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AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

March 22, 1948

DEPARTMENT OF SAFETY

AIR MAIL

CONFIDENTIAL

To Members and Associates
of Subcommittee on Carcinogenicity

Gentlemen:

Doctor McIver Woody, Chairman, requests me to send you the enclosed copy of his confidential report which submits a resolution designed to activate the recommendations adopted by the Medical Advisory Committee at its meeting held in Chicago on November 13, 1948.

Members and associates who have attended meetings of the subcommittee, held recently in New York, are requesting prompt action in the matter; therefore, it is hoped that the resolution may receive the unanimous support of the subcommittee, be adopted by the Medical Advisory Committee, and be transmitted through the Safety Committee of the Board of Directors to the Executive Committee of the Board of Directors for action at the meeting scheduled to be held on April 15, 1948, at Washington, D.C.

Very truly yours,

D. V. Stroop

D. V. Stroop

DVS:d

Enc.

mc: For Information of Members
and Associates of Medical Advisory Committee.
For Information of Members
of Safety Committee of Board of Directors.

C O N F I D E N T I A L

REPORT OF CHAIRMAN
OF
SUBCOMMITTEE ON CARCINOGENICITY
TO
API MEDICAL ADVISORY COMMITTEE
April 2, 1948

.....

- I On behalf of the Subcommittee on Carcinogenicity, I recommend to Medical Advisory Committee for transmittal to the Safety Committee of the Board of Directors and for adoption by the Executive Committee of the Board of Directors a resolution authorizing the establishment of a comprehensive research project on cancer-causing hydrocarbons as follows:

"RESOLUTION

"WHEREAS, in recent months there has been widespread publication of general statements to the effect 'that men working around gasoline, coal tar, lubricating oils, and certain dyes are exposed to cancer-causing hydrocarbons'; and,

"WHEREAS, such general statements appear to be without foundation but there are correlated results of experimental research work which indicate the presence of cancer-causing hydrocarbons in some heavy catalytic cycle oils; and,

"WHEREAS, the situation is such that the industry is in need of authoritative information on all phases of the subject and that need may best be met through the establishment of an industry-wide research project; NOW, THEREFORE BE IT

"RESOLVED BY THE EXECUTIVE COMMITTEE OF THE BOARD OF DIRECTORS THAT:

- "1. The Institute is authorized to establish a comprehensive research project for the development of fundamental facts, analytical techniques and related information pertaining to cancer-causing hydrocarbons which may occur or be produced in petroleum or petroleum products.
- "2. The Institute is authorized to enter into an agreement with the Kettering Institute of Applied Physiology (University of Cincinnati) to provide necessary facilities and services and conduct the work under a program to be established on a continuing basis by the Medical Advisory Committee subject to approval by the Safety Committee of the Board of Directors.
- "3. The Safety Committee is authorized to solicit contributions to a special research fund, outside of the API Maintenance Fund, in the amount of \$110,000 to meet the costs for the first year which will include \$50,000 for non-recurring capital expenditures for construction of extraordinary experimental facilities at the laboratory.
- "4. Responsibility for the continuation of the program of research is delegated to the Safety Committee of the Board of Directors which is hereby authorized to approve and underwrite future annual budgets and to solicit contributions to the special research fund as may be necessary to meet approved budgets."

- II In support of the resolution, I append a confidential subcommittee memorandum pertaining to the need for this research project.

McIver Woody, M.D.
CHAIRMAN

API 04734

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

March 24, 1948

DEPARTMENT OF SAFETY

AIR MAIL

CONFIDENTIAL

To Members and Associates
of Subcommittee on Carcinogenicity

Gentlemen:

You are requested to substitute the
enclosed CONFIDENTIAL MEMORANDUM (corrected March 24, 1948)
for the one which was attached to our letter of March 22.

The uncorrected copy should be
destroyed.

Very truly yours,



D. V. Stroop

DVS:d

Enc.

cc: For Information of Members
and Associates of Medical Advisory Committee.
For Information of Members
of Safety Committee of Board of Directors.

C O N F I D E N T I A L

APPENDIX

TO

REPORT OF CHAIRMAN OF SUBCOMMITTEE ON CARCINOGENICITY

MEMORANDUM -- CORRECTED MARCH 24, 1948

RE: REASONS FOR CARRYING OUT RESEARCH AND EXPERIMENTAL WORK ON HEAVY CATALYTIC CYCLE GAS OILS AND RELATED OILS.

It is well recognized that certain coal tars cause the development of skin cancer in man. In numerous foreign countries and in several states in this country this is recognized as a compensable disease.

During the past fifty years there have been more than 1,500 cases of skin cancer caused by exposure to shale oils in England. Laws have been passed requiring all such cases to be reported to the government in England. In contrast, few cases of skin cancer in the United States have been reported to have been caused by petroleum or petroleum products. Actually, about fifty cases of skin cancer caused by exposure to petroleum hydrocarbons during the processing of paraffin wax and a few cases of skin cancer in oil field workers have been reported in the United States. There are more than thirteen states that have laws in effect at the present time making cancer caused by petroleum products a compensable disease.

During the last four or five years the catalytic cracking process has been put into use in the petroleum industry. As a result of catalytic cracking treatment of oil, large quantities of high-boiling fractions of oil are produced. This high-boiling material has been shown to cause cancer in experimental animals. Animal experimental studies have been carried out in three well-known hospitals and universities on three different samples of this material from three different petroleum companies. All three samples were shown to produce tumors when applied to the skin of experimental animals in up to 100 per cent of the animals. These tumors became malignant in most cases. Only a very small amount of the material is necessary to produce cancer in an experimental animal such as the mouse; for example, 15 milligrams applied to the skin of a mouse once a week for twenty-six weeks produced cancer.

Individuals within and outside the petroleum industry, including doctors and chemists in the industry who have studied the problem, are reasonably certain that the chemical compound 3, 4-benzopyrene and related compounds present in coal tar and known to cause cancer are also present in the high-boiling oil fractions from the catalytic cracking operations. It is therefore felt that this oil is capable of causing cancer in man, although no cases in man have been reported to date. It is felt that one of the reasons for this is that it generally takes ten or more years of exposure to a carcinogenic material for a cancer to develop in man, and since this oil has only been in production for about four years, the period of exposure to this material has been short.

Field studies in the petroleum industry show that several thousand employees have daily or frequent contact with this material or blends of this material; while it is estimated that tens of thousands of customers are potentially exposed to blends of this material.

The above evidence indicates that the petroleum industry is faced with a serious potential cancer problem. There are many unanswered questions concerning the nature of this hazard and how it might be prevented or controlled. These questions can only be answered by carrying out a program of medical research along the lines which the Medical Advisory Committee is recommending.

In case more detailed information is desired, it can be arranged for a member of the Medical Advisory Committee to discuss this question with members of the Safety Committee or Executive Committee of the Board of Directors.

SAFETY COMMITTEE
OF THE
BOARD OF DIRECTORS

AMERICAN PETROLEUM INSTITUTE

(FOR 1948)

John R. Suman (Chairman) Standard Oil Co. (New Jersey), 30 Rockefeller Plaza,
New York 20, N.Y.

K. S. Adams Phillips Petroleum Co., Bartlesville, Okla.

R. B. Anderson Waggoner Estate, Vernon, Texas.

Paul G. Blazer Ashland Oil & Refining Co., Ashland, Ky.

H. S. M. Burns Shell Oil Co., Inc., 50 West 50th St., New York 20,
N.Y.

R. G. Follis Standard Oil Company of Calif., 225 Bush St.,
San Francisco 20, Calif.

P. N. Fortin Yale Refining Co., Billings, Mont.

Jake L. Hamon Cox & Hamon, Box 627, Dallas 1, Texas.
(Ex-Officio - Vice President for Production)

E. J. Henry The Atlantic Refining Co., 260 So. Broad St.,
Philadelphia 1, Pa.

B. Brewster Jennings Socony-Vacuum Oil Co., Inc., 26 Broadway, New York 4,
N.Y.

W. Alton Jones Cities Service Co., 60 Wall St., New York 5, N.Y.
(Ex-Officio - Vice President for Transportation)

B. L. Majewski Deep Rock Oil Corp., P. O. Box 725, Chicago 90,
Ill.
(Ex-Officio - Vice President for Marketing)

R. Ogarrio The Texas Co., 135 East 42nd St., New York 17, N.Y.

W. L. Stewart, Jr. Union Oil Company of Calif., 617 West Seventh St.,
Los Angeles 14, Calif.

W. G. Violette Standard Oil Co. (Kentucky), Louisville, Ky.

1-15-48
Amended 3-22-48

C O N F I D E N T I A L

REPORT OF CHAIRMAN
OF
SUBCOMMITTEE ON CARCINOGENICITY
TO
API MEDICAL ADVISORY COMMITTEE

April 2, 1948

.....

I On behalf of the Subcommittee on Carcinogenicity, I recommend to the Medical Advisory Committee for transmittal to the Safety Committee of the Board of Directors and for adoption by the Executive Committee of the Board of Directors a resolution authorizing the establishment of a comprehensive research project on cancer-causing hydrocarbons as follows:

"RESOLUTION

"Whereas, in recent months there has been widespread publication of general statements to the effect 'that men working around gasoline, coal tar, lubricating oils, and certain dyes are exposed to cancer-causing hydrocarbons'; and,

"Whereas, such general statements appear to be without foundation but there are correlated results of experimental research work which indicate the presence of cancer-causing hydrocarbons in some heavy catalytic cycle oils; and,

"Whereas, the situation is such that the industry is in need of authoritative information on all phases of the subject and that need may best be met through the establishment of an industry-

wide research project; NOW, THEREFORE BE IT

"RESOLVED BY THE EXECUTIVE COMMITTEE OF THE BOARD OF DIRECTORS
THAT:

- "1. The Institute is authorized to establish a comprehensive research project for the development of fundamental facts, analytical techniques and related information pertaining to cancer-causing hydrocarbons which may occur or be produced in petroleum or petroleum products.
- "2. The Institute is authorized to enter into an agreement with the Kettering Institute of Applied Physiology (University of Cincinnati) to provide necessary facilities and services and conduct the work under a program to be established on a continuing basis by the Medical Advisory Committee subject to approval by the Safety Committee of the Board of Directors.
- "3. The Safety Committee is authorized to solicit contributions to a special research fund, outside of the API Maintenance Fund, in the amount of \$110,000 to meet the costs for the first year which will include \$50,000 for non-recurring capital expenditures for construction of extraordinary experimental facilities at the laboratory.
- "4. Responsibility for the continuation of the program of research is delegated to the Safety Committee of the Board of Directors which is hereby authorized to approve and underwrite future annual budgets and to solicit contributions to the special research fund as may be necessary to meet approved budgets."

II In support of the resolution, I append a confidential subcommittee memorandum pertaining to the need for this research project.

CONFIDENTIAL

RD
See 7 pages
Appendix 2
and 3 on page 4

APPENDIX

TO

REPORT OF CHAIRMAN OF SUBCOMMITTEE ON CARCINOGENICITY

MEMORANDUM

RE: REASONS FOR CARRYING OUT RESEARCH AND EXPERIMENTAL WORK ON HEAVY CATALYTIC CYCLE GAS OILS AND RELATED OILS.

It is well recognized that certain coal tars cause the development of skin cancer in man. In numerous foreign countries and in several states in this country this is recognized as a compensable disease.

During the past fifty years there have been more than 5,000 cases of skin cancer caused by exposure to shale oils in England. Laws have been passed requiring all such cases to be reported to the government in England. In contrast, few cases of skin cancer in the United States have been reported to have been caused by petroleum or petroleum products. Actually, about fifty cases of skin cancer caused by exposure to petroleum hydrocarbons during the processing of paraffin wax and a few cases of skin cancer in oil field workers have been reported in the United States. There are more than thirteen states that have laws in effect at the present time making cancer caused by petroleum products a compensable disease.

During the last four or five years the catalytic cracking process has been put into use in the petroleum industry. As a result of catalytic cracking treatment of oil, large quantities of high-boiling fractions of oil are produced. This high-boiling material has been shown to cause cancer in experimental animals. Animal experimental studies have been carried out in three well-known hospitals and universities on three different samples of this material from three different petroleum companies. All three samples were shown to produce tumors when applied to the skin of experimental animals in up to 100 per cent of the animals. These tumors became malignant in most cases. Only a very small amount of the material is necessary to produce cancer in an experimental animal such as the mouse; for example, 15 milligrams applied to the skin of a mouse once a week for twenty-six weeks produced cancer.

Individuals within and outside the petroleum industry, including doctors and chemists in the industry who have studied the problem, are reasonably certain that the chemical compound 3, 4--benzpyrene and related compounds present in coal tar and known to cause cancer are also present in the high-boiling oil fractions from the catalytic cracking operations. It is therefore felt that this oil is capable of causing cancer in man, although no cases in man have been reported to date. It is felt that one of the reasons for this is that it generally takes ten or more years of exposure to a carcinogenic material for a cancer to develop in man, and, since this oil has only been in production for about four years, the period of exposure to this material has been short.

