenicity of an oil such as solvents, viscosity and enhancing compounds. Obviously the intricate nature of the problem of developing an accurate analytical tool plus the identification of the causative agents in sufficiently broad classes to permit evaluation of carcinogenic refinery

streams will require more time and effort than originally anticipated. Without an analytical tool, any laboratory proof of carcinogenicity rests upon animal testing which is expensive and time-consuming (three to twelve months required for each test on mice).

3. Preventive Measures - Animal experimentation and practical experience in industry where occupational cancer hazards have existed indicate that this hazard can be controlled by minimizing exposure and by adequate medical supervision which will include periodic physical examinations.

Minimizing exposure entails:

a. Identifying the sources of exposure.

b. Informing the persons who may be exposed, of the hazard involved and of preventive measures.

c. Providing of protective equipment or facilities where exposure is otherwise unavoidable.

d. Good personal cleanliness.

Skin cancer if detected early is curable. An adequate medical program will insure early detection.

4. Epidemiological Survey - It is not possible to transfer directly the data from the mouse testing experiments into figures representing relative carcinogenicity of the various fractions for man. From a scientific standpoint it would be desirable to test carcinogenic potency on several higher species of animals including man. However, such testing is not feasible at the present time. Interpretation of the significance of the experimental data, therefore, must await procurement of data on human cases from epidemiological surveys. An epidemiological survey will develop the facts concerning the incidence of cancer among petroleum workers and, if correlated with the occupational history, should disclose whether any particular occupation in the petroleum industry is associated with an occupational cancer hazard. In addition, it will detect any

increase in cancers which may be the result of failure of protective measures. Without such information a problem of major magnitude could develop undetected and protection of the petroleum industry from unsubstantiated claims for compensation for alleged occupational cancer would be almost impossible. This phase of the program must be continued for a number of years in order to be of value. This study is now underway and the annual cost is low.

CONCLUSION - Occupational cancers comprise a very small percentage of the total number of cancers. However, experience in the British coal tar industry where over 1,400 cases of skin cancer were diagnosed in a 20-year period, and experience from contact with British shale oil where over 1,500 cases of skin cancer were diagnosed in a similar period, indicate that a cancer hazard may assume a serious magnitude in industry before control measures are instituted. British statistics are probably more accurate than those in the United States because reporting of cases to the Government is required and enforced. Medical literature and unpublished reports both in this country and abroad incriminate certain petroleum products which, having been demonstrated on animals to have a low degree of carcinogenicity, have caused human skin cancers after exposure of many years duration.

The importance of such observations to the petroleum industry emphasizes the necessity of a continuing program to develop the facts as well as to promote any precautionary measures that may be indicated. In this connection certain petroleum companies in the United States have already instituted precautionary measures within their own organizations. In Great Britain it is now mandatory that white lubricating oil be used in one phase of textile manufacturing.

It is planned that the research project (MC-1) at Kettering Laboratory will proceed along lines of the objectives set forth above. Such

research activities have now reached the peak and it is expected that there will be a gradual decline in a year or two from now unless unforseen situations arise in the interim.

This committee will be pleased to render any further progress reports which you may desire.

Submitted on behalf of the committee by

/s/ M. N. Newquist
Chairman

Members of Research Project (MC-1) Advisory Committee.

M. N. Newquist, M.D., Chairman	The Texas Company
E. W. Adams	Standard Oil Co. (Indiana)
L. C. Beard, Jr.	Socony-Vacuum Oil Co., Inc.
Kieffer Davis, M.D.	Phillips Petroleum Co.
R. E. Eckardt, M.D.	Standard Oil Development Co. (N.J.)
T. M. Frank, M.D.	Pan American Refining Corp.
C. H. Hine, M.D.	Shell Development Co.
R. M. Landon	Gulf Oil Corporation
E. K. Linder, M.D.	The Atlantic Refining Co.
K. G. Mackenzie	The Texas Company
R. C. Mithoff	California Research Corp.
R. M. Shepardson	Standard Oil Development Co. (N.J.)

PAYMENTS BY API

to

UNIVERSITY OF CINCINNATI

for

RESEARCH PROJECT (MC-1) ON CARCINOGENICITY

2-1-46	$ 6,000.00	
7-1-46	0	
1-1-47	0	
7-1-47	0	
1-1-48	0	
7-1-48	65,000.00	(includes $40,000 grant for animal quarters)
1-1-49	0	
7-1-49	49,413.00	
1-1-50	39,963.39	
7-1-50	50,000.00	
1-1-51	9,065.12	
7-1-51	50,000.00	
1-1-52	31,692.42	
	$ 301,133.93	to June 30, 1952

Budget July 1, 1952, to June 30, 1953 $ 104,760.00

AGENDA

Subcommittee on Carcinogenicity
of the
Medical Advisory Committee A.P.I.
Parlor I, Netherland Plaza Hotel, Cincinnati
2:00 P.M. April 18, 1952

1 - Introduction of new members.

2 - Review of action taken November 3, 1951, by the Medical Advisory Committee on the report of this subcommittee.

3 - Comments on action taken at R.P.A. Committee meeting on November 26, 1951.
(100% approval of minutes by subcommittee obtained by letter ballot)

4 - Comments on action taken at R.P.A. Committee meeting on February 26, 1952.
(Approval by letter ballot)

5 - Progress report by Dr. A. W. Horton.

6 - Progress report on Epidemiological survey by Dr. J.J. Phair.

7 - Steps to be taken to expedite the epidemiological survey.

8 - Promotion of campaign for personal cleanliness in industry.

9 - Budget for research program for one year beginning July 1, 1952.

10 - Report on activities of this subcommittee to the Liaison Committee of the Central Committee of the Div. of Refining.

11 - Other.

m.c. Members and Associates Subcommittee on Carcinogenicity
Dr. E. K. Linder
Mr. D. V. Stroop
Dr. R. A. Kehoe (4)

135 East 42nd Street
New York 17, N.Y.
October 17, 1951

Members and Associates
Subcommittee on Carcinogenicity

I am enclosing a summary of the 39 replies to the questionnaire which was sent to you on August 20. Of the Subcommittee, answers were received from all 13 members and from 8 of 12 associate members. In addition, replies were received from 8 of 15 members and 10 of 18 associate members of the Medical Advisory Committee at large. The 39 replies are from members and associates from practically all of the companies represented on the Medical Advisory Committee.

While the individual replies varied somewhat, it was possible to group them essentially as shown in the summary on the next two pages. A more detailed tabulation of the replies to each question is also enclosed.

You will no doubt wish to review this summary prior to the November meeting. It, together with any further suggestions you may have, should provide a good basis for the Committee to collaborate effectively in shaping plans for future work on the carcinogenicity project at Kettering Laboratory.

Thanking you for your cooperation, I am

Very truly yours,

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

MNN:GH
Attach.

mc. Members and associates, Medical Advisory Committee
Dr. R. A. Kehoe
Mr. D. V. Stroop

SUMMARY OF REPLIES
TO
QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

1. Should animal tests be made on samples selected in 1949 but as yet not tested; specifically those from desulfurization, steam cracking, rod waxes, coal tar, domestic and British shale oil?

No	10
Yes	14
Certain ones only	13

2. Should additional samples representing any of the processes and products in the 1949 list be tested on animals? If so, which ones?

No	21
Yes	5
Some	3
Other processes and products	6
No answer	2

3. Should the animal testing program be continued on its present scale for one more year or for two more years, by the selection of additional samples from various processes or should it taper off and be confined to the necessary animal tests in connection with the development of an analytical technique?

Taper off on animal tests and expand on analyt.tech.	26
Continue at present scale	7
As decided by Committee	3
No answer	1

4. Should a large-scale animal testing program be initiated on fuel oils to determine their potential hazards, if any, or should evaluation of these fuels await the development of an analytical technique?

Await analytical technique	28
Initiate animal testing program	8
No answer	1

5. Should efforts be directed toward development of a technique to eliminate the carcinogenic effect of an oil by removal or conversion of the carcinogens?

No	28
Yes	6
No answer	3

SAFETY COMMITTEE OF BOARD OF DIRECTORS

REPORT OF CHAIRMAN - JOHN R. SUMAN

Concurrently with important developments in refining methods, processes, and products, the industry's toxicological problems are growing in number and complexity. Oil companies are making substantial increases in their medical staffs and facilities.

These developments led to the creation of the Institute's Medical Advisory Committee in 1945. Since then the committee has served constructively by making useful information available to oil companies for their protection of employees and customers against accidental injury and for the defense of industry against unreasonable and unnecessary laws and regulations, as well as unjustified and false claims for damages.

The organization of this committee and its semiannual meetings have facilitated an informal exchange of medical information of intangible but substantial value in the prevention and treatment of industrial injuries and occupational disease.

The committee also has been instrumental in organizing special studies and investigations on important toxicological problems with cooperative grants-in-aid at the University of Cincinnati and Harvard University.

The initiation of this work promptly after the end of the war has placed the industry in a favorable position at a time when numerous proposals are being made to give government new and far-reaching controls in the field of industrial medicine and hygiene.

The individual members of the committee, through their several professional channels and associations, acquire valuable information regarding these trends in regulatory legislation. The pooling of the information thus obtained clearly indicates trends which are disquieting.

Highlighted by the California smog problems and supplemented by the reports on the Donora situation, there is an active drive to impose an American Standard Code on Industrial Hygiene. This proposal is put forward by the American Conference of Governmental Industrial Hygienists, which has drafted a code that is far from realistic and shows little sympathy for the practical needs of industry. If adopted generally, such an arbitrary code would impose unreasonable and unnecessary restrictions upon industry, and might readily become the basis for state laws and regulations.

Another indication of the growing interest of government is a letter recently received from the Chief, Division of Industrial Hygiene, Public Health Service. He suggested a meeting with the Medical Advisory Committee to discuss potential health hazards and possible control procedures in the petroleum industry. The committee has invited him to attend its regular mid-year meeting in April and has held some preliminary discussions with his representatives at a recent subcommittee meeting held at Kettering Laboratory in Cincinnati.

Because of enforcement difficulties it may be safe to assume that statutory and regulatory control of industrial hygiene will be unreasonably restrictive and unnecessarily so for responsible and progressive companies which voluntarily are adopting policies to insure hygienic working conditions.

It is encouraging to note the number of companies which are adopting such progressive policies because it suggests the possibility of avoiding some or most statutory and regulatory controls.

CONFIDENTIAL

AMERICAN PETROLEUM INSTITUTE

SUBCOMMITTEE ON CARCINOGENICITY

MINUTES OF INTERIM MEETING

June 3, 1949

Copy letter to Dr. Woody of 6/8 attached [illegible]

An interim meeting of the Subcommittee on Carcinogenicity was held on Friday, June 3rd, 1949, at 15 West 51st Street, New York City.

MEMBERS PRESENT	ASSOCIATES PRESENT
Marshall Clinton	L.C. Beard, Jr.
T.M. Frank	H.P. Lankelma
A.E. Hoag	K.G. Mackenzie
J.P. Holt	R.M. Shepardson (representing H.G.M. Fischer)
T.J. Kelly	H.H. Zuidema
M.N. Newquist	
McIver Woody	

GUESTS

R.W. Faulk - Shell Oil Company
A. Wesley Horton - University of Cincinnati

ADVISOR

D.V. Stroop - API

TOTAL IN ATTENDANCE - 15

MEMBERS ABSENT	ASSOCIATES ABSENT
L.E. Curtis	R.S. Bonsib
W.R. Levis	A.E. Dooley
C.A. Swan	H.G.M. Fischer

Minutes of the meeting of March 11th were approved as issued.

Mr. Stroop stated that the API prefers not to be included in the American Cancer Society's list of grants-in-aid for cancer research.

Dr. Horton submitted a progress report. (Copy of the report is attached as Appendix A).

Dr. Woody said the Federal Security Administration has awarded over $450,000. in federal grants for cancer control and teaching activities. The

largest amount, $35,000. went to the Pennsylvania Department of Health, where Dr. Shilen, Director of the Division of Industrial Hygiene, has set up an occupational cancer control program with a physician and a nurse. At a later date, two engineers and a statistician will be assigned to the project. The attached forms (Appendix B) are being prepared in quantity for use in their surveys and are essentially identical with the form submitted to them by Dr. Hueper to insure uniform data from the various states participating in the industrial cancer program. The oil industries located in the Philadelphia area are high on their agenda.

