FILE NAME: Oil Industry and American Petroleum Institute (API)

DATE: 1954 July-Dec

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DOCUMENT DESCRIPTION: Letters, Memos, Reports, Financial Reports & Other Relevant Documents from July-Dec, 1954

BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF THE POTENTIAL CANCER HAZARD OF THE

PETROLEUM INDUSTRY

SPONSORED BY THE MEDICAL ADVISORY COMMITTEE

of the

AMERICAN PETROLEUM INSTITUTE

July 1, 1953 - June 30, 1954

Salaries (Based on proportion of time actually spent on project)		
Direct Salaries	$38,500.00	
Indirect Salaries		
Histopathological Preparation	$ 5,000.00	
Other Services	$28,450.00	
		$ 71,950.00
Miscellaneous Expense		
Purchase of Animals	$ 2,500.00	
Special laboratory supplies	$ 6,800.00	
Travel	$ 5,000.00	
Overhead (Proportion of heat, gas, electricity, steam, telephone, general laboratory supplies, postage, annuities, pensions, maintenance, etc.)	$17,823.00	
		$ 32,123.00
Total		$104,073.00

BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF THE POTENTIAL CANCER HAZARD OF THE

PETROLEUM INDUSTRY

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AMERICAN PETROLEUM INSTITUTE

July 1, 1953 - June 30, 1954

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

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

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

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

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

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

.....

Indirect Salaries include Histopathological Preparation and other services.
Miscellaneous Expense includes purchase of animals, special laboratory supplies, and travel.

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

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

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

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

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

V. Epidemiological Program

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

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

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

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

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

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

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

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

July 2, 1954

To Members
Medical Advisory Committee

Gentlemen:

Chairman George M. Saunders has noted Dr. Eckardt's letter of June 22, 1954, copies of which were sent to all members, and has requested me to set a dead-line for the receipt of comments or objections on the publication of the manuscript entitled "Carcinogenesis of the Skin, I".

Accordingly, we shall assume you have no objection to publication unless your specific objection is received by Dr. George M. Saunders, with carbon copy to me, on or before July 31, 1954.

Very truly yours,

DVS:js

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

July 6, 1954

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

Dear Mr. Stroop:

I am returning to you herewith four copies of the agreement between American Petroleum Institute and University of Cincinnati, which have been executed by the Board of Directors of the University. I should appreciate your returning two copies to us when they have been signed by representatives of American Petroleum Institute.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

ef

Enc.

API 05877

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

June 23, 1954

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1955, according to the terms of the agreement dated January 8, 1946, and on the basis of a maximum budget for operating expenses of $72,250.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $36,125. The balance of $36,125, less the unexpended balance in the fund on June 30, 1954, will be paid on January 1, 1955.

It is understood that any balance remaining in the fund on June 30, 1955 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 Frank M. Porter
President

By
Secretary

Accepted and Approved:

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By Renton K. Brodie
Renton K. Brodie, Chairman

By Ralph C. Bursiek
Ralph C. Bursiek, Clerk

API 05878

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

June 23, 1954

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1955, according to the terms of the agreement dated January 8, 1946, and on the basis of a maximum budget for operating expenses of $72,250.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $36,125. The balance of $36,125, less the unexpended balance in the fund on June 30, 1954, will be paid on January 1, 1955.

It is understood that any balance remaining in the fund on June 30, 1955 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 Frank M. Porter
President

By [signature]
Secretary

Accepted and Approved:

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By Renton K. Brodie
Renton K. Brodie, Chairman

By _____
Ralph C. Bursiek, Clerk

API 05879

file: Medical Advisory Committee - UNIV. OF CINCINNATI Expenditures

June 23, 1954

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

Dear Doctor Kehoe:

Enclosed you will find four copies of the continuation agreement covering API Medical Research Project M-1 for the fiscal year ending June 30, 1955.

As Secretary Lacey Walker will be out of town until July 6, we suggest that you have the contracts signed on behalf of the University and return them to us so we may send you our check for the first half of the budget for the next fiscal year.

We shall send you two copies of the agreement as soon as they are signed by Messrs. Porter and Walker.