Field studies in the petroleum industry show that several thousand employees have daily or frequent contact with this material or blends of this material; while it is estimated that tens of thousands of customers are potentially exposed to blends of this material.

The above evidence indicates that the petroleum industry is faced with a serious potential cancer problem. There are many unanswered questions concerning the nature of this hazard and how it might be prevented or controlled. These questions can only be answered by carrying out a program of medical research along the lines which the Medical Advisory Committee is recommending.

In case more detailed information is desired, it can be arranged for a member of the Medical Advisory Committee to discuss this question with members of the Safety Committee or Executive Committee of the Board of Directors.

REPORT TO THE MEDICAL ADVISORY COMMITTEE
BY THE SUBCOMMITTEE ON CARCINOGENICITY
Dr. McIver Woody - Chairman

1. During the past six months, many articles have appeared in magazines and newspapers denouncing petroleum oils as a frequent cause of cancer. There is some basis for the accusation. Our own animal experiments ~~just completed~~ at the University of Cincinnati seem to bear this out; for, of the 8 samples of heavy gas-oil submitted, 2 produced cancer of the skin in mice, and one sample proved to be highly carcinogenic.
2. The present situation is somewhat similar to that which confronted the petroleum industry 23 years ago, when tetraethyl lead was discovered to be toxic. Fortunately, only one manufacturer was directly involved, and the Public Health Service promptly took the position that any dangerous substance could be handled safely once the hazard was properly evaluated and suitable preventive measures instituted. The present hazard is much more complicated and affects every refiner and nearly every marketer of petroleum products. In the present state of our knowledge, all gas-oils must be regarded as potential causes of cancer, and most heavy blends are suspect. Once again, the solution lies in the evaluation of the hazard, followed by the application of reasonable safeguards.

3. Now that ^{our} ~~the~~ preliminary animal experiments have been completed, it is essential that adequate provision be made for a well-rounded and all-inclusive program of research at a central point, where the work ~~which has~~ already ~~been~~ done by several large companies can be correlated. It would also be desirable to provide facilities for the routine testing of oil samples at the expense of the company which submits them.
4. Such a program ^{will} ~~would~~ be ~~fairly~~ expensive, not only because the field work must cover the entire industry from driller to consumer, but also because the laboratory work must approach the limits of our present knowledge of cancer and petroleum chemistry. Nevertheless, the program must not be left for government agencies to carry through, as they surely will, if we hesitate. Rather, the solution of a problem which is so pressing and which concerns us so closely should be sought by the industry itself especially when the industry ~~which~~ has been so successful in organizing and supporting research in applied science.
5. The proposed program has the following objectives:

Medical

- a. To obtain accurate information ^{on} ~~of~~ the incidence of cancer, particularly of the skin, among workers in the petroleum industry, and to correlate the data with the frequency of exposure to various petroleum products.

- b. To test samples of products which may be carcinogenic; to study any changes they may produce in the cells of the skin and correlate these with the earliest signs of malignancy.

Chemical

- c. To devise physical and chemical tests which will show whether a given oil contains carcenogens.
 - d. To develop refining processes which will destroy any carcenogens which may be present.
 - e. To discover ways to remove carcenogens from ~~the~~ finished products or neutralize their action by the addition of inhibitors.
7. Such a program will call for the best sort of cooperative research based on a broad knowledge of statistics, ~~of~~ cancer, and ~~of~~ chemistry. At the moment, it seems doubtful whether any one investigator can be found who has all these qualifications. It would seem more likely that two full-time men will be needed; one a physician who is interested in cancer and has had some experience in public health work, the other a chemical engineer who has had experience in the petroleum industry or perhaps a biochemist.
8. It is recommended that a center of investigation and research on cancer in the petroleum industry be established at the University of Cincinnati under the guidance of Professor Robert A. Kehoe, with two full-time investigators together with the necessary secretarial and technical assistants. One investigator would be chosen on the basis of his knowledge of cancer and epidemiology; the other would be chosen on the basis of his knowledge^{of} chemistry and refining processes. The activities of both would be

coordinated by Dr. Kehoe as Director of the Kettering Laboratory. It is estimated that such a program would require an annual appropriation of \$60,000.

9. Also, it is recommended that, in addition to the above, contributions be sought from the larger petroleum companies to construct an animal house on the roof of the laboratory wing now being erected. With this additional space, we could count on using some 25% of the completed building which would be sufficient for our purposes (see memorandum B). On the basis of present building costs, this capital fund need not be more than \$50,000.

~~CONFIDENTIAL~~

APPENDIX
TO
REPORT OF Chairman
April 2, 1958
MEMORANDUM

Submitted on 11/1/58

~~Personal and Confidential~~

To: Dr. Melver Woody:

RESEARCH AND

Re: Reasons for carrying out experimental work on Heavy Catalytic Cycle Gas Oils and related oils.

It is well recognized that certain coal tars cause the development of skin cancer in man. In numerous foreign countries and in several states in this country this is recognized as a compensable disease.

During the past fifty years there have been ^{MORE THAN} ~~over~~ 5,000 cases of skin cancer caused by exposure to shale oils in England. Laws have been passed ~~that~~ ^{and} that all such cases be reported to the government in England. In contrast, few cases of skin cancer in the United States have been reported to have been caused by petroleum or petroleum products. ^{15,000 / 1,500} Actually, about fifty cases of skin cancer caused by exposure to petroleum ~~products~~ ^{products} during the processing of paraffin wax and a few cases of skin cancer in oil field workers have been reported in the United States. There are more than thirteen states that have laws in effect at the present time making cancer caused by petroleum products a compensable disease.

During the last ~~four~~ ^{four} or five years the catalytic cracking process has been put into use in the petroleum industry. As a result of catalytic cracking treatment of oil, large quantities of high-boiling fractions of oil are produced. This high-boiling material has been shown to cause cancer in experimental animals. Animal experimental studies have been carried out in three well known hospitals and universities on three different samples of this material from three different petroleum companies. All three samples were shown to produce tumors when applied to the skin of experimental animals in up to 100% of the animals. These tumors became malignant in most cases. Only a very small amount of the material is necessary to produce cancer in an experimental animal such as the mouse; for example, 15 milligrams applied to the skin of a mouse once a week for twenty ~~six~~ weeks produced cancer.

Individuals within and outside the petroleum industry, including doctors and chemists in the industry who have studied the problem, are reasonably certain that the chemical compound 3, 4-benzpyrene and related compounds present in coal tar and known to cause cancer are also present in the high-boiling oil fractions from the catalytic cracking operations. It is therefore felt that this oil is capable of causing cancer in man, although no cases in man have been reported to date. It is felt that one of the reasons for this is that it generally takes ten or more years of exposure

to a carcinogenic material for a cancer to develop in man, and, since this oil has only been in production for about four years, the period of exposure to this material has been short.

Field studies in the petroleum industry show that several thousand employees have daily or frequent contact with this material or blends of this material; while it is estimated that tens of thousands of customers are potentially exposed to blends of this material.

The above evidence indicates that the petroleum industry is faced with a serious potential cancer problem. There are many unanswered questions concerning the nature of this hazard and how it might be prevented or controlled. These questions can only be answered by carrying out a program of medical research along the lines which the Medical Advisory Committee is recommending.

In case more detailed information is desired, it can be arranged for a member of the Medical Advisory Committee to discuss this question with members of the A. P. I. to whom the above information goes.

J. P. Holt/es
J. P. Holt, M. D.

JPY:mt

[Dictated but not read.]

MEMORANDUM

March 31, 1948

SUBJECT: RECEIPTS AND DISBURSEMENTS - API MEDICAL RESEARCH FUND.

Contributions to Fund

1945 Solicitation	\$ 28,900.00	
1947 Solicitation	<u>27,800.00</u>	
Total		\$ 56,700.00

Disbursements from Fund

Harvard University

Toxicological Reviews	\$ 27,000.00 ✓	
Cutting Oil Dermatitis	<u>2,500.00</u>	
		29,500.00

University of Cincinnati

Carcinogenicity	6,000.00	
Fluorine Study	<u>2,500.00</u>	
		8,500.00

Miscellaneous

Book for Committee Use	57.77	57.77
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Total Disbursements		<u>\$ 38,057.77</u>
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BALANCE ON DEPOSIT		\$ 18,642.23
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AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

April , 1948

Mr. Andrew J. Brewer, Secretary Treasurer
Astma Oil Company, Inc.
1202 South Third Street
Louisville 3, Kentucky

Dear Mr. Brewer:

For your consideration I enclose confidential copy of resolution approved and adopted by the Executive Committee of the Board of Directors at meeting held in Washington on April 15th. The resolution authorizes the establishment of research project at Batturing Laboratory to develop information pertaining to cancer-causing compounds which may occur or be produced in petroleum. A confidential memorandum in support of the resolution is also enclosed.

You will note that the resolution provides for a special research fund to be raised by voluntary contributions outside of the API Maintenance Fund.

You are invited to contribute to this fund ratably in proportion to your contribution to the Maintenance Fund. On this basis your share of the \$110,000 will be

Please send your contribution or your pledge to Lesley Walker, American Petroleum Institute, 50 West 50th Street, New York 20, New York, as promptly as possible.

Very truly yours,

John E. Suman, Chairman
Safety Committee of Board of Directors

Enclosures

April 20, 1948

Mr. John R. Suman, Chairman
Safety Committee of Board of Directors
c/o Standard Oil Company (New Jersey)
30 Rockefeller Plaza
New York 20, N.Y.

Dear Mr. Suman:

For your comments and approval we enclose suggested draft of letter to be issued over your signature pursuant to action taken by the Executive Committee at meeting held April 15.

Lacey Walker will handle all of the details of issuance if, as, and when you approve the draft.

Very truly yours,

WVS:d
Enc.

April , 1948

Dear Mr.

For your consideration I enclose confidential copy of resolution approved and adopted by the Executive Committee of the Board of Directors at meeting held in Washington on April 15th. The resolution authorizes the establishment of research project at Ketting Laboratory to develop information pertaining to cancer-causing compounds which may occur or be produced in petroleum. A confidential memorandum in support of the resolution is also enclosed.

You will note that the resolution provides for a special research fund to be raised by voluntary contributions outside of the API Maintenance Fund.

You are invited to contribute to this fund ratably in proportion to your contribution to the Maintenance Fund. On this basis your share of the \$110,000 will be _____.

Please send your contribution or your pledge to Lacey Walker, American Petroleum Institute, 50 West 50th Street, New York 20, New York, as promptly as possible.

Very truly yours,

John H. Suman, Chairman
Safety Committee of Board of Directors

Enc.

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

~~April 5, 1948~~

CONFIDENTIAL

~~To the Chairman and Members
Safety Committee of the Board of Directors~~

Gentlemen:

~~The Institute's Medical Advisory Committee, at a meeting held in Boston on April 2, voted to recommend for transmittal to the Safety Committee and for adoption by the Executive Committee of the Board of Directors a resolution authorizing the establishment of a comprehensive research project on cancer-causing compounds as follows:~~

RESOLUTION

(APPROVED AND ADOPTED BY EXECUTIVE COMMITTEE AT MEETING HELD APRIL 15 1948)
WHEREAS, in recent months there has been widespread publication of general statements to the effect that men working around gasoline, tars, and lubricating oils are exposed to cancer-causing compounds; and

WHEREAS, such general statements appear to be without foundation but there are correlated results of experimental research work which indicate the presence of cancer-causing compounds in some fractions derived from the catalytic processing of petroleum; and there are references in the medical literature to cases of cancer caused by certain petroleum crudes and fractions; and

WHEREAS, the situation is such that the industry is in need of authoritative information on all phases of the subject and that need may best be met through the establishment of an industry-wide research project; NOW, THEREFORE BE IT

RESOLVED BY THE EXECUTIVE COMMITTEE OF THE BOARD OF DIRECTORS THAT:

1. The Institute is authorized 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.
2. The Institute is authorized to enter into an agreement with the Kettering Laboratory of Applied Physiology (College of Medicine, University of Cincinnati) to provide or arrange for necessary facilities and services and conduct the work under a program to be established on a continuing basis by the Medical Advisory Committee subject to approval by the Safety Committee of the Board of Directors.

API 04752

3. The Safety Committee is authorized to solicit contributions to a special research fund, outside of the API Maintenance Fund, in the amount of \$110,000 to meet the costs for the first year which will include \$50,000 for non-recurring capital expenditures for construction of extraordinary experimental facilities at the laboratory.
4. Responsibility for the continuation of the program of research is delegated to the Safety Committee of the Board of Directors which is hereby authorized to approve and underwrite future annual budgets and to solicit contributions to the special research fund as may be necessary to meet approved budgets.