Dr. Hoag and Dr. Newquist spoke briefly concerning articles on cancer they have written for the Socony-Vacuum News and Texaco Topics respectively. It was agreed that other companies could well afford to follow their example.

T.M. FRANK
Secretary

McIVER WOODY
Chairman

APPENDIX A

API PROJECT ON CARCINOGENICITY AT THE UNIVERSITY OF CINCINNATI

The program at the Kettering Laboratory is roughly divided into three major phases. Of perhaps most immediate importance is the effort to pin point throughout the industry materials and operations which represent potential hazards from the cancer standpoint. The second phase, which will be prosecuted simultaneously with the first phase, will involve the concentration and isolation of the compounds responsible for the carcinogenic action of certain catalytically cracked oils which have already been tested biologically. From the physical and chemical properties of such concentrates, an effort will be made to develop an analytical tool which may then be applied to any refinery stream to determine its carcinogenicity without resorting to animal testing. The third major phase will be an epidemiological study of cancer in the petroleum industry.

In carrying out the first phase in the program, as described above, a series of typical refinery samples will be tested on suitable laboratory animals to determine their relative carcinogenic potencies. It is expected that, in the course of the coming year ending June 1, 1950, testing of approximately 150 to 200 such samples will be started at the Kettering Laboratory. Thus an average of about 12 samples from each of the following processes will be studied:

1. Non-catalytic gas oil cracking
2. Viscosity breaking of residues and extracts
3. Naphtha reforming
4. Polyforming
5. Coking operations
6. Houdry catalytic cracking
7. Fluid catalytic cracking
8. Thermofor catalytic cracking
9. Cycloversion
10. Houdryflow cracking
11. Hydroforming
12. Slack waxes and aromatic extracts therefrom
13. Solvent extracts from lube oils and heavy gas oils.

The potencies of the samples will be compared with those of coal tar and shale oil fractions on which clinical data is available from England.

In considering the selection of samples from each of the processes listed, attention is at present being restricted to those intermediates or products with a distillation end point above 650°F. On the basis of confidential information supplied to the Kettering Laboratory by each of the API member companies on such materials and the unit operations producing them, a sampling program is being organized which will cover the current range of variations in each process. Careful consideration is being given not only to the characteristics of the particular products which will be tested for carcinogenicity but to the feed stocks and the unit operating conditions as well. In this manner it will be possible to correlate the effect of the trends in available charge stocks and refining practices with the relative carcinogenic potencies of products formed. Thus, the results of the testing program now planned should permit prediction of potential hazards as unit operations change in the years to come.

As yet, a list of the specific samples to be tested during the coming year has not been prepared since the necessary data from the individual companies is not complete. However, sufficient information is available to permit the selection of a small number of samples from thermal cracking of high boiling materials, both virgin gas oils and those previously subjected to catalytic cracking. In addition it is planned to request samples of high boiling oils from TCC units since to date no physiological testing of the heaviest products from these operations has been carried out.

In reporting results of tests on future oil samples, a direct comparison with a solution of a known concentration of a standard carcinogenic hydrocarbon in a standard solvent will be made. Preliminary tests are being run with solutions of methylcholanthrene in benzene, at concentrations from 0.01% to 0.6%. Previous results have indicated that the tumor incidence curves for typical heavy catalytically

cracked oils may be compared nicely with the curves for such standard solutions.

In further work the effect of the benzene solvent on the tumor incidence and the induction period in mice will be determined. Various non-volatile solvents, such as methylnaphthalene, are being considered for this purpose. However, it must be kept in mind that benzene solutions of methylcholanthrene have been employed as standards for many years in studies by English scientists. Their use may therefore facilitate the interpretation of our laboratory results in terms of practical hazards to exposed workers.

A. Wesley Horton

June 3, 1949.

BIH-C-1a

OCCUPATIONAL CANCER RECORD

1. Name — 2. Place of Death: City: — Hospital:

Residence

3. State: — City: — Street:

4. Social Security No. — 5. Sex — 6. Color or Race:

Age

7. Date of Birth: — 8. Years: Mos. Days: — 9. Date of Death:

10. Occupation: — 11. Industry or Business:

Method of Diagnosis

12. Cause of Death: — 13. Clinical: Biopsy: Autopsy: Other:

14. Name of Physician: — 15. Street: — 16. City:

17. Clinical Diagnosis: — 18. Pathologic Diagnosis: — 19. Primary Site:

20. Date of First Symptoms: — 21. Date of First Visit to Physician:

22. Date of First Diagnosis: — 23. Stage of Disease at First Diagnosis:

24. History of Other Illnesses of Site Affected: — 25. History of Injury to Site Affected:

APPENDIX B

26. Exposure: Have you ever handled or worked near any of the following? If yes, give details.

NAME OF SUBSTANCE	NAME OF EMPLOYER	DATE	LENGTH OF EXPOSURE	DESCRIBE TYPE OF EXPOSURE AND ESTIMATE PERCENT OF WORKING TIME EXPOSED:

BIH-C-1b
Occupational Cancer Record - Page 2

27. Occupational History: List Occupations in Chronological Order beginning with last or present one.

Dates FROM	Dates TO	NAME OF EMPLOYER	ADDRESS OF EMPLOYER	TYPE OF BUSINESS OR PRODUCT MADE	TITLE OF JOB	TYPE OF WORK PERFORMED

28. Are there any other important materials to which you have been exposed? (Hobbies; Habits; Medicines; Cosmetics; Diets; Environment)

29. Additional Information Obtainable at: (List Physician; Laboratory; Hospital; Insurance Co; Plant Medical Department Clinic; Tumor Registry, etc.)

Name: Address:

Name: Address:

Name: Address:

30. Any other information pertaining to Tumor (Multiplicity, sites, etc.):

APPENDIX B

BIH-C-2

APPENDIX 2

PLANT CANCER RECORD

1. Name of Company

2. Location:

3. In operation since:

4. Products Manufactured:

5. Number of workers employed:

		In plant:	In office:
	Male:		
	Female:		
	White:		
	Colored:		

6. Name of plant official

7. Name of Plant Physician

8. Insurance Carrier:

9. Carcinogenic hazards:

10. Operations involved:

11. Number of workers exposed:
    a. Constant exposure
    b. Intermittent exposure
    c. Occasional exposure

12. Sex of exposed workers: Male: Female:

13. Race: White: Colored:

14. Duration of exposure: Number: Years:
    Number: Years:
    Number: Years:

15. Rate of turnover in exposed group (s)

16. Cancers Observed in exposed group (s) Total number: Period:

17. Cancers by sites:

APPENDIX B

BIH-C-3

PLANT CANCER RECORD

Date:

1. Name of Company:

2. Location: 3. In Operation since:

4. Products Manufactured:

5. Number of Workers: Total / Females / Males / White / Colored — Office: — Production:

6. Name of Plant Manager: 7. Plant Physician:

8. Insurance Carrier:

9. Carcinogenic Hazards:

10.

Operations Involved	Number of Workers Total, White	Colored	Male	Female	Exposure Constant	Intermittent	Occasional
a							
b							
c							
d							
e							
f							
g							
h							
i							
j							
k							
l							
m							
n							

11.

Type of Exposure Inhalation	Skin	Ingestion	Other	Duration of Exposure Average	Longest	Cancers Observed Site	Number	Period
a								
b								
c								
d								
e								
f								
g								
h								
i								
j								
k								
l								
m								
n								

12. Rate of Labor Turnover:

(Interim Sub-Com. Med.Adv.API)

Meeting held in New York,
Friday, June 3, 9:30 A.M.
Room 673, ESSO S.O. Co.,
15 W. 51st St.

NOTES FOR THE MEETING

Samples from processes listed in February 1 meeting.

Attempt to show effect of varying feed stocks and operating conditions with minimum number of samples.

Reserve 150 of the 200 samples for refinery samples. Rest on samples for analytical tool from laboratory.

Specific Samples

1. Clarified slurries from FCCU already indicted - some variation shown. 3632 nearly most potent.
2. Effect of thermal cracking on heavy cat. cycle stock.
3. Effect of selected feeds in Houdry and TCC.
4. Highly aromatic samples from 2 and 3 - pass Houdry operation. Does recycling increase carcinogen concentration or destroy carcinogens previously formed?
5. Effect of sulfur and nitrogen Hydrogenation by Union HCOOH extraction of N bases.
6. Slack wax (or slop on outside of presses). Crude sources of those causing scrotal cancers.
   Rhodessa, E. Texas Ok.

Started 6 concentrations of Me-chol. in benzene from 0.01% to 0.6% 3 times a week.
Also 3631 and 3632.

Ask Levis about meeting at Chester, Thursday, June 23.

May 31, 1949

CONFIDENTIAL

AMERICAN PETROLEUM INSTITUTE
SUBCOMMITTEE ON CARCINOGENICITY

SPRING MEETING

Minutes of Meeting
April 1, 1949
Book-Cadillac Hotel
Detroit, Michigan

MEMBERS PRESENT

Marshall Clinton
L.E. Curtis
T.M. Frank
J.P. Holt
T.J. Kelly
M.N. Newquist
McIver Woody

ASSOCIATES PRESENT

L.C. Beard, Jr.
R.S. Bonsib
A.E. Dooley
H.G.M. Fischer
H.P. Lankelma
K.G. Mackenzie
H.H. Zuidema

VISITORS

V.C. Baird
F.F. Boys
Kieffer Davis
A.E. Hoag
E.K. Linder
E.P. Luongo
R. Clinton Page
B.B. Reeve

E.W. Adams
R.C. Cole
N.J. Gothard
R.M. Landon
F.M. Watkins

GUESTS

S.J.M. Auld	Institute of Petroleum, London
R.D. Bent	Atlantic Refining Company, Philadelphia
J.W. Hammond	Humble Oil Company, Houston
R.A. Kehoe	University of Cincinnati
W.L. Simpson	Detroit Institute of Cancer Research
J.B. Stucker	Pure Oil Company, Chicago
H.G.S. vanRaalte	Shell Oil Company, Curacao, Neth. Antill.
H.R. Warrick	The Texas Company, New York

ADVISOR

D.V. Stroop - API

TOTAL IN ATTENDANCE - 36

MEMBERS ABSENT

W.R. Levis
C.A. Swan

New members of the Subcommittee and guests were introduced.

Minutes of the three previous meetings, November 11th, 1948, February 1st, 1949 and March 11th, 1949 were approved after a change was made on Page 3, Line 9 of the March 11th, 1949 minutes by substituting the word "suggested" for "approved".

Dr. Kehoe stated that of the $40,000. capital funds provided by the API, $30,478. had been applied to building costs and $8,264. had been put into special equipment, leaving a balance of $1,258. to provide additional equipment as needed. Of the API grant for current expenditure, there remained a balance of $22,598. as of December 31st, 1948, of which about $14,660. would be used during the first six months of this year, giving a balance of some $7,000. as of July 1st, 1949. Current expenses from July 1st, 1949 to June 30th, 1950 were estimated at $122,600., of which about 25% would be covered by from payments from individual companies for testing their samples, leaving some $90,000. to $100,000. to be provided by the API.

Thanks to the API grant for capital expenditures, which came in the nick of time, facilities would be available by July 1st for a colony of 10,000 mice which would permit simultaneous studies on 175 to 200 samples. The API would have first claim on these facilities; but after that, samples submitted by any individual company would be accepted for testing provided that they would not interfere with the API schedule.

In addition to Dr. Kehoe, Dr. Heyroth and Dr. Dutra, 11 other persons would be required. Of these, Dr. A. Wesley Horton was already engaged in securing the necessary refinery and chemical data. Dr. J.J. Phair would start work on the epidemiological phases of the problem after July 1st. Other personnel would include: a chemist to assist Dr. Horton; a record clerk to maintain complete records on all the mice; three technicians to do the actual application of samples to the mice; one technician to prepare tissue sections for the pathologist; and two animal caretakers. A principal investigator was yet to be selected. This investigator would have to be an excellent pathologist, as well as a good administrator because he would be responsible for:

a. Supervising application of the samples to the mice.

b. Establishing standard criteria for:

   1. Determining existence of tumors.
   2. Differentiating between tumors and dermatitis.
   3. Establishing whether tumors are benign or malignant.