Very truly yours,

DVB:js
Enclosures (4)
cc: George M. Saunders, M. D.
Lacey Walker

API 05880

June 23, 1954

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1955, according to the terms of the agreement dated January 8, 1946, and on the basis of a maximum budget for operating expenses of $72,250.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $36,125. The balance of $36,125, less the unexpended balance in the fund on June 30, 1954, will be paid on January 1, 1955.

It is understood that any balance remaining in the fund on June 30, 1955 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 _____

By _____

API 05881

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

July 8, 1954

AIR MAIL

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

Dear Dr. Eckardt:

Reference is made to your letter of June 22 in which you request approval of the report on the activities of the Subcommittee on Carcinogenicity which is to be submitted to Dr. G.M. Saunders. Upon rereading the memorandum of the April 27th meeting of the Operating Subcommittee of the Medical Advisory Committee, it is indicated that the Medical and Health Committee has asked that each report on the subcommittee contain a statement which would not only define the scope of the project and its justification, but also a prediction of the anticipated benefits to the oil industry.

In light of this request, I believe that as chairman you might add a statement which would describe the benefits which the study undertaken by the Subcommittee on Carcinogenicity is expected to accomplish for the oil industry.

Other than for this suggestion, I approve of the report which the Subcommittee on Carcinogenicity has prepared under your direction.

I will be happy to assume chairmanship of your subcommittee for its next meeting, Friday, September 10, at the Conrad Hilton Hotel in Chicago.

Very truly yours,

C. H. Hine, M.D., Ph.D.
Consulting Toxicologist

CHH/jck
bc: T.B. Albin
H. Gershinowitz
J.R. Morrison
T.B. Rendel
G.M. Saunders
D.V. Stroop

API 05882

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

July 12, 1954

MR. MATTOCKS FILE

Mr. David V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I herewith acknowledge with thanks receipt of a continuation of agreement dated June 23, 1954, between the American Petroleum Institute and the University of Cincinnati, together with their check in the amount of $36,125 covering expenditures to be made on their behalf.

Very truly yours,

E. R. Fortlage, Secretary to
Dr. Kehoe

ef/phd

API 05883

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee
July 12, 1954

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

June 30, 1954

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

Dear Mr. Stroop:

I am sending you herewith the minutes of the fifteenth meeting of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council of Great Britain (MRC.54/454) forwarded from Colonel Auld. I thought you might want to have this duplicated and distributed to the members of the Medical Advisory Committee.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk
Encl.

C
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Y

MEDICAL RESEARCH COUNCIL

For Specified (Normal Committee) Circulation

MRC.54/454

COMMITTEE OF THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the Fifteenth Meeting, held at 38 Old Queen Street, London, S.W.1, on Thursday, 29th April, 1954, at 4.00 p.m.

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

Attended: Dr. B. S. Lush.

An apology for absence was received from Professor R. D. Passey.

127. Minutes

The Minutes of the previous meeting were approved and signed.

128. Progress Report by Professor Cook (CAMO.54/1)

Professor Cook said that Dr. Carruthers had been concentrating on two particular sub-fractions and, using methods agreed with Professor Morton, had been making aromatic extracts. From these aromatic extracts he had isolated 2:7-dimethylanthracene and 2:3:6-trimethylanthracene and two other anthracene hydrocarbons which had not as yet been identified. It was not known whether any of these compounds were carcinogenic, but this was the first occasion on which the first two had been isolated from petroleum. The average molecular weight of these compounds appeared to be about 220. This was not inconsistent with Professor Morton's estimate that the average molecular weight of the fractions was about 300, since aromatic compounds tended to have higher boiling points than aliphatic.

129. Progress Report by Professor Morton

Professor Morton had circulated copies of his preliminary report prior to the meeting. In explanation of the nomenclature he said that the samples designated by the letter "D" were from the K_4S fraction. The suffix "R" indicated a raffinate, and the suffix "E" the aromatic extract. Professor Morton added that not too much reliance should be placed upon the figures given because the method had not yet been confirmed as applying accurately to the samples which they had been investigating. For example, the proportion of aromatics appeared to be unusually high, but this may be due to a high sulphur content. However, this would not be known until the sample had been subjected to a full analysis. He said he hoped that the continous extraction process would soon be in operation.