~~In support of the resolution there is appended a confidential memorandum from the Medical Advisory Committee pertaining to the need for this research project.~~

Very truly yours,

~~W. F. Stacey~~
~~W. F. Stacey~~

~~DVS:ed~~
~~Enc.~~
~~cc: Members of Executive Committee~~
~~of the Board of Directors~~
~~Members and Associates~~
~~of Medical Advisory Committee~~

C O N F I D E N T I A .

~~April 2, 1948~~

MEMORANDUM

RE: THE NEED FOR THE PROPOSED RESEARCH PROJECT.

It is well recognized that certain coal tars cause the development of skin cancer in man. In numerous foreign countries and in several states in this country this is recognized as a compensable disease.

During the past fifty years there have been more than 1,500 cases of skin cancer caused by exposure to shale oils in England. Laws have been passed requiring all such cases to be reported to the government in England. In contrast, few cases of skin cancer in the United States have been reported to have been caused by petroleum or petroleum products. Actually, about fifty cases of skin cancer caused by exposure to petroleum hydrocarbons during the processing of paraffin wax and a few cases of skin cancer in oil field workers have been reported in the United States. There are more than thirteen states that have laws in effect at the present time making cancer caused by petroleum products a compensable disease.

During the last four or five years various catalytic processes, such as catalytic cracking, have been put into extensive use in the petroleum industry. In the catalytic treatment of oil, relatively large quantities of high-boiling fractions can be produced. This high-boiling material has been shown to cause cancer in experimental animals. Animal experimental studies have been carried out in three well-known hospitals and universities on three different samples of this material from three different petroleum companies. All three samples were shown to produce tumors when applied to the skin of experimental animals in up to 100 per cent of the animals. These tumors became malignant in most cases. Only a very small amount of the material is necessary to produce cancer in an experimental animal, such as the mouse; for example, 15 milligrams applied to the skin of a mouse once a week for twenty-six weeks produced cancer.

Individuals within and outside the petroleum industry, including doctors and chemists who have studied the problem, are reasonably certain that condensed ring compounds, such as 3, 4-benzpyrene and related compounds, known to cause cancer are present in the high-boiling oil fractions from the catalytic cracking operations. It is therefore felt that this oil is capable of causing cancer in man, although no cases in man have been reported to date. It is felt that one of the reasons for this is that it generally takes ten or more years of exposure to a carcinogenic material for a cancer to develop in man, and since this oil has only been in production for about four years, the period of exposure to this material has been short.

Field studies in the petroleum industry show that several thousand employees have daily or frequent contact with this material or blends of this material; while it is estimated that tens of thousands of customers are potentially exposed to blends of this material.

The above evidence indicates that the petroleum industry is faced with a serious potential cancer problem. There are many unanswered questions concerning the nature of this hazard and how it might be prevented or controlled. These questions can only be answered by carrying out a program of medical research along the lines which the Medical Advisory Committee is recommending.

In case more detailed information is desired, it can be arranged for a member of the Medical Advisory Committee to discuss this question with members of the Safety Committee or Executive Committee of the Board of Directors.

API 04754

UNION OIL COMPANY OF CALIFORNIA

Union Oil Building
Los Angeles 14, California

Reese H. Taylor
President

May 18, 1948

Mr. John R. Suman, Chairman
Safety Committee of Board of Directors
American Petroleum Institute
50 West 50th Street
New York 20, N.Y.

Dear John:

This is in answer to your letter of April 28 concerning the establishment of research project to develop information regarding the possible occurrence of cancer-causing compounds in certain petroleum crudes and/or fractions.

It is our feeling at the present time that API's interest in a research program to develop information concerning cancer-causing compounds which may occur in certain petroleum fractions appears to have been activated by fear of future personal damage suits from users of petroleum products and possible increases in industrial accident and health liabilities. In the light of the very limited information currently available to us on the subject, we consider the advisability of the API's embarking on such a program to be highly debatable.

In the confidential memorandum attached to your letter it is stated that certain petroleum fractions, when applied to the skin of a mouse once a week for twenty-six weeks, produced a cancer. It is further stated that it generally takes ten or more years of exposure to a carcinogenic material for a cancer to develop in man. It would seem to us rare that an individual would be exposed at regular and frequent intervals to some carcinogenic petroleum fraction for a period of years.

In our opinion the final results of the proposed program might be of academic interest, but would have little practical significance. Unless the Safety Committee can supply more cogent reasons for the need of the proposed program than were contained in the attachments forwarded with your letter, the Union Oil Company feels justified in declining participation at this time.

Kindest personal regards.

Yours most sincerely,

/s/ Reese

(C O P Y)

API 04755

RECEIVED 60
MAY 24 1948
JOHN R. SUMMERS

SENT TO
DVS 11
5/24/48

STANDARD OIL COMPANY

(INDIANA)

ROBERT E. WILSON,
CHAIRMAN OF THE BOARD

910 SOUTH MICHIGAN AVENUE

CHICAGO 80, ILL.

May 21, 1948

Mr. Lacey Walker, Secretary
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Sirs:

Attached hereto is our check in the amount of \$10,000 to cover our proportion of the Institute's project of filtering laboratory to develop information pertaining to cancer-causing compounds which may occur or be produced in petroleum.

1. ~~Enclosed for our contribution~~ was contained in Mr. John R. Summ's letter of April 28, 1948, in which he requested that our contribution be placed to ordinarily contribute to all of our sent direct to you.

2. On an average, 25 of our best companies to make their contributions every 10 years.

Attachment

cc - The Attachment is necessary to carry out an approved project, Lacey Walker consideration in making his allocation of companies.

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

Handwritten signature: David V. Strop

DAVID V. STROOP
ASSISTANT TO THE PRESIDENT

May 24, 1948

Mr. G. Stewart Brown
Standard Oil Company of California
225 Bush Street
San Francisco 20, California

Dear Mr. Brown:

Your letter of May 19 to Mr. Suman has been referred to me because the allocation of shares in the special cancer research project was set up by Lacey Walker, Assistant Treasurer, who is out of town this week.

Based upon our experience in the raising of special funds such as this, we find it necessary to increase the percentages to be contributed by fully integrated oil companies over and above the percentages paid by them to the maintenance fund because of several factors as follows:

1. The maintenance fund does not represent 100 per cent of the Institute's budget.
2. Supply companies contribute to the maintenance fund but not to special funds.
3. Many smaller or non-integrated oil companies contribute to the maintenance fund but do not ordinarily contribute to all special funds.
4. On an average, one or two major companies fail to make their contributions in full or in part.

.....

In cases where it is necessary to raise a stated total to carry out an approved project, Lacey Walker takes these factors into consideration in making his allocation of amounts to be paid by oil companies.

It is remarkable how closely the results bear out his estimates.

Very truly yours,

Handwritten signature: D. Strop

DVS:d

cc: Mr. John R. Suman
Mr. Lacey Walker

API 04757

STANDARD OIL COMPANY OF CALIFORNIA

**Standard Oil Building
San Francisco 20, California**

**Public Relations Department
G. Stewart Brown, Manager**

May 19, 1948

**Mr. John R. Suman, Chairman
Safety Committee of Board of Directors
American Petroleum Institute
50 West 50th Street
New York 20, New York**

Dear Mr. Suman:

Your letter of April 28th, seeking this company's contribution of \$8,000 to a fund of \$110,000 for a special cancer research project at Mettering Laboratory, has been thoroughly and sympathetically reviewed. We would like to inquire, however, before proceeding further, as to the basis for the amount allocated to us, which is 7.27% of the total. You explain that our contribution to the maintenance fund has been used for the basis of this proration. However, the percentage in that case is 5.77% and would represent, for the cancer project, \$6,347.

We will appreciate hearing from you and will then expedite in every way possible the final decision.

Very truly yours,

**/s/ W. J. Held
G. Stewart Brown**

WJH:ed

(C O P Y)

API 04758

UNIVERSITY OF CINCINNATI
CINCINNATI 19, OHIO

MAC

July 9, 1948

LETTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS: KETLAB. CINCINNATI
TELEPHONE: UNIVERSITY 2665

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

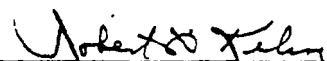
Dear Mr. Stroop:

I take pleasure in acknowledging receipt of your letter of July 6 with its enclosure of the check for \$65,000.00, payable to the University.

I am off tomorrow for a vacation trip and will not return to my desk until July 25. It so happens that Doctor Heyroth will also be away through the greater portion of the month of July. You will recognize from this that we do not expect to accomplish much during July, but we have taken a series of steps which we believe will result in our discovery of the proper personnel for the conduct of the anticipated work.

You will probably be pleased to know that very good progress is being made in the construction of the addition to the Laboratory. After many delays the work should progress now and we should be moving into some of this space late in September or early in October, unless we run into additional difficulty. I presume that you and your associates are aware of the extreme difficulties associated with construction work at this time. We can only do our best and hope for the best.

Sincerely yours,


Robert A. Kenoe, M. D.

FAK ef

C.C.: Dr. M. N. Newquist
Mr. Lacey Walker
Dr. McIver Woody

July 6, 1948

Dr. Robert A. Roboe
Kettering Laboratory of Applied Physiology
College of Medicine
University of Cincinnati
Cincinnati 19, Ohio

Dear Doctor Roboe:

Pursuant to the terms of our letter dated June 15, two approved copies of which you returned with your letter of June 29, we enclose Institute check in the amount of \$65,000 payable to the University of Cincinnati.

We do not anticipate a need for a third executed copy of the letter of June 15th.

Very truly yours,

DWS:d

Enclosure

cc: Dr. H. H. Bengtist
Mr. Lacey Walker
Dr. Elmer Woody

API 04760

UNIVERSITY OF CINCINNATI
CINCINNATI 19, OHIO

June 29, 1943

ENTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: UNIVERSITY 2885

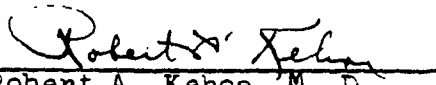
Mr. D. V. Stroop,
The American Petroleum Institute,
50 West 50th Street,
New York City 20.

Dear Mr. Stroop:

I am returning to you herewith two copies of the letter of June 15, 1943, extending the scope of our work for the American Petroleum Institute. This has been duly executed by the proper officials of the University. One copy has been retained by the Business Manager of the University, and another has gone into our files. If you should require a third signed copy for any reason, we should be glad to forward the executed copy after having made a typewritten copy for our own files.

With kindest personal regards,

Cordially yours,


Robert A. Kehoe, M. D.

RAK ef

Enc.

0

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

June 15, 1948

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work and to expand the scope of the investigation of the toxicity and mode of action of certain petroleum products according to the terms of the agreement dated January 8, 1946 and on the basis of the following budget for the period ending June 30, 1949:

- | | |
|---|---------------|
| 1. For non-recurring capital expenditures | \$ 40,000 |
| 2. For operating expenses | <u>50,000</u> |
| | \$ 90,000 |

Upon receipt of your approval of the continuation and expansion of the project with this budget we shall pay you the sum of \$65,000, the balance of \$25,000 to be paid on January 1, 1949.

It is understood that any balance remaining in the fund on June 30, 1949 will be returned to the American Petroleum Institute, and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By *W. Boyd*

President

By *W. R. Walker*

Secretary

Accepted and Approved

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By *Frank J. Winsmore*

Frank J. Winsmore, Chairman Board of Directors

By *N. R. Plutner*

Clerk

1

June 15, 1948

Dr. Robert A. Kahoe
Kettering Laboratory of Applied Physiology
College of Medicine
University of Cincinnati
Cincinnati 19, Ohio

Dear Doctor Kahoe:

In response to your letter of June 12 which was delivered here today, we enclose four copies of the continuation agreement which have been signed by the President and Secretary.

As stated in the agreement, we shall send you a check in the amount of \$65,000 promptly upon return of two copies which have been accepted and approved on behalf of the University of Cincinnati.

Very truly yours,

DVS:d

Enclosures

cc: Dr. M. H. Newquist
Mr. Lacey Walker
Dr. Melver Woody

June 15, 1948

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work and to expand the scope of the investigation of the toxicity and mode of action of certain petroleum products according to the terms of the agreement dated January 8, 1946 and on the basis of the following budget for the period ending June 30, 1949:

- | | |
|---|------------------|
| 1. For non-recurring capital expenditures | \$ 40,000 |
| 2. For operating expenses | 50,000 |
| | <u>\$ 90,000</u> |

Upon receipt of your approval of the continuation and expansion of the project with this budget we shall pay you the sum of \$65,000, the balance of \$25,000 to be paid on January 1, 1949.