Dr. Newquist asked about the method of selecting samples for testing. Dr. Kehoe replied that this would be the duty of Dr. Horton, working with the Subcommittee and its technical advisors.

Mr. Beard asked whether results of tests of samples submitted by individual companies would be available to the API. Dr. Kehoe said they would be available only with the consent of the particular company and then only on a confidential basis.

Mr. Fischer thought the proposed program was well organized but wondered whether the personnel proposed by Dr. Kehoe would be sufficient to carry on all the necessary work.

Dr. Newquist thought experiments on primates should be started at an early date because of the time required to get results. Dr. Kehoe replied that investigators of carcinogenicity of petroleum and its products had two objectives: first, to find a tool for determining potencies; and second, to determine whether results of animal tests are applicable to man. The first phase required a group of stable, non-variable animals, such as the highly inbred C_3H mouse strain. This stability and lack of variability between the individual animals was not found in primates. As to the second phase, there was no definite evidence as yet that the results obtained in mice were applicable to man. It might be necessary to use other animals to establish the relationship. In that case, the laboratory had other animals available and, while it was not anticipated that monkeys would be used at first, this might be done later. Human experiments could not be set up until a good deal more information and knowledge was available, and even then only carried out under his personal responsibility.

Dr. Simpson pointed out that since susceptibility varies between individuals and since humans are not homogeneous, any tests on humans would have to be done with statistically significant groups (many thousands) and that therefore, as far as establishing potencies is concerned, this approach would not be practical. Furthermore, a carcinogen too low in amount to produce a local reaction, might be absorbed and produce a carcinoma elsewhere in the body.

Col. S.J.M. Auld, Chairman of the Research Group of the Institute of Petroleum, London, described the carcinogenicity problem in England and asked for an exchange of information between the API and the Institute of Petroleum. Mule spinner's cancer was still a problem in England, 20 deaths having occurred in 1947. After the earlier work in the nineteen twenties, there had been a lull but the subject was brought up again after the war, largely due to the action of the trade unions. The University of Birmingham had started research work and had found that extracts from solvent refining operations produced skin conditions which were "more than a mere dermatitis". More recently suspicion had been cast on some cutting oils and some motor oils from Scotland (not shale oils). The publicity attending the use of mineral oils as cooking oils during the war caused the Government to enter the picture with the result that the Medical Research Council (a government group) and the Institute of Petroleum (which succeeded the Petroleum Board) were now cooperating as a joint committee. Under the direction of Messrs. Squiers, Cook, Ferguson, Woodhouse, Irvine and Auld, a long-range research study has been started, beginning with an investigation of these three crudes:

Venezuelan crude - naphthenic type

Middle East crude - Kuwait

Mid-Continent crude (USA) - of importance in lubricants.

A certain amount of support was given still to the unfortunate formula by Twort regarding refractivity; but later work indicated that the higher the aromaticity, the higher the carcinogenicity. The industry in England had made white oils available but there has been little demand for them as yet. There was no evidence that solvent refined oils are carcinogenic. Shale oils were going out of the picture. Some preliminary idea on potency of oils might possibly be had by determining their effects on plants. It appeared that the fractions which are the most active plant poisons are those that seem to possess the highest carcinogenic potency and that perhaps by fractionating the oils and testing these

fractions on plants some index of carcinogenicity might be developed.

Dr. Woody read a letter from the American Cancer Society requesting the API to report the amount of money it was spending on cancer research, so the Society could include it in their report of grants-in-aid for cancer research. Mr. Stroop was asked to obtain information on how this data would be used by the American Cancer Society.

Action by the Subcommittee - It was voted to recommend to the Medical Adivsory Committee that:

1 - Information on carcinogenicity be exchanged with the Institute of Petroleum.

2 - The budget for the year beginning July 1st, 1949 for the program at Kettering Laboratory be increased to $100,000.00

McIver Woody
Chairman

A.E. Dooley
Secretary

Rec'd 3/24/49

CONFIDENTIAL

D. Horton

MINUTES

SUBCOMMITTEE ON CARCINOGENICITY

March 11, 1949

A meeting of the Subcommittee on Carcinogenicity was convened at 10 A.M., Friday, March 11th, 1949, at 15 West 51st Street, New York City.

MEMBERS PRESENT:

A.E. Hoag	R.S. Bonsib
J.P. Holt	A.E. Dooley
W.R. Levis	H.G.M. Fischer
M.N. Newquist	H.P. Lankelma
McIver Woody	K.G. MacKenzie

GUESTS:

A.W. Horton - University of Cincinnati
J.J. Phair - University of Cincinnati
D.V. Stroop - American Petroleum Institute

TOTAL IN ATTENDANCE - 13

MEMBERS ABSENT:

L.E. Curtis	L.C. Beard
T.M. Frank	~~A.J. Kocwing, Jr.~~
T.J. Kelly	H.H. Zuidema
C.A. Swan	

Dr. J.J. Phair, Professor of Preventive Medicine, University of Cincinnati, was introduced. Minutes of the meeting of February 1st were approved.

Dr. Horton reported that his laboratory equipment is being assembled and his new facilities will be available about May 1st. In the meantime, he is visiting refineries and studying the various types of catalytic cracking units and their operation for the purpose of making the proper choice of samples.

He stated that Shell had offered to cooperate in a pilot-plant operation to yield samples which could be used to determine effects of variables, such as natures of

feed, temperature, rate of through-put, etc. He thought this approach to the problem might yield valuable data and samples that could be studied concurrently with: (a) the search for an analytical tool, and (b) the animal testing of the list of materials recommended by the technical advisors to the Subcommittee in its January 31st, 1949 meeting.

Dr. Holt said that before deciding on the inclusion of the pilot plant approach, the technical advisors should be consulted.

Mr. Fischer felt that the pilot plant phase, while of scientific interest, might not answer the practical problems because of the great variations in feed stocks. He feared that it might bog down the animal testing program and believed that it should receive a low priority until answers to the practical phases of the problem had been obtained.

Mr. Bonsib agreed with Mr. Fischer's comments because of the many variations in feed stocks.

Dr. Horton replied that refinery samples would present these same variations and complications. It was his plan to get the pilot plant runs on three selected feeds containing; 0, 30 and 60 per cent aromatics respectively.

Mr. Lankelma, while agreeing with Mr. Fischer, believed that sooner or later this phase would have to be a part of the study.

Mr. MacKenzie thought that the nature of the charge stock was of minor importance compared to operating conditions; and that one run on a paraffinic stock should settle the question of the effects of time and temperature.

Mr. Fischer said that his company had tested samples from different feed stocks and had concluded that fluid-catalytic cracking operations presented a carcinogenicity problem. He recommended that the analytical study be given priority.

Dr. Horton urged that Shell's offer be considered because of the time required to prepare the samples. He pointed out that oil 3632 was being fractionated and that the fractions would be tested on animals. An attempt was being made to isolate the carcinogens in hope of obtaining an analytical tool.

It was the unanimous opinion of the Subcommittee that the analytical work on oil 3632 should go ahead.

Dr. Horton said that this analytical work may be long and complex; he thought that the other phases should not be delayed.

Dr. Holt divided the problem into four aspects:

1. Does a problem exist? That was the question two or three years ago. Work to date indicates that there is a potential problem.

2. Where does it exist; in what operations, oils, fractions, materials, etc. is there a hazard that requires protective measures?

3. Can these operations be changed to control the problem?

4. Development of a technique to eliminate animal testing.

If a study of the processes were added, there would not be sufficient facilities available. He recommended that a list be made of all samples to be studied and that the Subcommittee then schedule them for priority in testing.

Mr. Fischer said that such a list of samples had been approved at the last meeting of the technical advisors and that Dr. Horton was to collect the samples listed and report to the Subcommittee. The proposed schedule of testing them and the analytical work on oil 3632 should be continued concurrently. His personal view was that samples obtained from a pilot plant run should be placed way down on the list.

Dr. Horton estimated that when the new facilities are available about June 1st, 4,500 mice could be handled which would mean that 150 to 200 samples could be undergoing tests at one time.

Dr. Hoag said that the first oils to study were those to which exposures are now occurring, in order to determine control measures.

Dr. Newquist was of the opinion that, while it was very important to test various oils in order to determine which ones present a hazard and call for protective measures; nevertheless, the analytical work should be continued. Also, because of the limited number of samples that can be tested, the pilot plant studies should get under way.

Dr. Woody said that this question would be up for discussion again at the April meeting in Detroit and that, in the meantime, Dr. Horton would discuss it with Dr. Kehoe and Dr. Heyroth.

Dr. Holt proposed that Dr. Horton prepare a summary showing the total number of samples that may be desirable to study at Cincinnati between July 1949 and July 1951 and the order in which they should be studied. Dr. Horton agreed to submit such a list by May 15th.

Reporting on the National Cancer Conference recently held in Memphis, Dr. Hoag said that Dr. Holt and Mr. Fischer were to be congratulated on their handling of the subject. Dr. Newquist added that the cancer question was now an open story. He also commended Dr. Holt for his presentation; no hysteria was aroused and what was said was not embarrassing.

Dr. Woody submitted a revision of our confidential memorandum of April 2nd, 1948 proposed by Dr. Curtis. On page 3, the third sentence in the last paragraph was changed to read as follows:

"Experiments in the laboratory have shown that certain of the high-boiling materials from these newer processes cause the development of tumors and cancers on mice."

and the foot-note was omitted.

Dr. Phair said that he planned to get acquainted with the medical directors of the various companies to see what medical records are available and to determine whether epidemiological techniques could be applied to advantage. The long "incubation period" was one of the factors that complicated the problem. The adoption of control measures might be better than attempts to eliminate the hazard. In response to a question from Dr. Newquist, Dr. Phair said that a cancer registry for the petroleum industry was an inherent objective of the control program. He added that he had doubts as to the successful enforcement of laws requiring the reporting of cancer cases, as has been proposed by some investigators.

The next meeting of the Subcommittee will be held in Detroit April 1st, 1949.

McIver Woody
Chairman

A.E. Dooley
Secretary

API - meeting
Technical Com

STANDARD OIL DEVELOPMENT COMPANY
RESEARCH AND DEVELOPMENT DEPARTMENT
15 WEST 51ST STREET, NEW YORK 19, N. Y.

H. G. M. FISCHER
ASST. MANAGER

February 9, 1949

~~S.O.D.~~ CONFIDENTIAL

minutes attached

Dr. McIver Woody
Medical Department
B u i l d i n g

Dear Dr. Woody:

In response to your request as Chairman of the Subcommittee on Carcinogenicity of the Medical Advisory Committee of the A.P.I., dated November 22, 1948, an invitation was extended to the members of the Medical Advisory Committee to attend a meeting for the purpose of considering the problem of sample testing. The meeting was held on January ~~31, 1949~~, in the A.P.I. Board Room and the recommendations arrived at are given in the attached.

The outcome of the discussion was reviewed by the writer at the meeting of the Subcommittee on Carcinogenicity on February 1, 1949, and since no serious objections were voiced by the members of your Committee, I assume that the technical advisors have discharged their assignment in a manner acceptable to the Subcommittee.

I believe it was agreed that you will send copies of the attached review of the discussion to all members of the Medical Advisory Committee.

Very truly yours,

H. G. M. FISCHER

HGMF:HC
CC:Mr.D.V.Stroop

~~S.O.D.~~ CONFIDENTIAL

~~S.O.D.~~ CONFIDENTIAL

MEETING OF THE TECHNICAL ADVISORS
OF THE
SUBCOMMITTEE ON CARCINOGENICITY
MEDICAL ADVISORY COMMITTEE
AMERICAN PETROLEUM INSTITUTE

January 31, 1949
New York, N.Y.