It is understood that any balance remaining in the fund on June 30, 1949 will be returned to the American Petroleum Institute, and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By _____
President

By _____
Secretary

Accepted and Approved

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By _____
Chairman

By _____
Clerk

API 04764

WRP
WE HAVE RECEIVED
\$86,875. IN CONTRIBUTION
FOR THIS PARTICULAR JOB AND
HAVE UNOBLIGATED BALANCE OF
ABOUT \$18,000 IN OTHER MEDICAL
RESEARCH FUNDS -
PLEASE SIGN ALL FOUR COPIES
OF AGREEMENT
6-15/48 DV

UNIVERSITY OF CINCINNATI

CINCINNATI 19, OHIO

June 12, 1948

ENTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: UNIVERSITY 2665

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

Dear Mr. Stroop:

I have delayed my reply to your letter of May 24, until I should have some figures that enabled me to deal in a definitive manner with the questions raised. I am now able to reply intelligently.

pursuant to our conversations and correspondence, I had the necessary drawings made by our architect, and the additional facilities required in connection with the A.P.I. project have been put to the several contractors for bids. These bids have now been received, and I now know what the building structure will cost. We are going into the question of the additional equipment required for the conduct of the work, and on this I do not have precise figures at the moment. However, I have assembled all of the data that are available, and on the basis of the most generous estimates that can be made I am now safe in saying that no more than \$40,000.00 will be required for the capital expenditures. In fact, I believe that it will be somewhat under \$40,000.00, finally, but in order that we may be safe, the sum of \$40,000.00 should be made available. If there should be any residue of this sum, I can assure you that it will be expended in such a manner as to apply to the activities in which you and your associates are interested.

I cannot tell you at this time what our expenditures will be for the prosecution of the work during the fiscal year which ends June 30, 1949. We shall not be able to get our work started as of June 30 of this year, nor is it likely that we shall be able to obtain the required personnel by that time. Our efforts are being made, and on this phase of the matter we hope to be able to report real progress soon. However, because of the delay in obtaining suitable facilities for our work, and because of the potential delay in obtaining the personnel to carry on the experimental work, we shall not require the funds contemplated for a full year's work. It is entirely possible, and in fact I consider it likely, that we shall not be able to get the testing work under way before the end of September. Therefore, we shall not employ someone to do this work until we are ready to begin it, unless we find that it is necessary to take on a person promptly who would not be available to us if we were to delay. On the other hand, I wish to remind myself and you that certain of the members of the Medical group were keenly interested in our undertaking to develop the means of obtaining complete information of a clinical nature from the petroleum industry. You will remember that one of your group pointed out that he considered this to be the most important aspect of the problem, which, unless it were done, might invalidate or render useless much of the rest of the work. So far as I know we have not

Mr. D. V. Stroop - (3, - June 12, 1948

I trust this clarifies the entire situation from my viewpoint and I shall be pleased to hear from you at your early convenience.

Cordially yours,

Robert A. Kehoe
Robert A. Kehoe, M. D.

RAK ef

C.C.: Dr. M. N. Newquist
Dr. McIver Woody

May 24, 1948

Dr. Robert A. Kehoe
Lettering Laboratory of Applied Physiology
College of Medicine
University of Cincinnati
Cincinnati 19, Ohio

Dear Doctor Kehoe:

Many thanks for your recent longhand note about the funds to cover the enlarged research project.

For your consideration I enclose draft of letter which we propose to have sent to you to cover continuation of agreement dated January 8, 1946. If this is acceptable to you we shall have it signed and sent to you as soon as the sum of contributions received equals the amount of the budget of the period ending June 30, 1949.

It may be practicable to have the continuation letter signed more promptly if you believe it may be possible to indicate a somewhat smaller budget for the fiscal year. If the capital expenditures may be restricted to some figure less than \$50,000, it seems to me that we might safely assume that the operating budget for the first year may be less than the \$60,000 which was used as the basis of the program. In other words, if we could use the figures of \$40,000 and \$50,000 for capital and operating expenses for the period ending June 30, 1949 we could execute our letter as soon as \$90,000 is available. This might save considerable time because of the fact that we may not receive the remaining \$20,000 for several weeks or even months.

Please let me have your suggestions on the feasibility of showing a moderate reduction in expenditures for the first year.

Very truly yours,

DVS:d

Enc.

cc: Dr. M. H. Newquist
Dr. McIver Woody
Mr. Lacey Walker

from the desk of
R. ROBERT A. KENNEDY

Dear Mr. Stoughton:-

In reply to your letter of May 17th,
may I express my thanks for the information.
Since my secretary is on a much-needed
vacation, I write informally to cover
the issues and the other secretarial help
available to me, and to save time.

It is wholly unnecessary for
my viewpoint to execute a new agreement
it may be advisable, and yours, to issue
a letter, copy of which can go to our Board,
stating the case as to the extension of
the work. That should be as you wish.
The matter is of more direct importance. (over)

to it is that the funds intended specifically
for capital investment in space and equipment
be in my hands at the earliest possible
time, since I cannot make formal
commitment ^{(I have made an informal commitment. I shall} of expenditures along these
lines, under the law, until funds are
available. This is unfortunate but ~~the~~
nevertheless it is a fact. The Board
will take appropriate action to support me
at the proper time, if I have some official
or documentary evidence of funds
forthcoming for this specific purpose from
a responsible source, not otherwise they
will be involved in an illegal act in
authorizing and further building program. ^{immediately} ^{Robert}

DRAFT

Board of Directors
University of Cincinnati

Gentlemen:

This communication is authority to continue work and to expand the scope of the investigation of the toxicity and mode of action of certain petroleum products according to the terms of the agreement dated January 8, 1946 and on the basis of the following budget for the period ending June 30, 1949:

- | | |
|---|----------------------|
| 1. For non-recurring capital expenditures | \$ 50,000 (A) |
| 2. For operating expenses | 60,000 (A) |
| | <u>\$110,000 (A)</u> |

Upon receipt of your approval of the continuation and expansion of the project with this budget we shall pay you the sum of \$80,000 (A) ~~(A.A.A. Sum of \$70,000 plus one-half of operating budget)~~, the balance of \$30,000 to be paid on January 1, 1949.

It is understood that any balance remaining in the fund on June 30, 1949 will be returned to the American Petroleum Institute and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By _____
President

By _____
Secretary

Accepted and Approved

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By _____
Chairman

By _____
Clerk

May 17, 1948

Dr. Robert A. Kehoe
Lettering Laboratory of Applied Physiology
College of Medicine
University of Cincinnati
Cincinnati 19, Ohio

Dear Doctor Kehoe:

Many thanks for your note of May 14th and the report of expenditure made during the first quarter of 1948.

You are correct in your assumption that the reimbursement of the sum over-expanded may be taken care of under the provisions of the new and enlarged project.

You will be interested to learn that good progress is being made in the raising of funds to cover the cost of the program for 1948-49. If contributions continue to be received at the current rate, we shall be able to execute the agreement prior to June 15th.

Do you wish to have a new agreement negotiated or will it be satisfactory to extend and expand the scope of the one which we signed in January 1946?

Very truly yours,

DVS:d

cc: Dr. M. H. Newquist
Dr. McIver Woody
Mr. Lacey Walker

UNIVERSITY OF CINCINNATI
CINCINNATI 19 OHIO

May 14, 1948

KETTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS KETLAB CINCINNATI
TELEPHONE UNIVERSITY 2665

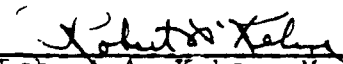
Mr. D. V. Stroop,
The American Petroleum Institute,
50 West 50th Street,
New York City 20.

Dear Mr. Stroop:

I send you herewith the report of expenditures made during the first quarter of 1948, in our prosecution of the work on carcinogenic agents sponsored by The American Petroleum Institute.

I am not at all concerned as to the manner and time of our reimbursement of the sum over-expended, inasmuch as I assume that this will be taken care of in due course under the provisions of the new and enlarged project. If I am mistaken in this, and if any other action should be taken, I shall expect you to let me know. Otherwise, we shall continue the work along present lines until we are duly authorized to proceed on the larger scale. Meanwhile Dr. Heyroth and I are undertaking to find the people required to carry on the larger program.

Very truly yours,


Robert A. Kehoe, M. D.

RAK ef

C.C.: Dr. McIver Woody

Enc.

P. S. It was a pleasure to see your daughter, and I was very much pleased that nothing very serious resulted from her examination by Dr. Stevenson.

R.A.K.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY OF APPLIED PHYSIOLOGY
ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

For the First Quarter of 1948

SALARIES (Based on Proportion of Time Actually
Spent on Project)

Robert A. Kehoe - Supervision	50.00
Karl Kitzmiller - Pathological Assistance	150.00
Sylvan Witherup - Technical Assistance	58.98
Harold Schlecht - Technical Assistance	<u>39.83</u>
	298.81

MISCELLANEOUS EXPENSE

Traveling Expense - Dr. Robert Kehoe	86.50
--------------------------------------	-------

Trip to New York City on March 3, 1948
Conference with Representatives of American
Petroleum Institute Medical Committee

Proportion of Secretarial, Library, Janitors, Wash Boys, Draftsman, Shipping Clerks, Animal Caretakers, Histopathological Pre- paration etc	180.17
--	--------

Proportion of Heat, Gas, Electricity, Steam, Gas, Telephone, Maintenance, Pensions, Annuities etc	129.75
---	--------

695.23

Balance Remaining for Work in 1948
at End of 1947 \$349.62

Expenditures 1st Quarter 1948 695.23

Balance due Kettering Laboratory . . . \$345.61

UNIVERSITY OF CINCINNATI
CINCINNATI 19, OHIO

August 10, 1948

LETTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

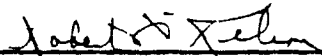
CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: UNIVERSITY 2665

Mr. D. V. Stoop,
The American Petroleum Institute,
50 West 50th Street,
New York City 20.

Dear Mr. Stoop:

I send you herewith for your information, an account of the expenditures made during the second quarter of 1948 in connection with the investigation of carcinogenicity. This, I believe, is self explanatory.

Cordially yours,


Robert A. Kehoe, M. D.

PAK ef

Enc.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY OF APPLIED PHYSIOLOGY
ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

For the Second Quarter of 1948

SALARIES (Based on Proportion of Time Actually
Spent on Project)

Robert A. Kehoe - Supervision	34.61
Francis Heyroth - Chemical and Toxicological Assistance	3.19
Karl Kitzmiller - Pathological Assistance	<u>17.30</u>
	55.10

MISCELLANEOUS EXPENSE

Traveling Expense -
Trip to Washington, D. C. on June 27, 28 and 29, 1948
Dr. Francis Heyroth 82.46

Proportion of Secretarial, Library, Janitors, Wash Boys,
Draftsman, Shipping Clerks, Animal Caretakers,
Histopathological Preparation 10.12

Proportion of Heat, Gas, Electricity, Steam, Gas,
Telephone, Maintenance, Pensions, Annuities etc . . . 10.23

157.91

Balance due Kettering Laboratory
at end of 1st Quarter 1948 \$345.61

Receipts 7-9-1948 -
For Experimental Program 25,000.00

Balance Remaining for Work in 1948 . . . 24,654.39

Expenditures 2nd Quarter 1948 157.91

Balance Remaining for Work in 1948 . . . 24,496.48

11-5-48
CONFIDENTIAL

REPORT ON THE CARCINOGENIC POTENCY
OF EIGHT OILS SUBMITTED BY THE
AMERICAN PETROLEUM INSTITUTE

At the annual meeting of the Medical Advisory Committee held in November, 1947, the progress made in the testing for carcinogenicity of each of the eight oils selected by the Subcommittee on Carcinogenicity was reported orally. Because, at that time, there were still survivors in several of the eight groups of mice employed as test animals, no attempt was made to present the data graphically. Such a presentation is now possible, since all of the mice have died or have been killed during the past year. During that period, the sample of oil that had been found to be carcinogenic was retested, employing for this purpose mice of another strain. Control observations have also been amplified in certain respects.

Materials Tested

Brief descriptions of the eight oils selected by the Subcommittee are given in Table 1, and such physical and chemical data regarding them as have been sent us are recorded in Table 2.

One-gallon samples of each of these oils were sent directly to the Laboratory and used in the tests. A 55-gallon drum of each of these oils is being stored at the Latonia Refinery of the Standard Oil Company of Ohio, to serve as a reserve supply in the event that a repetition of any of the experiments should be deemed desirable at some time in the future. All of these stored oils were reblanketed by us with nitrogen at the request of Dr. M. N. Newquist, because it was believed that there may have been slight differences in the manner in which the drums were purged of air at the various refineries. At the time the reblanketing was done it was found that all of the drums were under slight negative pressure. For purposes of analysis, samples of gas were removed from the 5-inch air space above the oil in the case of two of the drums (Oils 11980 and 11885). The values for the nitrogen content were 97.8 per cent and 97.2 per cent, respectively. The balance cannot be assumed to be pure oxygen, since sulfur dioxide and other gases may also have been present. The space above the oil in each drum was re-flushed with nitrogen, air being excluded by the use of a rubber dam which covered the opening of each bung. In all cases except one (Drum 4, Oil 11896), the drums were sealed

under a positive pressure of two pounds. Drum 4 (Oil 11896), which did not have standard fittings, was sealed at atmospheric pressure. On flushing the drums, strong odors, identified only as due to sulfur compounds, were noted in the case of two of the drums (Oils N-8295-3 and W-3631).

In control experiments, 20-methylcholanthrene, as purchased from the Eastman Kodak Company, was employed. Its melting point was not far below that reported in the literature.

White oil, U.S.P., was also tested. The sample (I-CC) was a coastal naphthenic crude coming from a Texas Gulf crude (Letter of Dr. J.P. Holt, January 20, 1947). Its physical, chemical and other characteristics are given in Table 3.

Experimental Methods

Animals

Mice were selected as the experimental animals for these tests because they are known to be susceptible to carcinogenic agents, and because abundant data are available in the literature on the effects of painting their skin with a large number of pure compounds. They offer also the advantages of being tractable, of having a relatively short life-span, and of requiring but little space for housing. In the reports of the pioneering experimental work conducted in England by Kennaway,

Cook, and others, no mention is made of the genetic origin of the white mice employed. In order to minimize variations in susceptibility, we decided to employ only mice of some well-studied inbred strain and, after consultation with several members of the staff of the National Cancer Institute, we chose dark-colored mice of the C₃H strain. Spontaneous carcinoma of the skin rarely, if ever, develops in mice of this strain. Since, however, carcinoma of the breast occurs quite commonly in female C₃H mice, only males were employed in this work. The source of our supply of these mice was the Jackson Memorial Laboratory, Bar Harbor, Maine. A limited number of the mice used were bred in the Laboratory from this stock, while others were used as purchased from Bar Harbor. The exact age of each mouse at the time an experiment was begun was, therefore, unknown, but it is believed that all their ages ranged between two and three months.

For purposes of comparison, one of the oils was also tested upon mice of the CFW strain, purchased from the Carworth Farms, New Jersey.

Technique

Each oil was tested upon a separate group of 20 mice, approximately 0.1 gram of an oil being applied upon the skin

of the back of each mouse once each week. This frequency was chosen after preliminary experiments had shown that under these conditions no one of the oils would be expected to give rise to systemic intoxication and so kill off the animals before carcinomas might develop. No depilatory was used and the hair was not clipped from the back prior to painting the animals. The quantity of oil that is readily retained by a camel's hair brush was applied by moving the brush down the middle of the back from the neck toward the rump. Preliminary experiments in which the brush was weighed before and after stroking the skin indicated that the amount applied was approximately 0.1 gram, but no effort was made to control the dosage with precision. At no time were any efforts made to remove the oil from the skin by washing. A separate brush was employed for each oil.

One control group of 20 mice was subjected to applications of water in order to confirm the non-occurrence of spontaneous tumors and to eliminate any effect that might be attributed to the handling of the animals. Three other control groups were subjected to contact with a known, potent carcinogenic agent, 20-methylcholanthrene, which was applied as a saturated solution in white mineral oil, a 0.3 per cent solution

in benzene, or a 0.6 per cent solution in benzene. The latter solution was also tested upon a group composed of 17 mice of the CFW strain.

Results

As the experiment progressed, most of the mice exhibited some loss of hair, which was particularly marked in the case of those subjected to contact with Oils W-3632, W-3631, W-3630, 8295-2, and 11885. In the case of carcinogenic materials, there began to appear, after 12 or more weeks, depending upon the nature of the material applied, a localized thickening of the squamous epithelium in the form of a discrete warty prominence in the otherwise smooth surface of the skin. In several instances, more than one such outgrowth appeared in the skin of the same mouse. These gradually increased in size and projected above the surface as hard, warty growths. In a very few instances, they regressed and disappeared. Generally, however, they continued to grow and in some cases attained a diameter of several centimeters. When such an outgrowth had attained a diameter of 1 mm., it was arbitrarily recorded as a tumor. At weekly inspections of the animals, records were made of the number of mice that (a) developed visible tumors during the preceding week, (b) died during that time without having shown

a tumor, (c) died and gave visible evidence of a tumor, (d) were still alive with tumors, and (e) were living without tumors. Most of the animals that died were subjected to necropsy, at which portions of the tumor-bearing skin were removed for microscopic examination. In a few instances necropsies could not be performed either because the mice had been devoured by their cage-mates, or because their tissues had undergone post-mortem decomposition by the time they were found.

The weekly records are presented in cumulative fashion in the graph. This graph was constructed during the progress of the experiment, without consideration of the results of the histological examination of the tissues. In a few instances, such examination disclosed the fact that outgrowths recorded as tumors were merely verrucous masses of epithelium or areas of advanced hyperkeratosis, and not malignant tumors. The graph has not been corrected so as to include only histologically demonstrable malignant tumors, but the microscopic findings are presented in the description of the individual experimental groups.

Control Experiments

These are presented on the left side of the graph.

Water

All of the mice in the experimental group subjected to contact with water alone died before the appearance of any outgrowth upon the skin. (In all of the graphs, mice that died at a time prior to the appearance of any swelling, as did all the mice exposed to water, are indicated by the sign. ) Examination of sections of the skin of three of the mice of this group revealed no abnormalities. The last survivor in the group was killed at the end of the ⁷⁵29th week. The absence of any tumors in this control group confirms the statement of others that the incidence of spontaneous tumors of the skin of male C₃H mice is low. The most common causes of death were pneumonia and nephritis.

White Mineral Oil

Since we desired to employ white oil as a solvent for 20-methylcholanthrene, a second control group was subjected to contact with white oil alone. At the beginning of the 38th week an abnormality was noted in the skin of one of the mice. It was recorded tentatively as a tumor, and is indicated in the graph by the code . This mouse died during the following week and is recorded as a mouse that died with a tumor present. 

Two other mice developed similar changes of the skin by the beginning of the 44th week and, as indicated in the graph, died within one or more weeks thereafter. The black blocks designate mice that died without showing tumors, but at a time when cutaneous outgrowths were apparent in some other mice of the group. Thus both the  and the black blocks denote mice that died without any tumors present on visual inspection.

The apparent production of tumors by white oil was not confirmed when sections of the suggestive areas of skin were examined microscopically. The examination of one of the tumors, believed to have developed in the 43rd week, revealed only a small area of desquamating epithelium, the base of which showed cellular infiltration and vascular congestion, and the margins of which showed acanthosis and parakeratosis. Sections of the affected area of the skin of another mouse showed only a patchy hyperkeratosis and one small area of acanthosis of the epithelium, together with congestion of the dermal vessels, and slight edema and cellular inflammatory reaction of the dermis. Another mouse, which had developed a suspicious area on the skin by the beginning of the 38th week, was not examined post-mortem. Of the other 17 mice in this group,

all of which died without any apparent sign of a tumor, 3 were not examined after death, and the skin of 2 others appeared so nearly normal that sections were not made of it. Microscopic examination of the skin of the remaining 12 mice revealed nothing abnormal in 8, evidence of chronic inflammation in 2, patchy hyperkeratosis in 1, and a slight degree of acanthosis in 1.

These observations indicate that contact with white oil did not induce a cutaneous malignant tumor in any one of 20 mice, although this oil cannot be regarded as entirely innocuous, since chronic inflammatory and other changes appeared in the skin of 6 of the 20 mice, and in 3 of them were of such a character as to have caused the affected areas to be recorded as tumors during life.

Methylcholanthrene in White Mineral Oil

This control group was included in order to test the behavior of a known active carcinogen in a solvent closely related to the oils to be tested. Unfortunately, 20-methylcholanthrene was found to be only slightly soluble in white mineral oil. A saturated solution was employed. Its concentration was not determined, but in all likelihood, it was considerably less than 0.3 per cent.

Only 7 of the 20 mice died without having developed a cutaneous lesion recorded as a tumor during life. The first tumor was recorded at the beginning of the 27th week. Microscopic examination revealed the presence of squamous-cell carcinomas in 3 of the 13 mice recorded as having tumors. Sections of the tumors of 9 of them have not yet been examined, and the remaining mouse was not examined after death. No visceral metastases were found. One of the 7 mice without tumors was not examined after death, and sections of the skin of 2 showed no malignant tumors but such changes as slight dyskeratosis, moderate to severe hyperkeratosis and moderate acanthosis. One showed an irritative dermatosis.

It may be concluded that a solution of 20-methylcholanthrene in white mineral oil exhibited definite evidence of its ability to act as a carcinogenic agent in mice of the C₃H strain.

0.3 Per Cent Methylcholanthrene in Benzene

This group was designed as a positive control. (Benzene was the solvent employed by the English workers in determining the carcinogenic activity of a large number of polycyclic aromatic compounds, the concentration being 0.3 per cent in

most instances.) All but 4 mice exhibited one or more tumors at the time of death. The first tumor was evident at the beginning of the 23rd week and the last had appeared by the 40th week.

Microscopic examination of the tumors borne by 4 of the mice, which may be regarded as representative of the group as a whole, showed that each was a squamous-cell carcinoma, usually of Grade III or IV (Broders' classification). The tumor had metastasized to the lungs of one mouse, but no visceral or axillary metastases were observed in any of the other 15 mice with tumors.

0.6 Per Cent Methylcholanthrene in Benzene

Of the 20 mice in this group, 2 died during the 5th week. All of the others developed lesions reported as tumors, which made their appearance between the 12th and 24th weeks. In some instances, they attained a diameter of 2.5 cm. The chief effect of doubling the concentration was, therefore, to decrease the latent period before tumors became evident.

Ten of the 18 outgrowths were examined microscopically. With the exception of 1 mouse, which had only a few cornified elevations of the size of a pin head, characterized microscopically by moderate hyperkeratosis with a patchy acanthotic

reaction, all of the others were found to be typical squamous-cell carcinomas containing atypical, often binuclear cells, many mitotic figures, and showing variable degrees of pearl formation. In many cases, there was invasion of the superficially placed skeletal muscle. Metastasis occurred in an axillary node of one mouse and in the lungs of another.

Very similar results were obtained in a repetition of the experiment with a group of 17 male mice of the CFW strain.

The Carcinogenic Properties of 8 Oils

Oil W-3632

Six of the 20 mice in this group died without having afforded any evidence of tumor formation. Two others reported as bearing small tumors died during the 30th and 31st weeks, respectively, but microscopic examination of their skin revealed only the presence of hyperkeratosis and acanthosis. Two mice had unquestionable tumors, (one weighed 8.5 g.) which were not examined microscopically. The tumors borne by the ^{other} 10 mice were all squamous-celled carcinomas. The gross and microscopic observations on each of the mice of this group are given in Table 4.

A repetition of the test of this oil, using CFW mice, is nearing completion. Since some of the mice are still

living, the data have not been incorporated in the graph, but it is apparent that the outcome will not differ greatly from that described in the case of the C₃H mice.

Oil W-3631

Five of the mice of this group exhibited very small localized areas of thickening or incrustation of the skin, which were recorded as tumors on the graph. The first of these was noted at the beginning of the 30th week, but the others appeared much later (48 to 55 weeks). One of these five mice was not examined post mortem. Examination of a section of the skin of another member of this group revealed a small area of malignant neoplasia of the skin (squamous cells) in relation to a verrucous hyperkeratotic lesion, the greater part of which was necrotic. There were numerous intradermal kerato-hyaline cysts in the adjacent skin. The tumor was classed as being of Grade I in malignancy (Broders' classification). A second section of this tumor displayed only verrucous hyperplasia with hyperkeratosis. Sections of the skin of the other 3 mice that had been reported as bearing tumors during life exhibited only moderate or slight hyperkeratosis and slight acanthosis. It is believed that the changes observed during life were

related to areas of hyperkeratosis with the formation of kerato-hyaline plugs in the epithelial crypts. Similar changes were observed microscopically in the skin of 6 of the mice that failed to arouse suspicion of tumor formation during life. This oil must be regarded as inducing an irritative dermatosis, and in the case of 1 of the 20 mice, a tumor of a low-grade of malignancy developed.

Oil W-3630

None of the 20 mice of this group gave any evidence of tumor formation during life. Necropsies were not performed on 6 of these mice and no section of the apparently unaltered skin was taken on two others. No evidence of malignant change was found on examination of sections of the skin of 12 of the mice, although very slight hyperkeratosis was noted in those of 4, and slight dyskeratosis in those of 2. In addition to hyperkeratosis, one showed an area of verrucous proliferation. No abnormalities were noted in any of the others.