A meeting of the Technical Advisors of the Subcommittee on Carcinogenicity was held in the A.P.I. Board Room, 30 Rockefeller Plaza, New York City, at 10:00 A.M., January 31, 1949. Present were:

R. C. Cole
A. E. Dooley
N. J. Gothard
A. E. Hoag
A. W. Horton
K. G. Mackenzie
H. P. Lankelma
W. R. Myers for H. W. Field
C. A. Swan
H. R. Warrick
N. B. Wilson for H. H. Zuidema
McIver Woody
H. G. M. Fischer, Acting Chairman

Letters were received from the following regretting their inability to attend:

E. W. Adams
L. C. Beard, Jr.
R. S. Bonsib
H. H. Zuidema

Review of Discussion

1. Purpose of Meeting

The acting chairman read his letter of January 7, 1949, to Mr. D. V. Stroop (copy attached) outlining the purpose of the meeting to the effect that the technical advisors would redefine the objectives of the program to be co-ordinated by Dr. Horton and aid him with the selection of samples suitable for study by the Kettering Laboratory of Applied Physiology, University of Cincinnati, College of Medicine, under the direction of Dr. R. A. Kehoe. The group concurred in this.

2. Objectives

There appear to be two main objectives, which were worded as follows:

(a) It is desired to establish in what crudes and fractions thereof compounds are present that may possess carcinogenic properties and the type of processes that may either concentrate or create them and, if so, under what conditions.

(b) Establish analytical procedures that will permit distinguishing between fractions, according to biological testing, that possess carcinogenic properties and those that do not. It would be useful if an index could be devised whereby a refiner could measure the degree of carcinogenicity in fractions that are being handled in a refinery or in products that are delivered to the trade.

Mr. Mackenzie proposed that priority be given Item (b) because a suitable and reliable analytical procedure would obviate the need for biological testing of an unnecessarily large number of samples. The analytical procedure would screen the inactive or the least active from the most active materials for biological testing and would serve to avoid overtaxing the capacity of available facilities.

The group agreed to the objectives as outlined, and to Mr. Mackenzie's proposal.

3. Selection of Samples for Testing

(a) Crudes

The thought was expressed that the testing of various types of crudes from different sources (domestic and foreign) would produce information of value to the producing and operating companies. However, it was the concensus of the group that the testing of crudes should be deferred until the examination of feed stocks from various sources to a variety of conversion processes and the study of products resulting therefrom discloses specific properties that should be traced to crude source, in which case selected crudes should receive closer scrutiny in the future.

(b) Processes

It appears that conversion processes, both thermal and catalytic, deserve prime attention. These were listed as follows:

Thermal - Gas Oil
Resids
Reforming
Coking
Gas Reversion
Steam Cracking

In this connection, Dr. Les Beard, in his letter of January 13 to H. G. M. Fischer, suggested that serious consideration should be given to "thermally cracked residuum from processes operating at high temperatures and on aromatic charge stock. If requested to do so, I believe that it would be possible for us to supply you with a sample of vapor phase (DeFlorez) tar from an old DeFlorez unit operating on Mirando charge with a transfer line temperature of about 900."

Catalytic - Houdry
TCC
Fluid
Houdriflow
Cycloversion
Hydroforming

Catalytic desulfurization was also mentioned; however, it was decided that this would be of marginal interest in view of the fact that the operation is carried out under relatively mild conditions with little, if any, conversion of the feed stock to lower or higher molecular weight products. This operation may merit consideration at a later date.

(c) Miscellaneous

Rod Wax
Slack Wax
Raw lube stocks (unrefined)
Solvent extracts
(Furfural, Phenol, SO_2, etc.)

In this connection, acid sludge or oily products derived from acid sludge were mentioned. The group agreed that this would be of marginal interest in view of the fact that most acid oils contain relatively large quantities of sulfuric acid and additional processing would be required to render them suitable for animal experimentation. The item will remain on the program for future consideration.

Referring to the previously quoted letter, Dr. Les Beard also suggested "slack wax from pressing paraffin distillates, preferably where the paraffin distillate has had no acid treatment", and "Rod Wax - that paraffin which accumulates in the collecting lines and crude tanks, particularly from wells in California, which, because of their depth, produce 'warm' crude."

It was agreed that Dr. Horton will solicit from the companies participating in this program representative samples of the feed stocks to the processes listed and products therefrom, and whatever information can be obtained on operating conditions and yields, and that he will concentrate his investigation primarily on such samples as can be expected to yield the most pertinent information for tying together the biological and analytical phases of the problem.

Dr. Horton briefly outlined the scope of his analytical program. In this connection, the acting chairman stated that extensive information had already been obtained which may prove useful to Dr. Horton and expressed the hope that all companies having such information in their possession would freely disclose it to him. Dr. Horton stated that in his preliminary contacts with various companies he had received excellent co-operation.

4. Samples Tested by the Kettering Laboratory

Dr. Horton reviewed the results of the studies by the Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, on eight samples which had been selected some time ago by the Subcommittee on Carcinogenicity. The results were reported in detail under date of November 5, 1948, by Dr. F. F. Heyroth. Only one sample, Oil No. W-3632 (a clarified oil from catalytic cracking) disclosed a high order of carcinogenic activity. Another oil, W-3631, (a residual from thermal cracking) produced only one tumor of a low grade of malignancy. A third oil, No. 11980, (a low-boiling distillate from catalytic cracking) produced changes in the skin of two animals which gave a moderate evidence of malignancy. In this connection, Dr. Horton stressed the need for subjecting as many animals as possible to a pathological examination in order to avoid errors that frequently arise from gross observation. He cited an example where lesions that had been reported as tumors by visual inspection (Oil No. 3631) were found to be not malignant when areas of the skin were examined microscopically. In another case (Oil N-8295-2) a tumor was found that was not detected by visual examination.

The group agreed that the largest possible number of animals should receive a pathological examination in order to make the results of the biological testing as reliable and useful as possible. Gross examination appears to be adequate for judging the results of samples which have a high carcinogenic activity.

The question was raised whether information was available on the feed stocks to the processes from which the eight A.P.I. samples were produced, and also yield data and operating conditions. Mr. Warrick, who had been instrumental in obtaining these samples, stated that such information had not been requested, as it was doubted that it would have been furnished; however, he agreed to acquaint Dr. Horton with his contacts in procuring these samples and Dr. Horton will attempt to obtain whatever information the respective companies may be in a position to disclose to him.

5. Products from Other Industries

In order to permit drawing suitable comparisons between products derived from petroleum and products from other related sources, it is recommended that samples be obtained of coal tar, water gas tar, and shale oil (domestic and foreign) for study.

6. Funds Available

In view of the possibility that appropriated funds may not be adequate to finance the work to be undertaken by the Kettering Laboratory when the full program goes into effect, the question was raised as to how much money was available. According to information supplied by Mr. Stoop, the Kettering Laboratory received a grant of

$25,000 in 1948 which appears to be sufficient to cover their operating expenses until July 1, 1949. An additional $25,000 is on deposit which can then be made available if needed. In addition, Mr. Stroop has included in his list of subscriptions a request for $25,000 to be ready for Dr. Kehoe on January 1, 1950, to cover the six months' period to July 1, 1950. Dr. Horton indicated that he expected to have laboratory facilities available by June 1, 1949, and that the biological laboratory will be in a position to handle about one hundred samples, with provisions for approximately 4,500 mice.

It is anticipated that in order to carry out the recommendations arrived at by the technical advisors, the Kettering laboratory may require the services of an additional pathologist, and Dr. Horton may require the addition of another member to his staff.

The meeting adjourned at 12:45 P.M.

Roxy Dowling
Acting Secretary

2/8/49

(C O P Y)

STANDARD OIL DEVELOPMENT COMPANY

Research and Development Department
15 West 51st Street
New York 19, N.Y.

January 7, 1949

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

Dear Mr. Stroop:

You will recall that among the recommendations adopted at the meeting of the API Medical Advisory Committee Sub-Committee on Carcinogenicity on November 11, 1948, at Chicago, Item 4 (appearing in the minutes) reads as follows:

> "That the fundamental chemical and physical studies that are indicated to investigate the operational technical aspects of this problem may require considerably more money than anticipated; and it is recommended that the technical advisers group consider the problem again and present their recommendations to the Sub-committee on Carcinogenicity."

In this connection, Dr. McIver Woody, Chairman of the Sub-committee on Carcinogenicity, has written me as follows:

> "Now that Dr. A. Wesley Horton has been selected by Dr. Kehoe to investigate the chemical aspects of the problem, it will be greatly appreciated if you would call a meeting of the technical advisers to confer with Dr. Horton on methods of selecting samples for future testing, taking into account the nature of the crude, its source, the temperature conditions, etc."

As I understand the situation, it is desired that the technical advisers redefine the objectives of the program to be coordinated by Dr. Horton and aid him with the selection of suitable samples for study by the Kettering Laboratory of Applied Physiology, University of Cincinnati, College of Medicine, under the direction of Dr. R. A. Kehoe.

I shall be glad to conduct this meeting in response to Dr. Woody's invitation and would suggest the date of January 31, 1949, in the API Board Room on the 20th floor at 50 West 50th Street, New York City, at 10:00 A.M.

Since the group will wish to arrive at definite conclusions and recommendations, it is hoped that the technical advisers will find it convenient to attend this meeting in person.

If you are in agreement with this method of putting into effect the recommendation adopted by the Medical Advisory Committee, I shall appreciate your extending an invitation to Dr. Horton and the associate members of the Medical Advisory Committee to attend this meeting and to others who you feel would be interested in participating in the discussion.

Please advise.

Very truly yours,

/s/ H. G. M. Fischer
H. G. M. FISCHER

HGMF:HC
CC: Dr. McI.Woody
Dr. J.P.Holt

6. Should the epidemiological study
   a. be continued for an indefinite period on an industry-wide basis,
   b. be maintained as a current registry of actual cases from petroleum products, or
   c. be limited to studies of a smaller number of refineries and other operations where medical departments exist and reliable medical data can be obtained?

a	5
b	16
c	25
None	1
Revise present procedure	2
Opinion deferred	2
No answer	2

7. Has sufficient information been developed to date in these studies to enable the individual companies to formulate adequate control measures
   a. for their own employees,
   b. for their customers?

Employes	Yes	19	No	15
Customers	Yes	6	No	28
No answer	3			

8. For how long should the total expenditures be continued at the present rate of $100,000 per year or should they be reduced to an amount sufficient to cover specific objectives only?

Reduce for specific objectives	26
Continue at present rate	10
No answer	1

9. What other comments or recommendations do you have?

See attached exhibit

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 1

Should animal tests be made on samples selected in 1949 but as yet not tested; specifically those from desulfurization, steam cracking, rod waxes, coal tar, domestic and British shale oil?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
No	2	2	2	4	10
No - if analytical technique is sufficient			1	1	2
Yes	4		2	2	8
Yes - newly collected samples, domestic materials before Brit.			1	1	2
Yes - limited number	1	1			2
Yes - rod waxes only		1	1		2
Yes - rod waxes, coal tar, British shale oil only	1	2			3
Yes - rod waxes, coal tar, crudes only	2	1			3
Yes - shale oil only	1	1	1	2	5

SUMMARY

No	10
Yes	14
Certain ones only	13

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 2

Should additional samples representing any of the processes and products in the 1949 list be tested on animals? If so, which ones?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
No	5	3	3	6	17
No, probably		1			1
Not too important	1				1
No - if analytical technique is sufficient			1	1	2
Yes	1	1			2
Yes, probably	1				1
Yes - only in connection with analytical technique		2			2
Yes - high potency products only			1	1	2
Yes - some, based on Dr. Kehoe's advice	1				1
Yes - rod waxes			1		1
Yes - asphalts, lube oils, aromatic solvents, cutting oils and other products where exposure factor is high	2	1			3
Yes - sulfur dioxide extract oils from cat.gas oils; methyl naphthalene, heavy nitrogen cyclic cpds., heavy virgin gas oils; HF acid soluble oils; heavy oils from dehydrogenation of butane and butylene			1	1	2
No answer			1	1	2

SUMMARY

No	21
Yes	5
Some	3
Other processes and products	6
No answer	2

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 3

Should the animal testing program be continued on its present scale for one more year or for two more years, by the selection of additional samples from various processes or should it taper off and be confined to the necessary animal tests in connection with the development of an analytical technique?