Oil N-8295-2

Only one of the mice of this group exhibited any

cutaneous abnormality during life. A large dark red spot which appeared on the back of this animal became an open lesion that failed to heal during the progress of the experiment, but, as there was no apparent outgrowth, it was not recorded on the graph as a tumor. However, microscopic examination of the skin revealed hyperkeratosis with a large area of pyoderma. In addition, there was a large sub-epithelial tumor composed of closely packed cells extending to and involving the muscle layer. These cells were oval or spindle-shaped and possessed hyperchromatic nuclei. The tumor apparently arose in an inflamed dyskeratotic surface area and undermined the surrounding relatively normal epithelium. It was concluded that this was a pleomorphic squamous-cell carcinoma of grade III. Skin sections of 10 other mice revealed no malignant changes, although 7 showed slight to moderate hyperkeratosis and 3 showed acanthosis, which in one case was noted in the surface epithelium and in that of the hair follicles and shafts.

Oil N-8295-3

None of these mice developed any tumors during life. Their absence was confirmed by microscopic examination of sections of the skin of 14, one of which gave evidence of an

irritative dermatosis. Two showed definite verrucous papillomas, and several others varying degrees of hyperkeratosis, dyskeratosis and acanthosis.

Oil 11896

No malignant tumors were observed during the life of any of the mice of this group and no evidence of malignant change was found on microscopic examination of sections of the skin of 14 of these mice. One showed verrucous hyperkeratosis and a moderate degree of acanthosis, but, in general, changes of this nature were slight and infrequently encountered.

Oil 11885

No tumor formation was noted during life in any of the 20 mice and no malignant tumors were found on microscopic examination of skin from 11 of these mice, although 2 of them showed verrucous papillomata with well-marked hyperkeratosis and acanthosis.

Oil 11980

During life no evidence of tumor-formation was noted, but well-marked histopathologic changes were noted in skin of most of the 15 animals subjected to microscopic examination. In one instance, the changes were such as to afford moderate

evidence of malignant alteration, and, in another, they represented a close approach to malignancy. Verrucous hyperkeratosis and acanthosis were noted in 8 instances, and in 5 these changes were localized in papillomatous areas, one of them pedunculated. In several sections, focal collections of tarry oil were noted in the dermis.

DISCUSSION

Not one of these 8 oils failed to affect the skin in some manner. Oils W-3630 and 11896 gave the least evidence of an irritative action. Oils 11885 and N-8295-3 produced a few verrucous papillomata. Oil 11980 gave rise to several papillomatous areas, and in 2 of the animals painted with it the changes were on the border line of malignancy. One malignant growth was found in each of the two groups of 20 painted with Oils 3631 and N-8295-2, respectively. Oil 3632 was highly carcinogenic, being about as active in this respect as a 0.3 per cent solution of 20-methylcholanthrene in benzene. In its carcinogenic activity, it far exceeds any of the other oils tested.

In 1925, Kennaway (British Medical Journal 2, 1(1925)) showed that a sample of California crude petroleum which failed to produce a tumor in any one of 100 mice, acquired carcinogenic

properties when passed at a rate of 12 to 15 ml. per hour over a porous plate kept at 880° in an atmosphere of hydrogen. Our most potent Oil W-3632 had been subjected to a reaction temperature of 1000°F., and about 40 per cent of it distilled between 688 and 760°F. Oil 3631, which produced one tumor, had been subjected to thermal cracking at a coil outlet temperature of 940°F. In the absence of more detailed information on the operating temperatures to which the other oils had been subjected, no further appraisal can be made of the effect of high temperatures in forming carcinogenic hydrocarbons.

The control experiments with methylcholanthrene suggest that the greater the concentration of the carcinogenic hydrocarbon, the earlier will cancers appear. There is, indeed, a surprising uniformity in the time of appearance of the tumors in groups of C₃H and CFW mice, painted with a 0.6 per cent solution of methylcholanthrene in benzene. The graph includes the results of an experiment performed in England in which mice of an undesignated strain were painted twice per week with a 0.3 per cent solution. The incidence of tumors is very similar to that which we observed in the case of mice painted once per week with a 0.6 per cent solution.

However, further repetitions of these experiments are necessary in order to establish the degree of reproducibility of the results.

Attempts are now being made to develop a method of plotting the data so as to permit the numerical characterization of the potency of an oil or of a solution of a carcinogen. Such a numerical characterization may be of great value in any systemic approach to the study of the influence of various factors in conferring carcinogenic potency upon petroleum products. It may also be of use in learning more exactly the effects of progressive dilution of an active product upon its potency.

From the Kettering Laboratory of Applied Physiology,
College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Experimental Work by:

Wm. B. Deichmann, Ph.D.

Sylvan Witherup, B.A.

Harold Schlecht

Pathologic Observations by:

K. V. Kitzmiller, M.D.

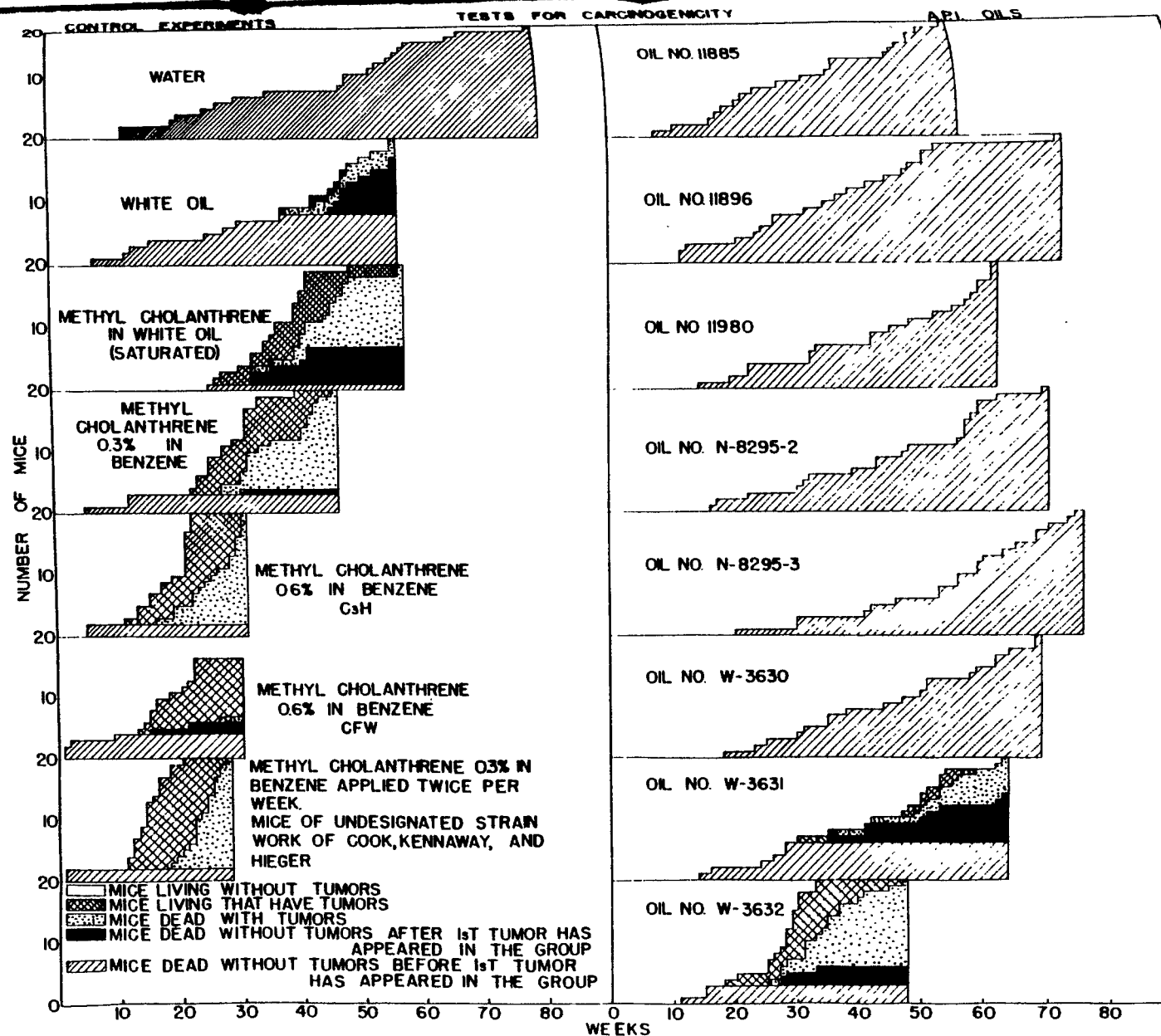
Report by:

Francis F. Heyroth, M.D.

Approved

Robert A. Kehoe
Robert A. Kehoe, M. D.
Director

Date November 5, 1948.



[illegible]

Dept file No.

Dept file No.

Table 1

Labels Borne By the Eight Oils

<u>Identification Number</u>	<u>Company</u>	<u>Remarks on Label or In Letter</u>
W-3632	Shell Oil Company, Wilmington, California	Fluid Cat, Clarified Oil, Cat.
W-3631	Shell Oil Company, Wilmington, California	Unflashed Th. Residue
W-3630	Shell Oil Company, Wilmington, California	Untreated Cat. Gas Oil
N-2295-2	Union Oil Company of California, Wilmington, California	TCC Tars
N-2295-3	Union Oil Company of California, Wilmington, California	Thermo Recycle
No. 11896	General Petroleum Corporation, Process Laboratory, Los Angeles, California	Straight Run Gas Oil from Wilmington
No. 11885	General Petroleum Corporation, Process Laboratory, Los Angeles, California,	Straight Run Residual from Wilmington
No. 11980	General Petroleum Corporation	TCC Recycle Stock (from Torrance TCC Unit T4, operating with a 24-foot bed of bead catalyst on a charge of mixed straight run gas oil from California High Pour and Wilmington Crudes).

Table 2
Analytical Data on Three of the Oils

Table 1

Labels Borne By the Eight Oils

<u>Identification Number</u>	<u>Company</u>	<u>Remarks on Label or In Letter</u>
W-3632	Shell Oil Company, Wilmington, California	Fluid Cat, Clarified Oil, Cat.
W-3631	Shell Oil Company, Wilmington, California	Unflashed Th. Residue
W-3630	Shell Oil Company, Wilmington, California	Untreated Cat. Gas Oil
N-8295-2	Union Oil Company of California, Wilmington, California	TCC Tars
N-8295-3	Union Oil Company of California, Wilmington, California	Thermo Recycle
No. 11896	General Petroleum Corporation, Process Laboratory, Los Angeles, California	Straight Run Gas Oil from Wilmington
No. 11885	General Petroleum Corporation, Process Laboratory, Los Angeles, California,	Straight Run Residual from Wilmington
No. 11980	General Petroleum Corporation	TCC Recycle Stock (from Torrance TCC Unit T4, consisting of 2000 gal. of oil)

Table 3

Analytical Data on White Mineral Oil

Specific Gravity at 60° F.	.860 Min.	.870 Max.
Color, Saybolt	+30 Up	
Viscosity, Say. Univ. at 100° F.	85	95
Flash, Pensky-Martens Closed, ° F.	330	
Pour Point, ° F.		0
Copper Test, 2 hr. at 212° F.		5
Odor		2
Taste		2
Acid Test (U.S.P. Test for Carbonizable Substances)		2*
U.S.P. Cloud	Must Pass	
U.S.P. Acidity Test	Must Pass	
U.S.P. Sulfur Compounds	Must Pass	
Peroxide Stability at 300° F., minutes	20*	
Sunlight Peroxide Stability (S-1 Lamp), hrs.	3*	
Sunlight Odor, minutes	5*	
Mercury Index		2*

* Desired but not guaranteed.

Table 4

Gross and Microscopic Observations on the Skin of Mice Subjected to
Cutaneous Contact With Oil W-3632

Number of Mouse	Serial Number of Week in Which a Tumor Appeared	Serial Number of Week in Which The Mouse Died	Gross Observations	Microscopic Observations
5400	29	35	3 to 4 elevated areas of incrustation, measuring 1 x 1 or 1 x 2 mm.	Neoplastic proliferation of squamous epithelium associated with extensive pyogenic inflammation, hyperkeratosis, acanthosis.
5401	31	46	Tumor mass, weighing 8.5 g. and measuring 3 x 2.5 x 2 cm.	No section
5402	27	28	No necropsy	
5403	19	26	Ulcerated tumor, 1 cm. in height and 1.2 x 0.8 cm. in area. Not fixed to underlying fascial.	Epithelial tumor composed of anaplastic squamous cells with vesicular, hyperchromatic nucleic and frequent mitotic figures, growing in irregular sheets and trabeculae and ex- tending into the corium. Much keratiniza- tion and pearl formation. Superficial ulceration. Adjacent epithelium hyperkera- totic and acanthotic with large areas of necrosis. No visceral metastases.
5404	29	41	Tumor, 3 x 5 x 15 mm.	Squamous-cell carcinoma of skin with much keratinization. A large portion of the tumor has undergone degeneration and necrosis with associated pyogenic inflamma- tory reaction. No metastases.
5405	31	48	Tumor, 3.5 x 2.5 x 2 cm.	Bulky verrucous tumor with widespread malignant squamous cell neoplasia. Diagnosis- Squamous-cell carcinoma of Grade II.

Table 4 (Page 2)

Number of Mouse	Serial Number of Week in Which a Tumor Appeared	Serial Number of Week in Which the Mouse Died	Gross Observations	Microscopic Observations
5406	--	32	Incrustation, 1 mm. in diameter	Hyperkeratosis and slight acanthosis. No tumor.
5407	34	42	Cornified area, 10 x 10 x 2 mm.	Pronounced hyperkeratosis, acanthosis, hyperkeratinization with pearl formation, associated with well-defined malignant tumor of squamous epithelium. Many large giant nuclei, numerous binucleated cells, hyperchromatism. Large area of degeneration and necrosis.
5408	21	32	Biopsy in 26th week. At Death: Site of application on back covered with loose sloughing necrotic epithelial tissue, matted hair, and dried blood. Odor characteristic of moist necrotic tissue. Skin scar at site of previous biopsy. Sloughing tissue removed exposing discrete finely fungoid glistening gray tumor (15 x 10 x 4 mm.), under surface of skin. One tiny nodule (4 mm.) probably small tumor by direct extension.	An ulcerated papillomatous squamous-cell carcinoma invading and destroying the most superficial lamina of stratified muscle. The tumor is composed of atypical large keratinized cells with large vesicular nuclei; mitotic figures, mostly atypical, are fairly common and binucleated cells are numerous; there is edema and infiltration of the underlying connective tissue by large mononuclear cells, lymphocytes and a few polymorphonuclear cells. Section removed after death: Squamous-cell carcinoma of skin. No metastases in lymph nodes or viscera.

Table 4 (Page 3)

Number of Mouse	Serial Number of Week in Which Tumor Appeared	Serial Number of Week in Which the Mouse Died	Gross Observations	Microscopic Observations
5409	30	36	Very small tumor (0.5 cm.) with crusting of epidermis	Squamous-cell carcinoma of skin.
5440	26	38	Cornified epithelial tumor 10 x 6 x 3 mm. Dark brown and very hard.	Malignant tumor of squamous-cell origin. Skin surface hyperkeratotic with extensive pyogenic inflammation. Numerous tumor giant cells with hyperchromatic nuclei.
5441	26	36	Tumor of interscapular area (3 x 2.5 x 1.5 cm.), brownish discoloration, thickened crusted epidermis, patchy loss of hair. Section of tumor permits the escape of a large amount of whey-like fluid and small particles of tissue. Cortex of tumor is irregular and glistening. Gray white cut surface. No involvement of subjacent muscle.	Bulky, squamous-cell carcinoma with a great deal of keratinization and pearl formation. Surface of tumor covered with hyperkeratotic epithelium. No metastases. Axillary nodes not remarkable.
5442		38	Crusted area of 3 x 4 mm. with one brownish, circumscribed elevation 1 x 1 x 1 mm.	Pronounced acanthosis and hyperkeratosis without definite evidence of malignant change.
5443		16	No necropsy.	

Table 4 (Page 4)

Number of Mouse	Serial Number of Week in Which Tumor Appeared	Serial Number of Week in Which the Mouse Died	Gross Observations	Microscopic Observations
5444		28	No evidence of tumor-like growth.	Skin section not remarkable.
5445		16	No tumor	No cutaneous or visceral tumor.
5446		12	No necropsy	
5447	30	32	Crusted area, 1 x 2 x 2 mm.	Acanthosis, hyperkeratosis, with area of neoplastic proliferation of atypical squamous epithelium with some penetration of derma. No visceral metastases.
5448		29	No tumor	Skin section not remarkable.
5449		34	No tumor	

CONFIDENTIAL

M I N U T E S

SUBCOMMITTEE ON CARCINOGENICITY

November 11, 1948

A semi-annual meeting of the Subcommittee on Carcinogenicity was convened at 11:00 A.M. Thursday, November 11, 1948, in Private Dining Room #1 of the Stevens Hotel, Chicago.

MEMBERS PRESENT

L.E. Curtis
T.M. Frank
A.E. Hoag
J.P. Holt
W.R. Lewis
M.N. Newquist
C.A. Swan
McIver Woody

L.C. Beard, Jr.
A.E. Dooley
H.G.M. Fischer
H.R. Warrick
H.H. Zuidema

VISITORS

V.C. Baird
W.W. Brooks
F.F. Boys
Kieffer Davis
B.B. Reeves

E.W. Adams
R.C. Cole
N.J. Gothard

GUESTS

Dr. Robert A. Kehoe - University of Cincinnati
Dr. Francis F. Heyroth - " " "
Dr. A. Wesley Horton - " " "
Dr. W.D. Seyfried - Humble Oil & Refining Company
Dr. S.S. Shaffer - " " " "
Dr. H.W. Stevenson - Shell Petroleum Company, Ltd., London
Dr. W.J. Sweeney - Standard Oil Development Company

Total in Attendance - 28

MEMBERS ABSENT

T.J. Kelly

R.S. Bonsib
A.J. Koewing, Jr.
H.P. Lankelma

The new members and guests, L.F. Curtis, C.A. Swan, R.A. Kehoe, Francis F. Heyroth, A.W. Horton, W.D. Seyfried, S.S. Shaffer, H.W. Stevenson, W.J. Sweeney were introduced.

Dr. Kehoe reported on the status of the experimental studies at the Kettering Laboratory and pointed out the desirability of:

- 1 - Facilities adequate to select materials needed to be tested.
- 2 - Means whereby samples could be studied as to their relative potencies.
- 3 - Systematic data on the incidence of malignancy in petroleum workers exposed to these materials.

As to the progress of the building program at Cincinnati, he said that the new wing originally scheduled for completion in May 1948 would surely be ready for occupancy by March 1949 and would include a special animal house on the roof, which has been designed for mice and other small animals which are used in cancer studies. He reminded us that this additional space and the equipment to be installed therein was made possible by the recent A.P.I. grant for capital expense and he assured us that this space, or its equivalent elsewhere in the building, would be reserved for our work.

Dr. A. Wesley Horton, who has just been appointed as Assistant Professor of Industrial Hygiene, was introduced by Dr. Heyroth, who explained that his entire time would be devoted to our problem. In making this appointment, they have selected an organic chemist with practical experience in polycyclic compounds, a knowledge of physical chemistry and an understanding of our industrial problems and technical processes.

Dr. Kehoe said that their new Professor of Preventive Medicine, who is one of the three outstanding epidemiologists in the country, will be able to devote half his time to the A.P.I. project during the coming year.

Dr. Heyroth then reported on the results of tests of the eight A.P.I. samples. His report and charts will be reproduced and distributed to members of the Committee.

Dr. Holt recommended that a wider range of samples be studied, especially those in the higher boiling ranges (above 700° F) and that waxes be investigated also. He cited an article in the N.Y. Times of November 7, 1948 and said that Standard Oil (N.J.) will cooperate fully with the U.S. Public Health Service in its activities in this field. Jersey has found that, if the heavy oil is diluted with 71% white mineral oil, the activity is reduced to about one-fourth its original potency.

Dr. Newquist referred to recent statements in the literature which say that any skin tumor should be considered as potentially malignant.

Dr. Frank thought it would be desirable to study the effects of these oils following repeated applications and washings, thus simulating the actual exposure of employees.

Dr. Hoag read a report prepared by the Metropolitan Life Insurance Company on "Statistics on Cancer Among Workers in the Oil Industry". He also suggested that some ways be found to challenge incorrect newspaper articles; for example, a recent statement referring to paraffin wax as being carcinogenic.

Dr. Beard read a letter from Col. Auld of the Institute of Petroleum (England) and suggested that Col. Auld be invited to attend a future meeting of the Medical Advisory Committee and describe the work being done in England.

Dr. Stevenson explained that any information given Col. Auld on the problem in the United States would be considered confidential; that the Institute of Petroleum was similar to the A.P.I.

Mr. Warrick stressed the desirability of finding out more about the formation of carcinogens and urged that the technical advisers meet soon with Dr. Horton to discuss these matters.

Mr. Zuidema asked that a comparison between catalytic cracked and thermal cracked material be made.

Dr. Kehoe and Dr. Heyroth, in discussing future work, advocated:

- 1 - Careful consideration in selecting samples for future testing, taking into account the source, the nature of the crude, the temperature conditions, etc. This should be considered by Dr. Horton and the technical advisers.
- 2 - The collection of epidemiological data by an expert in that field. While laboratory methods can determine the relative carcinogenicity of various materials, the final answer will depend on human experience.
- 3 - Study of the reproducibility of results and the effects of dilution.

The following report to the Medical Advisory Committee was approved:

On behalf of the Subcommittee on Carcinogenicity, I present to the Medical Advisory Committee for transmittal to the Safety Committee of the Board of Directors and for adoption by the Executive Committee of the Board of Directors, the following report and recommendations:

- 1 - That the selection of Dr. A. Wesley Horton for Dr. Kehoe's staff is acceptable to us.
- 2 - That the selection of the epidemiologist for Dr. Kehoe's staff is acceptable to us.
- 3 - That an additional \$25,000. will be necessary to continue the program at the University of Cincinnati during 1949 to be followed by another \$25,000. for the first six months of 1950.

- 4 - 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 Subcommittee on Carcinogenicity.
- 5 - That the carcinogenic program which the American Petroleum Institute is sponsoring at the University of Cincinnati should include:
- (a) Biological testing program to determine the carcinogenicity of various samples.
 - (b) Biological or other experimental studies for the purpose of developing quicker techniques for determining the carcinogenicity of these materials.
 - (c) Experimentation directed toward defining protective procedures that might be used to protect individuals who may come in contact with these oils.
 - (d) Epidemiological studies of this problem in the industry.
 - (e) (Deleted by the Medical Advisory Committee).
 - (f) Investigation of solid and semi-solid natural petroleum constituents such as red wax.

McIVER WOODY, M.D.
CHAIRMAN

A.E. Dooley
SECRETARY

Statistics on Cancer Among Workers in the Oil Industry
(Prepared by the Metropolitan Life Insurance Company
at the request of Dr. Hoag and Mr. Beard)

We have reviewed the mortality studies available to us and have canvassed the literature on the subject of cancer among workers in the oil industry. So far as general mortality from cancer is concerned, the evidence indicates that the death rate for oil workers is probably no higher than the average. Gafafer's report on the occurrence of cancer among employees of an oil refinery published in Public Health Reports for August 23, 1940, to which Mr. Beard refers in his letter of May 26th, shows that the crude death rate for the oil workers was no higher than average. We have calculated the expected number of deaths among these oil workers ages 15 to 69, on the basis of death rates from cancer by ages prevailing among white males of the general population in the years 1933-1938. The calculated number of deaths expected for the six year period was 52.6, whereas there were actually only 46 deaths. Some information is given on cancers by site in the original article. Employees of the oil refining company show relatively more cancer of the digestive system than occurred among the adult male population, while the proportion of cancers of the genito-urinary system is somewhat less. We wrote to Dr. Gafafer to see if he had additional information for a more recent period, but he advised us that the 1940 report is his latest.

Some years ago we looked into the Group insurance experience in this matter. In the combined experience of six of the leading companies issuing Group insurance in the United States and Canada from 1927-1932, the mortality from all forms of cancer among all insured workers in the mineral oil industry regardless of the exact occupation, was 36 per 100,000 years of life exposed as against 62 per 100,000 among all of the general occupation group in which those in the oil industry have been classed. Detailed data by cause of death are not given in recent Intercompany Group reports.

Ordinary Department mortality experience is limited so far as cancer among oil workers is concerned. However, while we cannot calculate the ratio of actual to expected deaths from cancer among them, the facts presented in the Joint Occupation Study, 1928,* indicate that in a group of oil and gas field foremen and miscellaneous operatives represented by 51,000 life years of exposure, the cancer mortality was average or below average.

Our Industrial Department experience is quite limited, and the results are out of line with other studies. The number of deaths is so few, however, that the results are not significant. In the period 1937-1939, the standardized relative index for cancer among oil refinery workers, calculated in the manner outlined in our paper, "Occupational Mortality Experience of Insured Wage Earners," was 120, based on 15 cancer deaths; the standardized relative index for the years 1922-1924 was 130, based on 13 deaths.

There is a considerable literature on the occurrence of skin cancers among workers in the oil industry. The best reports of which we have a record are listed on the accompanying sheet. Particular attention is called to the work by Schwartz, Tulipan and Peck.

*Published by the Actuarial Society of America and the Association of Life Insurance Medical Directors.

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- Henry, S.A.
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- Hesper, W.C.
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Publisher. 1942. p. 896.
- Phillips, Charles
The relationship between skin cancer and occupation in Texas:
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Texas State Journal of Medicine. January, 1941, p. 613.
- Schwartz, L., Tulipan, Louis, and Peck, S.M.
Occupational diseases of the skin. Chapter XVI - Dermatoses
caused by petroleum. p. 232. Lea & Febiger, Philadelphia 1947.
- U.S. Public Health Service
Disabling morbidity, and mortality from cancer among the male
employees of an oil refining company with reference to age,
site, and duration, 1933-38, inclusive, by William M. Gafafer.
Public Health Reports, August 23, 1940, p. 1517.