	SUB-COMM.		NON-COMM.		TOTAL
	M	A	M	A	
Taper off on animal tests and expand analytical technique	4	1	4	8	17
Restrict new samples and complete analytical technique	1	4			5
Restrict and complete analytical technique, study fuel oils		1			1
Analytical technique only, if limited to one choice	1				1
Continue for 2 years at least	1		3	2	6
Should be continued for many years	1				1
Continue especially for analytical technique	1	1			2
Continue at such scale as decided by Medical Advisory Committee	2	1			3
No answer			1		1

SUMMARY

Taper off on animal tests and expand on analytical technique	26
Continue at present scale	7
As decided by Committee	3
No answer	1

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 4

Should a large-scale animal testing program be initiated on fuel oils to determine their potential hazards, if any, or should evaluation of these fuels await the development of an analytical technique?

	SUB-COMM. M	SUB-COMM. A	NON-COMM M	NON-COMM A	TOTAL
Await development of analytical technique	3	1	3	5	12
Await analytical technique - include 1920-1940 fuels without catalytically cracked fractions		2			2
Check analytical technique by animal tests	2		1		3
No animal testing for fuel oils	2	2			4
No need to concentrate on residual fuel oils	2	1			3
Review animal testing program before starting			1	1	2
Yes for animal testing	1	1			2
Yes, for animal testing on a limited scale for typical types of operations	1	1	1	3	6
Yes, after present project is completed or shows more positive results			1	1	2
No answer			1		1

SUMMARY

Await analytical technique	28
Initiate animal testing program	8
No answer	1

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 5

Should efforts be directed toward development of a technique to eliminate the carcinogenic effect of an oil by removal or conversion of the carcinogens?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
No	2	3	3	8	16
No - O.K. though in connection with the study of pure carcinogens	3	2			5
No - but determine the carcinogen	1				1
Premature - probably not a Med. Adv. Comm. function	2	2	1	1	6
Yes	2		2		4
Yes - preliminary efforts only		1			1
Yes - for consumer protection	1				1
Indefinite - conversion would be safer than removing carcinogens			1	1	2
No answer			1		1

SUMMARY

No	28
Yes	6
No answer	3

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 6

Should the epidemiological study
a. be continued for an indefinite period on an industry-wide basis,
b. be maintained as a current registry of actual cases from petroleum products, or
c. be limited to studies of a smaller number of refineries and other operations where medical departments exist and reliable medical data can be obtained?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
b and c only	5	2	2	3	12
b or c			1	3	4
a only	1	2	1		4
a if possible		1			1
c only	2	1	3	3	9
Modify present survey and then make an epidemiological study	1	1			2
Obtain Dr. Phair's opinion	1	1			2
No epidemiological study	1				1
No answer			1	1	2

SUMMARY

a	5
b	16
c	25
None	1
Revise present procedure	2
Opinion deferred	2
No answer	2

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 7

Has sufficient information been developed to date in these studies to enable the individual companies to formulate adequate control measures
a. for their own employes,
b. for their customers?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
Employes, yes - customers, yes			2	2	4
Employes, yes - customers, no	5	2	2	4	13
Employes yes - customers, yes (tentatively)	1			1	2
Employes, no - customers, questionable		2	1		3
Employes, no - customers, no	5	3	2	2	12
Cannot answer intelligently		1			1
No answer			1	1	2

SUMMARY

Employes	Yes	19	No	15
Customers	Yes	6	No	28
No answer	3			

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 8

For how long should the total expenditures be continued at the present rate of $100,000 per year or should they be reduced to an amount sufficient to cover specific objectives only?

	SUB-COMM.		NON-COMM.		TOTAL
	M	A	M	A	
For specific objectives only	3	3	6	8	20
Should taper off soon	1				1
At such scale as decided necessary by Med.Adv.Comm.	2	3			5
Continue for one year and then review				1	1
Continue for at least 2 years	1	1	1	1	4
Continue as at present	1				1
Contine at present rate but alter line of emphasis	1	1			2
Continue until completed, even if higher cost	2				2
No answer			1		1

SUMMARY

Reduce for specific objectives	26
Continue at present rate	10
No answer	1

REPLIES TO QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY

QUESTION 9

What other comments or recommendations do you have?

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
Study protective creams	7	4	2		13
Study protective creams and washing	3	1			4
Study protective clothing and devices	4	1			5
Study cleansing agents			1		1
Inhalation studies of potent oils as possible pulmonary carcinogens	3	2	1		6
Evaluate hazard to humans (using monkeys) of oil vapors alone	1	1			2
Animal tests with and without washing but stopping application when first tumor appears	1	1			2
Develop a non-biological test	1	1			2
Continue or expand work on isolation of pure carcinogens	1	1			2
Test monkeys or dogs to get better human correlation	1				1
Translate animal test results to humans		1			1

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
Develop information on what constitutes hazard with respect to concentration and length of exposure	1				1
Develop reasonable potency factor applicable to normal working conditions			1	3	4
Discuss matter of consumer risk			1	1	2
Develop information to compare properties of cat. and thermal oils which are potent to mice with slack waxes and spinning oils where human exposures are known	1				1
Study marketed products	1		1		2
Study lube oils (insoluble cutting oils) where exposure factor is high	1	1			2
Study soot from chimneys where oil and coal are used as fuel	1		1		2
Study single ring aromatics or 2-condensed ring aromatics to see if they act similarly to dodecyl benzene		2			2
Study cocarcinogenic effect of ultra-violet radiation			1		1
Continue sufficient studies to maintain a continuing reassurance that present conclusions are sound			1	2	3
Gather all possible information for possible future medico-legal use			1	1	2
Collaborate with General Comm. on Refining in the definition of future work	1				1

Replies to Questionnaire
Question 9

	SUB-COMM. M	SUB-COMM. A	NON-COMM. M	NON-COMM. A	TOTAL
Express commendation for excellent work done	1		1		2
Prefers to defer opinion until November meeting	2				2

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

August 20, 1951

Members and Associates
Subcommittee on Carcinogenicity

Gentlemen: .23 on the dollar for scientific research

This subcommittee is now in its seventh year and up to date approximately $218,000 has been expended on the API carcinogenicity project and an additional $100,000 has been earmarked for the year ending June 30, 1952. Dr. Kehoe's staff has done excellent work and the information obtained has been invaluable. However, it is conceivable that unless the program is reviewed in the light of the original objectives and needs of the petroleum industry, it might go on indefinitely at high cost and some of the information developed might not have much practical value to the industry.

Therefore, I will appreciate receiving your recommendations on the specific questions in the attached questionnaire in order that the Subcommittee can collaborate more effectively with Kettering Laboratory as regards samples to be tested, development of an analytical technique and other phases of the project. Comments are also invited from members and associates of the Medical Advisory Committee who are not on this Subcommittee.

For your information, I am attaching tables showing the number of animal tests and samples representing the processes and products selected by the Subcommittee on February 1, 1949 and the potencies of 50 samples or fractions therefrom. These figures are as of April 12, 1951, and undoubtedly, additional tests have been completed since then.

I will appreciate receiving replies of all members and associates of the Medical Advisory Committee not later than September 17, 1951. If the replies are widely divergent, it may be advisable to hold a meeting of the Subcommittee in Cincinnati about the second week in October. In such event, you will receive adequate notice.

As you know, a report on the carcinogenicity project is to be given to the General Committee, Division of Refining, API, by Dr. Kehoe on November 6. It is quite possible that the General Committee will want to know about our future plans for studying and handling this subject so it is doubly important for the Medical Advisory Committee to have some definite recommendations from you.

Very truly yours,

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

MNN:GH
Attach:
mc: Members and Associates, Medical Advisory Comm.
Dr. R. A. Kehoe

Table 1 - Number of samples being tested on animals as of April 12, 1951, representing processes and products selected in 1949 for study

	Number of samples	Number of tests*
STRAIGHT THERMAL PROCESSES		
GAS OIL CRACKING		
Charge	3	3
Recycle gas oil	1	1
Fuel oil	2	2
Tar	12	13
VISCOSITY BREAKING		
Cycle gas oil	1	1
Resid	2	2
NAPHTHA REFORMING		
Tar	3	3
COKING		
Charge	1	1
Gas oil	1	1
Heavy gas oil	3	3
Blow down oil	1	1
Wax Tailings	1	1
GAS REVERSION (POLYFORMING)		
Tar	3	3
STEAM CRACKING	0	0
CATALYTIC PROCESSES		
HOUDRY		
Heavy gas oil	6	6
THERMOFOR CATALYTIC CRACKING		
Cycle gas oil	1	1
Recycle gas oil	1	1
Synthetic bottoms	9	9
FLUID CATALYTIC CRACKING		
Gas oil	1	1
Heavy cycle gas oil	2	2
Bottoms (700°/) from heavy cycle gas oil	1	2
Decanted oil	8	33
Slurry	2	2
HOUDRYFLOW	0	0
CYCLOVERSION		
Heavy gas oil	1	1

* Does not include animal tests for cocarcinogenicity, effects of washing, or tests on methylcholanthrene or dimethyl benzanthracene standards.

	Number of samples	Number of tests*
HYDROFORMING		
Bottoms	2	2
DESULFURIZATION (marginal case)	0	0
SPECIFIC PRODUCTS		
ROD WAXES	0	0
SLACK WAXES		
Charge to press	1	1
Dewaxed oil	2	2
CERTAIN RAW LUBE STOCKS (UNTREATED)		
Naphthenic distillate	1	1
Gas oil	1	1
Resid	1	1
SOLVENT EXTRACTS		
Furfural	1	1
Phenol	2	2
Duosol	1	1
Nitrobenzene	1	1
Sulfur dioxide	1	1
ACID OILS FROM ACID SLUDGE		
Hydrolyzed acid sludge	1	1
White oil	1	1
PRODUCTS FROM OTHER INDUSTRIES		
COAL TAR	0	0
WATER GAS TAR	0	0
SHALE OIL - DOMESTIC AND BRITISH	0	0
	82	109

* Does not include animal tests for cocarcinogenicity, effects of washing, or tests on methylcholanthrene or dimethyl benzanthracene standards.

Table 2 - Potencies of oils (methylcholanthrene equivalents) as determined by animal tests reported as of April 12, 1951

High potency - above 0.1
Moderate potency - 0.02 - 0.1
Low potency - below 0.02

Potency	Description of Sample	API Sample Number
0.65	FCC Slurry	26
0.63	FCC Decanted oil	12
0.63	FCC Decanted oil W3632	8
0.60	FCC Press oil (85%) from decanted oil W3632	8-3
0.60	FCC Desulfurized press oil from decanted oil W3632	21
0.47	FCC Aromatic fraction (from silica gel) of decanted Oil W3632	8-5
0.33	FCC Dewaxed fraction (MEK-benzol) of a decanted oil	43-1
0.30	FCC Decanted oil	42
0.29	TCC Synthetic bottoms	31
0.24	TCC Gas oil - charge to thermal cracking	29
0.22	Fuel blend from cracking TCC gas oil (Sample 29)	30
0.22	TCC Synthetic bottoms	10
0.20	Coking - Heavy gas oil	33
0.20	Coking - Blow down oil	53
0.20	Thermal - Tar from FCC Heavy gas oil	24
0.16	FCC Heavy gas oil	23
0.16	Houdry - Heavy gas oil	11
0.16	Coking - Gas oil	28
0.16	FCC - Bottoms 700°+ from FCC heavy gas oil	25
0.15	Cycloversion - Heavy gas oil	22
0.15	Phenol extract, San Joaquin naphthenic distillate	27
0.14	Houdry - Heavy gas oil	51
0.14	Thermal - Tar from FCC gas oil	47
0.14	Thermal - Tar from TCC gas oil	61
0.14	Thermal - Tar from Houdry gas oil	35
0.14	Thermal - Tar	64
0.13	FCC - 50% Decanted oil W3632; 50% white oil + W. Texas Resid.	8-4
0.13	Thermal tar	55
0.14 0.12	Thermal tar - feed contained cat. cracked components	20
0.11	Thermal tar - 50% of above, 50% dodecyl benzene	20-1
0.12	Houdry - heavy gas oil	50
0.10	FCC Heavy gas oil	46
0.09	Houdry heavy gas oil	34
0.08	FCC - 50% bottoms 700° from FCC Heavy CGO, 50% white oil + W. Texas Resid.	25-1
0.08	Coking - heavy gas oil	52
0.08	Fuel blend - thermal cracking, feed cont'd cat cracked components	39
0.07	FCC Decanted oil fraction 510°-710°, 1-plate vac.dist.	12-4
0.07	FCC Decanted oil fraction 1010° - 1065°, 1-plate vac. dist.	12-5

Potency	Description of Sample	API Sample Number
0.06	Thermal tar, unflashed thermal resid.	6
0.06	Polyformer tar	37
0.04	Polyformer tar	13
0.04	Naphtha reforming - tar	19
0.03	FCC decanted oil, asphalt from pentane deasphalting	12-1
0.03	FCC decanted oil, resid boiling 1065°, 1-plate vac.dist.	12-6
0.03	TCC synthetic bottoms	9
0.015	FCC decanted oil, 2nd asphalt from pentane deasphalting	12-3
0.01	Phenol extract, Coastal 900X	16
0	Straight run gas oil	1
0	Straight run resid, Wilmington crude	5

QUESTIONNAIRE - SUBCOMMITTEE ON CARCINOGENICITY
August 20, 1951

1. Should animal tests be made on samples selected in 1949 but as yet not tested; specifically those from desulfurization, steam cracking, rod waxes, coal tar, domestic and British shale oil?

Test — Steam cracking already started
Scottish shale oil analyses available — Refle oils being tested at NIH
Coal Tar probably will be studied as part of a separate project.

2. Should additional samples representing any of the processes and products in the 1949 list be tested on animals? If so, which ones?

Some from all -
In particular - effects of cocarcinogens in high potency slurries from FCC or TC
Sidestreams
Tars from thermal cracking of virgin feeds from units in which no catg. ever process

3. Should the animal testing program be continued on its present scale for one more year or for two more years, by the selection of additional samples from various processes or should it taper off and be confined to the necessary animal tests in connection with the development of an analytical technique?

The tests, are being coordinated closely with the development of data pertinent to the questions important from the analytical standpoint

4. Should a large-scale animal testing program be initiated on fuel oils to determine their potential hazards, if any, or should evaluation of these fuels await the development of an analytical technique?

An analytical tool applicable to these heavy oils can be developed efficiently only when based on large numbers of biological tests on the type of oil in question - in this case blended fuel oils. A purely analytical approach might require decades (see API-6)

5. Should efforts be directed toward development of a technique to eliminate the carcinogenic effect of an oil by removal or conversion of the carcinogens?

Suggest that these efforts continue on present small scale until chemical and physical properties of active carcinogens or cocarcinogens in oil have been determined.

6. Should the epidemiological study
   a. be continued for an indefinite period on an industry-wide basis,
   b. be maintained as a current registry of actual cases from petroleum products, or
   c. be limited to studies of a smaller number of refineries and other operations where medical departments exist and reliable medical data can be obtained?

As to c. some of our badly needed info re a base line from human experience is coming from refineries without medical depts.

7. Has sufficient information been developed to date in these studies to enable the individual companies to formulate adequate control measures
   a. for their own employees,
   b. for their customers?

a. What about sidestream and thermal cracking of virgin feeds
b. At the minimum, some idea of potency of fuel oils and coal oils required.

8. For how long should the total expenditures be continued at the present rate of $100,000 per year or should they be reduced to an amount sufficient to cover specific objectives only?

None of the current 100,000 goes any place but into specific objectives discussed at API meetings and approved by MAC

9. What other comments or recommendations do you have?

Signed_____ Company_____ Date_____

Please return to Dr. M. N. Newquist, The Texas Company, 135 East 42nd Street, New York 17, N. Y.

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

Minutes
Apr. 23/1950

June 7, 1950

To Members and Associates
The Medical Advisory Committee

We enclose for your information the minutes of the meeting of the Subcommittee on Carcinogenicity held in Chicago on April 23, 1950.

D. V. Stroop

DVS:nc

Enc.

For Information Only - Not for Publication

AMERICAN PETROLEUM INSTITUTE

SUBCOMMITTEE ON CARCINOGENICITY

Minutes of Meeting
April 23, 1950
Hotel Sherman
Chicago, Illinois

Members Present

McIver Woody (Chairman)
Marshall Clinton
T. M. Frank
A. E. Hoag
J. P. Holt (Rep. by R. E. Eckardt)
T. J. Kelly
J. W. Long
M. N. Newquist
Chas. A. Swan

Associates Present

L. O. Crockett
Allan E. Dooley
R. W. Faulk
R. M. Landon
H. P. Lankelma
K. G. Mackenzie (Rep. by H. R. Warrick)
R. M. Shepardson

Members and Associates of Medical Advisory Committee

W. O. Armstrong
V. C. Baird
F. F. Boys
Kieffer Davis
E. K. Linder
E. P. Luongo
B. B. Reeve
E. R. Ware
E. W. Adams
R. D. Bent
R. C. Cole
T. E. DeVilliers
L. M. Henderson
C. A. Neilson
F. M. Watkins

Guests

N. W. Bolyard - Standard Oil Co. (Ind)
Philip Drinker - Harvard School of Public Health
J. W. Hammond - Humble Oil and Refining Co.
Howard Hansen - Esso Standard Oil Co.
A. W. Horton - University of Cincinnati
W. C. Hueper - National Cancer Institute, Bethesda. Md.
R. A. Kehoe - University of Cincinnati
R. C. Page - Standard Oil Co. (N. J.)
J. J. Phair - University of Cincinnati
H. G. S. van Raalte - Shell Oil Co., Curacao, N. Ant.
W. E. Smith - New York University
D. V. Stroop - American Petroleum Institute
P. M. Waddill - Phillips Petroleum Co.

Total in attendance - 44

Members Absent	Associates Absent
L. E. Curtis	L. C. Beard, Jr.
W. R. Levis	H. G. M. Fischer

The minutes of the November 10, 1949 meeting were approved.

Dr. A. W. Horton presented a progress report, copies of which had been sent to all members and associates on April 11. This report was supplemented by a series of lantern slides showing potencies of some of the oils which have been tested. With respect to the analytical phases, Dr. Horton stated that many compounds had been isolated but very few had been identified as yet. Perylene, 4-methyl pyrene and chrysene have been definitely identified as constituents of high-boiling catalytically cracked oils.

Dr. Horton described the data which was to be submitted for publication in "Cancer Research". The potency curves of oils 8 and 9 (see Table I of Dr. Horton's report) would be included as being typical examples of the oils being studied.

In the discussion which followed, many of the members and associates voiced a request that a complete and detailed report be prepared by Dr. Horton. It was pointed out that such a report would be of particular benefit to new members and associates.

Dr. Horton's report was accepted and approved.

Mr. R. M. Shepardson described the work of his company on the development of a quick laboratory test for measuring the potential carcinogenicity of petroleum products. As a numerical expression of potential carcinogenicity, the number of days required for 50 per cent of the mice to develop tumors after discarding all mice which had died

without tumors, has been tentatively chosen. Of 64 samples tested to date, a satisfactory correlation has been found between the biological tests and the ultra-violet absorption measured at 360 mu on the portion of the sample separated by distillation and boiling between 650° and 950° F., when correcting for difference in viscosity, mid-boiling point and concentration of the 650-950° F. material. This study is being continued on a larger number of samples.

The subcommittee expressed its thanks to Mr. Shepardson for his presentation.

Dr. R. E. Eckardt reported on some of the work* being done at Memorial Hospital. Cancers have been produced in two monkeys out of six who had been painted with a high-boiling oil twice a week for about five years. This is the first time that skin cancers have been produced experimentally in monkeys.

Dr. Eckardt reporting on washing experiments said that results to date indicate that washing offers some protection but not absolute protection. With groups of 30 mice, application of the oil and washing after five minutes resulted in a reduction in the number of tumors and no cancers after one year. Washing the mice one hour after application produced tumors in four mice and cancer in one mouse of the group of thirty. Washing the mice six hours after application resulted in the development of cancer in three mice.

In a group of sixty mice which were painted with only one application of a high-boiling oil, tumors were produced in two mice

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* See attached copy of paper "Experimental Analysis of the Carcinogenic Activity of Certain Petroleum Products" for additional information on this work.

and cancers in two additional mice. The first tumor appeared after 92 days and the first cancer after 274 days. No tumors or cancers appeared in a control group on 100 mice.

This subcommittee expressed its thanks to Dr. Eckardt for his presentation.

Dr. J. J. Phair presented a progress report on the epidemiological study which he plans to get under way about July 1, 1950. Dr. Phair distributed mimeographed copies of his report. During the discussion it was brought out that, to date, there have been no cases of skin cancer in which the employe has claimed that exposure to these high-boiling oils was the cause.

Dr. Phair's report was accepted and approved with the understanding that the word "approved" would be changed to "needed" where it fits the context of the report.

Dr. H. G. 'S. van Raalte told about a fishing village on the island of St. Martin where the inhabitants, all of Danish ancestry, can trace their ancestry back about 200 years on the island. He stated that most of the men develop skin cancers by the time they reach age 40. Most work at fishing and handle tarred nets and tackle. A few who have worked in the refinery or at Aruba apparently have not had skin cancers.

Dr. W. C. Hueper (National Cancer Institute) said that he had talked to a nurse in an asphalt shingle plant in the western part of the United States and that the nurse had reported cases of cancer on the dorsum of the hands. Dr. Hueper said that a petroleum asphalt

was being used and that it would be well to keep an eye on this material with respect to both producers and consumers.

The subcommittee recommended to the Medical Advisory Committee that it should approve:

1. Publication of the report as described by Dr. Horton in his letter of April 7, 1950 to D. V. Stroop.

2. The proposed epidemiological study as described by Dr. Phair.

Allan E. Dooley
Secretary

McIver Woody, M.D.
Chairman

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EXPERIMENTAL ANALYSIS OF THE CARCINOGENIC ACTIVITY OF CERTAIN PETROLEUM PRODUCTS*

William E. Smith, M.D., Douglas A. Sunderland, M.D., and Kanematsu Sugiura, D.Sc.

from the Institute of Industrial Medicine, New York University-Bellevue Medical Center, and the Sloan-Kettering Institute for Cancer Research, New York, U.S.A.

As part of the preventive medical program of a petroleum company, we conducted tests for carcinogenic activity on approximately 400 samples from refinery, laboratory and wax works operations. Each sample was tested by painting on a group of 30 mice.

Oils from Catalytic Cracking Process: Carcinogenic activity was found only in fractions distilling above 700° F. The carcinogenicity of the most potent oils studied was markedly reduced by dilution to approximately 10% concentration with non-carcinogenic oils. Blends containing not more than 10% of potent oils elicited only a few tumors and these were benign.

Waxes: Unrefined petroleum waxes elicited cancers late and infrequently, but their aromatic extracts were very active. The hazard in wax works thus appears to be associated with the aromatic compounds in unpurified wax and not with the paraffins.

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* These studies were carried out under a grant from the Standard Oil Co. (N.J.) and certain affiliates in cooperation with the Medical Department of that company. All samples were prepared and supplied by the Standard Oil Development Company.

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REVISED DRAFT

EXPERIMENTAL ANALYSIS OF THE CARCINOGENIC ACTIVITY OF CERTAIN PETROLEUM PRODUCTS.

William E. Smith, M. D., Douglas A. Sunderland, M. D. and Kanematsu Sugiura, D.Sc.

from the Institute of Industrial Medicine, New York University-Bellevue Medical Center, and the Sloan-Kettering Institute for Cancer Research, New York, U. S. A.