EXCERPTS FROM COLONEL S. J. M. AUID'S
LETTER OF AUGUST 6, 1948

" The subject of the relationship of petroleum to industrial carcinoma and indeed to cancer in general has developed rapidly during the last year or so and appears to be taking on an importance which may seriously affect the nature and provision of mineral oil products and therefore warrants our close attention from those aspects as well as from the serious pathological outlook which is concerned.

" During the early part of the war the matter was relatively quiescent, but came to the front again in respect of the alleged carcinogenicity of textile oils because of further work by Twort and the official adoption of the Twort "safety" formula based on a specific refractivity relationship. Special oils were set aside by the Petroleum Board in order to permit this formula to be met, but at the same time, and possibly due to the traversing of the Twort work from different sources, a movement was made to apply a test in vivo which related carcinogenic activity to change in refractive index of oils injected into the living animal.

" Towards the end of 1943 the matter suddenly came into still greater prominence, via the Ministry of Labour, both in connection with the provision of mule spinning lubricants and the use in increasing quantities of petroleum extracts as replacements for products of different types which were in short supply, particularly rubber extenders and drying oil substitutes.

" As a result, the Petroleum Board, through its Technical Advisers, embarked on biological work in the Pathological Department of the University of Birmingham for the express purpose of developing the whole subject on a reliable basis of observation. Around the same time discussions were started between the various Ministries and Government Departments concerned, representatives of the Spinners' Operatives (the trades unions), the Master Spinners, and the Petroleum Industry. At these meetings the representatives of the Oil Industry were Mr. J. A. Oriel of the Shell Company and myself. One of the matters thereby brought into consideration and now coming to a head, was the suggested adoption of technical white oils as textile lubricants.

" At a recent meeting the significance of this movement was closely canvassed and the Petroleum Representatives pointed out that whilst the research work subsidized by the Oil Industry had in successive reports indicated the biological inactivity of so-called technical white oils, it was necessary to express a warning that their adoption should not be regarded as the final step in either the investigation or the practical consideration of the occupational carcinoma concerned. Indeed, recommendation of the adoption of near white oils, wherever workers were subject to direct contact with petroleum products, might be misleading and dangerous because of the assumption that nothing else needed to be done.

"Moreover, the question of supplies, costs, etc., might render the situation impracticable. It might be far more important to develop the use under such conditions of solvent-treated oils of low biological activity combined with special attention to the avoidance of oil dispersion and to personal cleanliness.

" With the demerger of the Petroleum Board arrangements have been made for the research work, such as that at Birmingham, to be continued under the supervision of the Institute of Petroleum with funds bequeathed by the Petroleum Board and likely to be added to as required by the individual Oil Companies in the future. In accepting this responsibility the Institute of Petroleum appointed a special Research Group which has been placed under my Chairmanship and includes representatives of the major companies and certain University workers.

" Within the last month, quite separately, the Medical Research Council - a body of the highest standing and working directly under the Privy Council on grants allocated by the Treasury, has decided to investigate fully the question of the carcinogenicity of Petroleum Products. In this connection Sir Edward Mellanby, the Chairman of the Medical Research Council, has approached me as representing the Institute of Petroleum for the purpose of effecting contact and establishing co-operation with the Petroleum Industry in general and the I. P. Research Group in particular. From our conversations it appears that such collaboration will be arranged.

" I am informed that the Medical Research Council's interest in the subject has not developed from the textile considerations known to you but largely from observations made by the Medical Officers of the Government Factory Department indicative of dangerous and fairly widespread symptoms arising from the use of certain mould oils in Scotland and from work carried out on automatic tool operatives in the Midlands because of similar or allied occurrences presumably arising from contact of workers with cutting oils.

" The organization proposed by the Medical Research Council will be of a high standard and will bring in all the specialists in allied spheres of work in the United Kingdom. It is intended that the investigations shall be laid out as a succession of long-term projects. It is thought probable, however, that the ad hoc research work on which the Institute of Petroleum Research Group is prepared to embark may well fit as a particular phase of the bigger investigation.

" The Petroleum Industry here has noted with great interest the growing concern of the A.P.I. in the cancer problem in relationship to oil.

" It seems, therefore, of great moment that steps should be taken to correlate the work in the two countries not only to assist in the prosecution of the pathological investigation but from the broader important practical outlook of the Petroleum Industry in its relationship to health."

M E M O R A N D U M

November 22, 1948

Subject: PAPER READ BY DR. W. C. HUEPER ON THE SUBJECT OF
OCCUPATIONAL CANCER BEFORE THE APHA

Dear Doctor Woody:

A paper entitled Prevention and Control of Industrial Cancer was read by Dr. W. C. Hueper, Chief, Environmental Cancer Section, Cancer Control Branch, National Cancer Institute, Bethesda, Md., before the Industrial Hygiene Section and Subcommittee on Medical Care of the American Public Health Association. The occasion was the 76th Annual meeting of the APHA and an audience estimated by the writer at 200 - 300 people were in attendance at Talbot Hall, Mechanics Building, Boston, Massachusetts at 2:30 P.M., November 11, 1948.

In his preliminary remarks, Dr. Hueper indicated that research on the etiology of cancer indicated a strong link between environment and cancer incidence. Recent evidence has pointed out a definite correlation between cancer incidence and exposures to ultra-violet radiation, asbestos, benzol, certain organic amines, paraffin oils, as well as heavy petroleum distillates and degradation products such as tars, cokes, and pitches. He then discussed an idealized approach to the control of the problem which would involve the following points:

- 1) Evaluate the carcinogenicity of suspected compounds and materials through animal experimentation.
- 2) Investigate vital statistics records for cases of cancer and trace the employment history of these individuals. In certain instances it might be necessary to employ Social Security records to follow the employment of the individual.
- 3) In case that the foregoing provides evidence pointing to an unusual incidence of cancer in a certain industry, the plant records of that industry will be investigated to determine what activities and exposures within that industry produce the higher incidences of cancer.
- 4) Medical diagnostic procedures must be improved as a great many cases are being missed at the present time. Considerable work of this type is being done in private laboratories and the

November 22, 1948

Public Health Service is setting up such a laboratory at Georgetown University, Washington, D. C.

- 5) Initiate preventive measures as soon as possible since the identification of the offending agent is not necessary. Industrially, the approach would be as follows:
 - a) Through technical control aim at the complete elimination of the exposure, or,
 - b) Minimize the exposure by seeking improved industrial apparatus such as leak-proof equipment, closed systems, etc.
 - c) Provide suitable personal protective equipment such as gloves, boots, impervious clothing, etc.
 - d) Provide adequate sanitary facilities. This would require an expansion of locker facilities in most existing plants.
 - e) Instruct the workers in the proper use of the protective measures provided and tell them why their cooperation is required.
 - f) For certain operations in industry the exposure may be minimized by the use of teams, trained to perform their duties with a minimum of exposure, and provided with special safeguards.
- 6) Medical control programs must be set up, not only for current diagnosis and treatment, but aimed at following the worker throughout a latent period which may extend for 15-20 years.
- 7) A governmental factory inspection system would be set up to insure that the foregoing requirements are met.
- 8) Protection for workers in interstate commerce would be secured by setting up standards for containers and suitable warning labels.
- 9) Registration and licensing by a government agency would be required for those factories handling known carcinogens.
- 10) Amending of present State occupational disease laws to provide suitable compensation for occupational cancer and to insure the industrial control of exposures.

Clyde M. Berry

Clyde M. Berry,
Industrial Hygienist

November 23, 1948

Dr. McIver Woody
Esso Standard Oil Company
15 West 51st Street
New York, New York

Dear Dr. Woody:

During a visit yesterday to the Illinois State Division of Industrial Hygiene, Mr. Kenneth Morse, Director, told me that his Division would soon start an environmental cancer study in the state and begin work around Alton, Illinois. He indicated that this study would include the oil industry. The study is to be done at the request of U.S. Public Health Service and in cooperation with that agency. Representatives of the U.S.P.H.S. conferred with Mr. Morse about two weeks ago to make plans for this study.

Yours very truly,

Allan E. Dooley

Allan E. Dooley

MEMORANDUM

November 11, 1948

SUBJECT: RECEIPTS AND DISBURSEMENTS - API MEDICAL RESEARCH FUND

Contributions to Fund

1945 Solicitation	\$28,900.00	
1947 Solicitation	27,800.00	
1948 Solicitation	<u>94,300.00</u>	
TOTAL		\$151,000.00

Disbursements from Fund

Harvard University

Toxicological Reviews (3-15-48)	\$27,000.00	
Cutting Oil Dermatitis (11-19-47)	<u>2,500.00</u>	
		29,500.00

University of Cincinnati

Carcinogenicity (7-1-48)	71,000.00	
Fluorine Study (11-28-47)	<u>2,500.00</u>	
		73,500.00

Miscellaneous

Books for Committee Use	57.77	57.77
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TOTAL DISBURSEMENTS		<u>103,057.77</u>
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<u>BALANCE ON DEPOSIT</u>		47,942.23
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Allocations and Obligations

University of Cincinnati

Carcinogenicity (1-1-49)	25,000.00	
Fluorine Study (11-28-48)	<u>2,500.00</u>	
		27,500.00

Harvard University

Toxicological Studies (Aromatics and Catalysts) (?)	10,000.00	
Toxicological Reviews (3-14-49)	<u>10,000.00</u>	
		20,000.00

TOTAL ALLOCATIONS AND OBLIGATIONS		<u>47,500.00</u>
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<u>UNALLOTTED AND UNOBLIGATED BALANCE</u>		\$ 442.23
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UNIVERSITY OF CINCINNATI
CINCINNATI 19, OHIO

November 26, 1948

LETTERING LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS: KETLAB CINCINNATI
TELEPHONE: UNIVERSITY 2065

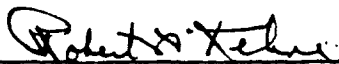
FILE
MAC

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

Dear Mr. Stroop:

I send you herewith an account of the financial status of the American Petroleum Institute project for the investigation of petroleum compounds as of October 1, 1948. You will note that, coincident with the comparatively small amount of work we have been able to do, the expenditures have been small. The only advantage represented therein is that the balance remaining for further investigative work is quite considerable.

Cordially yours,


Robert A. Kenoe, M. D.

IAK ef

Enc.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY OF APPLIED PHYSIOLOGY
ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR THE THIRD QUARTER OF 1948

SALARIES (Based on Proportion of Time Actually Spent
on Project)

Francis Heyroth - Chemical and Toxicological Assistance	115.07
Karl Kitzmiller - Pathological Assistance	17.30
	132.37

MISCELLANEOUS EXPENSE

Traveling Expense -
Trip to Whiting, Indiana August 19th, 1948
Dr. Francis Heyroth 31.94

Proportion of Secretarial, Library, Janitors, Wash Boys,
Draftsman, Shipping Clerks, Animal Caretakers, Histo-
pathological Preparation 34.45

Proportion of Heat, Gas, Electricity, Steam, Gas, Telephone,
Maintenance, Pensions, Annuities etc 35.88

\$234.64

Balance Remaining for Work in 1948
at End of Second Quarter 1948 \$24,496.48

Expenditures 3rd Quarter 234.64

Balance Remaining for Work in 1948 24,261.84

December 1, 1948

Dr. Robert A. Kehoe
University of Cincinnati
Kettering Laboratory of Applied Physiology
College of Medicine
Eden Avenue
Cincinnati 19, Ohio

Dear Doctor Kehoe:

Pursuant to recommendation accepted by the Institute's Medical Advisory Committee, at meeting held in Chicago on November 12, 1948 and in accordance with understanding reached in letters to and from you under dates of October 28 and November 5, 1947, we are enclosing check in the amount of \$2,500 payable to the University of Cincinnati as contribution towards development of information on fluorine and fluorine compounds.

Very truly yours,

DVS:d

Enclosure

cc: Mr. William E. Boyd, Jr.
Dr. A. E. Hoag and Members
of Medical Advisory Committee
Mr. Lacey Walker

UNIVERSITY OF CINCINNATI
CINCINNATI 19, OHIO

MBC

December 2, 1948

RESEARCH LABORATORY OF APPLIED PHYSIOLOGY
COLLEGE OF MEDICINE—EDEN AVENUE

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: UNIVERSITY 2665

Mr. D. V. Strop, Jr.,
American Petroleum Institute,
50 West 50th Street,
New York City 20.

Dear Mr. Strop:

I herewith acknowledge with thanks receipt of American Petroleum Institute's check in the amount of \$2500.00, covering expenditures to be made on behalf of the fluorine investigation.

Very truly yours,

E. F. Fortlage
E. F. Fortlage, Secretary to
Dr. Kehoe

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