Occupational tumor problems have been much less commonly observed in the petroleum industry than in the Scottish shale oil trade. Occasional tumors have, however, been described, and some petroleum oils have been shown to elicit tumors in experimental animals. For these reasons, the Standard Oil Company (New Jersey) and certain affiliated companies began a general investigation into the question of possible occupational tumor hazards for workers in refineries. In collaboration with this study, we have carried out tests for carcinogenicity on approximately 400 samples of oils and waxes derived from various phases of plant and laboratory processes. The samples were prepared by the Standard Oil Development Company.

The first group of materials studied were from an experimental catalytic cracking operation. In this process, developed extensively during the past ten years, oils are cracked at a relatively high temperature in contact with a catalyst generally composed of mixtures of silica and alumina. From the classic experiments of Kennaway, Cook, Twort and others, it was known that petroleum, like coal and other

bituminous materials, may acquire carcinogenic properties as a result of reactions brought about by extensive thermal decomposition.

Our first tests were conducted with samples of high boiling, catalytically cracked oils. These proved highly potent in bringing about cancer when painted on the skins of mice. They also elicited papillomas and occasional cancers from the skins of rabbits, and, after years of painting, from the skins of monkeys.

(slide #1) (slide #2) (slide #3) (slide #4)

Preliminary tests showed that white mice obtained from a commercial breeder (Rockland Farms) gave tumors somewhat more quickly than dark-skinned C57 mice, and we have routinely used white male mice from this breeder. It was found that for practical purposes essentially comparable information could be gained from mice tested in a group of 30 as compared with a group of 100 animals. We have therefore tested each sample on a group of 30 mice. If groups much smaller than this are used, difficulties may arise from loss of animals in the course of the necessarily long-term experiments.

The mice are painted with the test material three times a week throughout their lives, unless the experiment is discontinued earlier. Very potent samples have elicited papillomas as early as 29 days and cancer after 70 days; but for moderately potent materials a period of 250 days is usually necessary to gain an impression of their activity, and many samples must be painted much longer before tumors appear.

(slide) #5 Statistical methods proposed by the Standard Oil Development Company have been adopted which permit the data from each sample to be charted graphically in a manner that permits one to see at a glance the non-tumor mortality, the number of animals developing benign papillomas, the number developing cancers, and the rate at which the tumors appear. This slide shows such a graph, on which is given data obtained from mice painted with an acetone solution containing 0.3% of the pure carcinogen, methylcholanthrene. The days at which the animals were observed are indicated along the bottom. The percentage of survivors with or without tumors at any given time can be read off the scale at the right. The percentage of animals dying with or without tumors can be read off the scale at the left. The shaded area indicates the time of appearance of the first cancer and the number of cancers that developed. The percentage of animals dying without tumors can be read by reference to the lowest line on the chart. It may be guide to toxicity of the sample but often connotes deaths from fighting or intercurrent infection.

(slide) #6 The next slide gives the results of painting a sample of high boiling catalytically cracked oil. It shows a carcinogenic activity not greatly less than that of the 0.3% solution of methylcholanthrene just shown. A mixed colony consisting of 13 male and 12 female mice was used in this experiment. The data for each sample under test is entered from month to

(slide) #7 month on graphs such as these.

For convenience in comparing the carcinogenicity of large numbers of samples, two indices have been employed. The Tumor Index is the percentage of animals, surviving 90 days or longer, that develop either papillomas or cancers. The Cancer Index is the percentage of animals, surviving 90 days or longer, that develop cancers. The activity of each sample can then be rated by a simple numerical fraction, the Cancer Index over the Tumor Index.

(slide) #8 The next slide, divided into two groups, shows results at 250 days on 10 samples of catalytically cracked oils received from refinery operations. The first group, consisting of five samples, contained relatively little high boiling material (less than 30% distilling above 700° F.). It is seen that they were practically devoid of carcinogenic activity. Only two of the five induced any cancers and then in only a small percentage of animals. It is of interest to note that the most active sample in this group (207) contained the greatest percentage of high-boiling material (28%). By contrast, the second group of five samples gives the results on catalytically cracked oils that contained large amounts of high-boiling materials (over 45% distilled above 700° F.). It is seen that all of these possessed a very high carcinogenic potency.

(slide) #9 The carcinogenicity of such high-boiling oils can be effectively reduced by dilution with non-carcinogenic oils. Here is a set of tests on blends containing varying proportions of high-boiling material. No reduction in potency was

found when the blend contained 67% of the active oil. When only 55% was present, the carcinogenicity fell off; and when the amount was reduced to 29%, no cancers whatsoever resulted at 250 days, though a considerable percentage of animals still yielded benign papillomas. Further experiments with dilutions of another oil of this type have shown comparable results and are also shown in Slide #9. In these experiments it is indicated that when the concentration of the active oil was reduced by dilution to somewhere between 10 and 20% (8 and 16% boiling above 700° F.), the carcinogenicity of the oil is abolished in that no cancers are produced.

The carcinogenicity of these oil samples has thus been shown to be associated with the high boiling material. The (slide) #10 problem has been further narrowed down by demonstrating that the carcinogenic activity resides in the aromatic fraction of the oils. Here are tests on fractions of a high boiling oil subjected to chromatographic separation on silica gel. It is seen that the paraffinic components were devoid of carcinogenicity whereas the cumene eluate, which contained the aromatics, was extremely potent.

(slide) #11 This finding has been applied in the study of materials from wax-works. In the manufacture of waxes, certain oils are cooled and the solid material, or wax, which separates out is collected in a press. Samples of these crude waxes were melted at 60° and planted on mice. After 250 days, very few animals thus painted showed any tumors. When the painting was kept up for 450 days, however, tumors were induced by all

of 8 samples of crude waxes but the percentage of animals that developed tumors was small. Often, merely papillomas and no cancers resulted. By contrast, the aromatics extracted by silica gel from these crude waxes possessed very marked carcinogenic potency. In every instance, they elicited considerably more tumors than the whole crude wax from which they were obtained. Furthermore, the aromatic fractions regularly produced one or more malignant tumors.

It therefore appears that the carcinogenic hazard in the case of crude waxes is due to the presence in them of aromatic components, and not to the paraffins which compose the final purified waxes.

LIST OF SLIDES

1. Cancer and papilloma as seen on a mouse painted with a sample of high boiling catalytically cracked oil (color photo).
2. Histological section of tumor shown in Slide 1.
3. Papillomas on ear of rabbit painted with same material applied to mouse shown in Slide 1.
4. Ditto (monkey)
5. Graph showing data from painting methylcholanthrene (Exp. 22)
6. Graph showing data from painting a sample of high boiling catalytically cracked oil (Sample III, Exp. 11) N.B. We have removed the cross-hatching which this graph erroneously shows between 40 and 70 days.
7. Definition of Cancer and of Tumor Indices.
8. Cancer Index/Tumor Index data on oils with various boiling ranges.
9. Reduction of carcinogenicity of high boiling oils by dilution with non-carcinogenic oils.
10. Carcinogenicity of aromatic contrasted to paraffinic fractions of a high boiling catalytically cracked oil.
11. Carcinogenicity of crude waxes contrasted to that of their aromatic fractions.

SLIDE #7

TUMOR INDEX: $\frac{\text{TOTAL NUMBER OF ANIMALS THAT DEVELOPED TUMORS}}{\text{ORIGINAL NUMBER OF ANIMALS LESS THE NUMBER DEAD AT 90 DAYS WITHOUT TUMORS}}$

CANCER INDEX: $\frac{\text{TOTAL NUMBER OF ANIMALS THAT DEVELOPED CANCER}}{\text{ORIGINAL NUMBER OF ANIMALS LESS THE NUMBER DEAD AT 90 DAY WITHOUT CANCERS}}$

SLIDE #8

SAMPLE NO.	% DISTILLING ABOVE 700°F.	CI/TI at 250 days
217	less than 1	0/0
213	3	0/0
224	10	0/0
207	28	4/12
219	3	4/4

SAMPLE NO.	% DISTILLING ABOVE 700°F.	CI/TI at 250 days
206	74	33/67
173	78	38/57
223	78	38/77
216	45	46/71
212	78	67/87

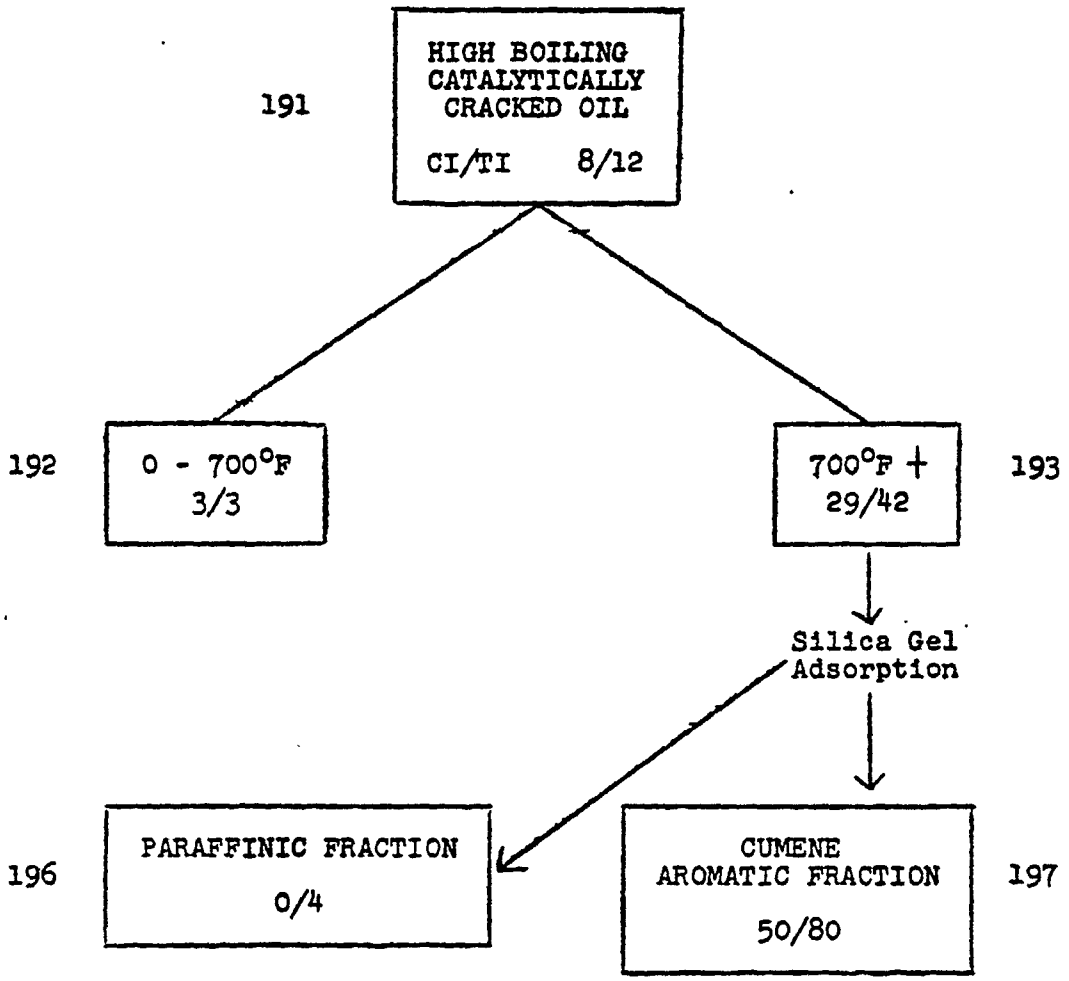
SLIDE # 9

REDUCTION OF CARCINOGENICITY OF A HIGH BOILING OIL BY DILUTION WITH NON-CARCINOGENIC OILS

		CI/TI at 250 days
	MH 101 (45% distilling above 700°F)	27/62
	BLEND CONTAINING:	
127	67% MH 101	23/67
121	55% MH 101	13/57
115	29% MH 101	0/27

	CI/TI at 281 days
173 (78% Distilling above 700°F)	36/50
175 Non-carcinogenic oil	0/0
176 10% 173	0/4
177 20% 173	16/36
178 30% 173	3/24
179 40% 173	44/59

SLIDE # 10



CANCER INDEX / TUMOR INDEX at 250 days

SLIDE #11

CANCER INDEX / TUMOR INDEX at 450 days

CRUDE WAX	AROMATIC EXTRACT
8/19	24/38
7/7	23/35
4/4	17/43
0/7	14/34
0/4	9/13
0/4	8/30
4/4	4/30
4/4	4/19

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AMERICAN PETROLEUM INSTITUTE

SUBCOMMITTEE ON CARCINOGENICITY

Minutes of Meeting
March 25, 1950
Kettering Laboratory
College of Medicine
University of Cincinnati
Cincinnati, Ohio

Members Present	Associates Present
McIver Woody (Chairman)	L. C. Beard, Jr.
Marshall Clinton	L. C. Crockett
T. M. Frank	R. M. Landon
A. E. Hoag	H. P. Lankelma
J. P. Holt (Rep. by R. E. Eckardt)	K. G. Mackenzie
T. J. Kelly	R. M. Shepardson
J. W. Long	
M. N. Newquist	

Visitors

T. E. Allen	E. W. Adams
F. F. Boys	R. D. Bent
J. W. Crookshank	R. C. Cole
Kieffer Davis	T. E. DeVilliers
E. K. Linder	L. M. Henderson
B. B. Reeve	

Guests

Lewis J. Cralley - U. S. Public Health Service
Francis Heyroth - University of Cincinnati
A. W. Horton - University of Cincinnati
R. A. Kehoe - University of Cincinnati
John J. Phair - University of Cincinnati
D. V. Stroop - American Petroleum Institute
J. G. Townsend - U. S. Public Health Service
H. R. Warrick - The Texas Company

Members Absent	Associates Absent
L. E. Curtis	R. W. Faulk
W. R. Levis	H. G. M. Fischer
Chas. A. Swan	Allan E. Dooley

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THE KETTERING LABORATORY OF APPLIED PHYSIOLOGY

Dr. Robert A. Kehoe, Director, welcomed the members and guests and gave them an historical review of the origin and growth of the Kettering Laboratory.

He expressed appreciation for the contribution of capital funds made by the petroleum industry and described the facilities which had been made possible by those funds.

He mentioned the types of industrial problems which are studied at the laboratory and reviewed in detail those problems which are under investigation for the petroleum industry.

He emphasized the exceptional character of the API project on carcinogenicity because it constitutes an organized study of a problem prior to the occurrence of trouble. Usually the trouble occurs before any investigation is made.

PROGRESS REPORT

1. Dr. A. Wesley Horton presented and discussed his report of March 15th, a copy of which is attached.

2. Dr. John J. Phair discussed progress and plans being made on the epidemiological studies for the project. See attached copy of Dr. Phair's report.

3. For the information of those present, D. V. Stroop read draft of progress report which was in preparation for John R. Suman, Chairman of the Safety Committee of the Board of Directors, to present to the Board at its meeting to be held in Houston, Texas on April 3rd.

   A copy of the report as presented by Mr. Suman is attached.

GUESTS

Dr. Woody introduced Dr. J. G. Townsend, Chief, Division of Industrial Hygiene, Public Health Service, who reviewed the division's long experience with scrotal and other forms of cancer incidental to workers in wax-pressing operations.

He reminded the members that the Public Health Service is not empowered to control or regulate industrial operations; it can only suggest or recommend precautionary and remedial measures to improve industrial hygiene conditions.

He called attention to the U. S. Public Health laboratory in Cincinnati and tendered the services of a liaison officer to work with Dr. Kehoe and to correlate plans so as to avoid duplication of work with that now being conducted for the Bureau of Mines on shale oil.

He expressed his appreciation of the opportunity to attend the meeting and to obtain first-hand information on the work being done by the industry at Kettering Laboratory.

Dr. Townsend introduced Dr. Cralley, who spoke briefly about his interest in the project.

TOUR OF LABORATORIES

Following a splendid luncheon served in the University of Cincinnati dining room, Drs. Kehoe and Heyroth conducted the members and guests on extended tours of inspection of the Kettering Laboratories.

EXECUTIVE SESSION

The members held a short executive session to discuss matters of business relating to the administration of the carcinogenicity project.

D. V. Stroop
Acting Secretary

Approved:

McIver Woody, M.D.
Chairman

4-18-50

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Report to Subcommittee on Carcinogenicity
of the
API Medical Advisory Committee
on

PROJECT ON CARCINOGENICITY AT THE
UNIVERSITY OF CINCINNATI

Operating data on the various cracking and lube refining processes have been received from over 90 per cent of the cooperating oil companies. Collection of the samples listed in Table 1 is under way, the materials being held temporarily in storage at the refineries until requested by the Kettering Laboratory for animal testing. Corresponding to each of the product samples listed, a sample of the feed stock to the particular unit is being collected at the same time. Thus, if any one of the products is found to have unusual carcinogenic properties, it will be possible to go back and determine the potency of the feed stream for a direct comparison.

Up to the present time, spectral analysis has continued to prove a reliable tool for the prediction of the carcinogenic potency of the various petroleum products to which it has been applied. Accordingly, it has been requested that this procedure be applied to each of the product samples listed in Table 1 by the company collecting it.

With all of the analytical and spectral absorption properties of the samples as well as the operating data on the units producing them before us, it will be possible to select the materials for animal testing in such a way that complete coverage of the various processes can be given and, at the same time, the validity of the spectral method of analysis for carcinogen concentration can be determined rigorously. The latter is a most important point since without a reliable analytical tool it might be necessary to keep a large scale animal testing program going continuously for several years.

This tentative sample list for the period, July 1950 to July 1951, is being submitted at this time for discussion and comments by the Members and Associates of the Medical Advisory Committee. We shall welcome any suggestions as to its organization. The complete list of the samples which are under study at the present time will be included in our April report which will be circulated in advance of the Chicago meeting. Doctor J. J. Phair will outline at that meeting the status of his epidemiological study.

A. Wesley Horton

AWH:fe
March 15, 1950

TABLE 1

UNIT	PRODUCTS							
	Heavy Gas Oils	Tars	Synthetic Bottoms	Slurry (Decanted Oil)	Coke	Slack Wax	Press Oil	Solvent Extracts
Gas Oil Cracking	5	23						
Viscosity Breaking	3	8						
Naphtha Reforming		4						
Coking	4				4			
Polyforming	1	4						
Houdry	5		8					
TCC	6		17					
FCC	12			10				
Cycloversion	2							
Hydroformer		2						
Wax Pressing						4	2	
Furfural Extraction								5
Phenol Extraction								15
Duosol Extraction								3
Nitrobenzene Extraction								1

TOTAL PRODUCT SAMPLES 148

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THE PROJECT ON CARCINOGENICITY
PROPOSED EPIDEMIOLOGICAL STUDIES

Objectives

Possible Approaches

Implementation

Preliminary Outline

for

The Subcommittee on Carcinogenicity

of the

API Medical Advisory Committee

March 25, 1950

OBJECTIVES

I. To determine as accurately as possible, the prevalence and incidence rates of retrograde, hypertrophic, and/or neoplastic responses in man following various degrees of exposure during production, processing, transportation and consumption to:-

   A. petroleum products obtained by catalytic cracking processes.

   B. petroleum products obtained by thermal cracking processes.

   C. products encountered in wax extraction.

   D. special chemical products.

   E. various crude oils.

II. To compare, insofar as possible, the prevalence and incidence rates found with similar rates of:-

   A. groups of workers in the petroleum industry not directly in contact with petroleum or its products.

   B. groups not employed in the petroleum industry, such as:-

      1. the general population

         a. of the nation.

         b. of the same geographic areas.

      2. the employees of other industries

         a. of the nation.

         b. of the same geographic areas.

III. To ascertain and evaluate, insofar as possible, the relative values of control procedures that are:-

A. accepted and employed at the present time by essentially the entire industry.

B. recommended but not adopted or employed except by a few companies.

C. additional measures which may become important during the course of this investigation.

IV. To recommend for consideration of all interested parties, employing the results of the laboratory and epidemiological studies, standardized safety and control procedures provided that:-

A. unusual incidence or prevalence rates are found justifying the control procedures.

B. the measures increase the safety and efficiency of the operation even though the rates might not indicate a significant hazard.

POSSIBLE APPROACHES

I. Historical

Under this approach, the cooperating companies will forward to the University of Cincinnati all available clinical and employment records of proven or suspected cases of neoplastic disease which have been reported among their employees during the past insofar as records are available.

II. Current Registry

A. Clinical and Employment Record Study

A central registry will be established by the University of Cincinnati group to receive reports of neoplastic disease as they are discovered by and/or reported currently to the various Medical Departments. With this plan, the various cooperating companies would submit a fairly complete clinical report and an adequate employment record using standardized record forms. These records can be expected to be somewhat more reliable than those forwarded under the Historical Approach, since they would be completed immediately upon the report of a case.

B. Central Pathology Service

As an adjunct to the central registry, it would seem desirable to plan for the establishment of a central pathology service so that a uniform tissue diagnosis would be available both for the study purposes and to stimulate the interest and cooperation of the various Medical Departments.

III. Employee Health Record Study

In this investigation the epidemiological team of the University of Cincinnati would attempt a review of the employee health benefit records,not only of the various companies of the petroleum industry but certain other cooperating industries, to establish, insofar as possible, comparable incidence rates for all diseases. This approach, with due regard for the many variables, should develop certain useful intra- and extra-mural comparisons.

IV. Dermatological Field Study

This plan envisions field studies among various groups of workers employed not only in the petroleum industry but also in other industries with the objective of establishing comparable incidence rates for retrograde or hyperkeratotic lesions on the exposed skin surfaces. The groups to be surveyed by a trained team from the University of Cincinnati should be selected by an authorized committee familiar with all the possible variables and capable of securing adequate cooperation by all interested groups. These rates, if some degree of correlation is shown, could be used to determine susceptibility of individuals or groups, to estimate the degree of hazard in various situations and to evaluate control proccdures that may be proposed.

V. Slack Wax Study

An investigation by one of the interested members of this group has pointed out an unusual hazard in their slack wax process. In view of this finding, it would be desirable for the survey group of the University of Cincinnati, working either independently or with some other company and/or companies, to repeat this investigation.

IMPLEMENTATION

I. Historical Approach

This approach was approved in principle at the November, 1949 meeting of the Medical Advisory Committee following the report of the Subcommittee. Actual work was held up until the various Medical Directors and Technical Advisors could be contacted individually for their suggestions regarding the clinical and employment records to be employed. It was necessary also to determine legal right of the various Medical Departments to release clinical records of their employees to an independent agency.

These questions have been fully clarified, and the new record forms embodying the various suggestions are being drafted. The proposed handling of the individual records so that the Medical Departments will not incur a liability because of their release to an independent agency with the standard records will be included in the formal report to be made at the April meeting in Chicago.

II. Current Registry

A. Clinical and Employment Record Study

Since the records and questions involved under this plan are very similar to those found with the Historical Approach, this effort has likewise awaited completion of the various interviews, although the concept was approved in principle at the November meeting. It is hoped that this work can begin early this summer.

II. Current Registry (Cont.)

B. Central Pathology Service

This is a new venture and one that is favored by many of the Medical Directors. Before it can be placed into operation, however, it will be necessary to determine if all believe that it is desirable and an acceptable method of financing.

III. Employee Health Record Study

This plan has been discussed only with a few of the Medical Directors. Before definitive action can be taken, this approach should be discussed thoroughly by the Medical Advisory Committee, since a great deal of effort will be required both from the various companies as well as the University of Cincinnati to bring it to a successful termination.

IV. Dermatological Field Survey

This, too, is a concept which has not been completely discussed and must be explored thoroughly by all interested parties. Financing and staffing would be problems, but this approach could be tested thoroughly within a very short time. If proven valid, it should give answers to the proposed objectives much more quickly and easily than any other method.

V. Slack Wax Study

It is apparent now that the probable implementation of this approach will require the cooperation of one or two companies in the industry. If the Medical Advisory Committee approves and interested companies can be found, this investigation could get under way very shortly without too much trouble.