He recalled that it was originally thought that the Lagunillas fraction, which showed the greatest carcinogenicity, was distilled at an overhead stream temperature of approximately 210°C. At present this cannot be done on the Steadman still without exceeding 300°C in the distillation pot. At the moment he was attempting to modify the still so that this could be achieved, but failing that it might be necessary to distill the Lagunillas fraction on a laboratory scale.

130. Report by Dr. Irwin (CAMO.54/2)

Dr. Irwin said that the figures were not, in fact, new, since they had been submitted at the last meeting of the Committee, but he thought that it was desirable to record them formally. It was significant, he said, that the response to the standard carcinogens by mice and rabbits was different, but their response to the various fractions was similar. It was generally agreed that it was preferable to use rabbits as the experimental animals as their response was more uniform and they are less liable to inter-current infections and other hazards.

131. Progress Report by Dr. Woodhouse and Professor Squire (CAMO.54/3)

Professor Squire emphasized that this report covered thirty weeks only and was circulated in case it should be helpful to the Committee in deciding on their future plans. He said that the log time response curves were reasonably straight, but to be useful for purposes of bio-assay they should also be parallel. They were not yet parallel although they were more so than in previous experiments.

Dr. Hieger asked why it was that the rabbits appeared to be more susceptible in the year 1953-54 than in the year 1952-53. Professor Squire agreed that the response did seem to be greater in the later year, but as the standard carcinogens had been used on each occasion the results were not invalidated since the relative potencies remained the same. Professor Cook thought it was worth while to draw attention to column VII of Table 3 in the report, which showed for the first time in this investigation that carcinogenicity was concentrated in the aromatic fraction. He asked whether the different responses by the mice and rabbits was due to a different response to a single carcinogen or whether there might be another factor - a co-carcinogen or an anti-carcinogen - which affected one species only. Professor Squire said that this could be decided by adding 9:10-dimethyl-1:2-benzanthracene to one of the Kuwait fractions and then applying it to both mice and rabbits. This would then demonstrate whether the carcinogen was different in its action from the dimethyl benzanthracene or whether there was an anti-carcinogen or a co-carcinogen present. Professor Cook said that he had 3 g. K_4S_2b and 9 g. K_4S_6b which contained substantially all the anthracenes. It was agreed that he should send 1.5 g. of the first and 5 g. of the other to Dr. Woodhouse to be used in the September series of tests.

132. Future Plans

Professor Squire said that they were able to do twenty-one tests per year, of which three were standards, leaving eighteen for testing substances. It was agreed that Birmingham should concentrate on the Kuwait fractions and that tests on the Lagunillas fractions should be carried out at Leeds.

Professor Morton undertook to proceed with the distillation and production of extracts from Lagunillas samples which he would send to Leeds for them to apply in a series of animal experiments beginning in January 1955. From the Kuwait fractions he would concentrate on the aromatic extracts K_4S_1A to K_4S_8A, from which Dr. Carruthers would prepare (a) anthracene fractions by maleic anhydride treatment, and (b) a picrate forming concentrate from the remainder. This would mean twenty-four samples, but as only fifteen tests were available (3 of the 18 available were to be used for testing the Glasgow Compounds - Minute 131) he might blend some of the lower aromatic fractions, for example K_4S_1 to K_4S_4.

It was agreed to wait for the preliminary results of the animal experiments on the anthracene sub-fractions before deciding whether it would be necessary to synthesize larger quantities of the anthracenes already isolated and identified by Dr. Carruthers.

Colonel Auld said that he hoped the Lagunillas and Oklahoma oils would not be overlooked in concentrating on the Kuwait oil, since all three were originally selected with great care as representing particular types of oil from various fields. He was also rather disappointed at the apparently slow rate of progress and wondered whether it would be any help if some of the tests could be undertaken in America where it was now accepted that the fundamental approach by the Committee was the correct one. It was agreed that it would be unwise to ask the Americans to undertake any of the tests because of the difficulties of communication which were already sufficiently awkward between the few centres involved in this country. It was also agreed that it was important to bear in mind the need to investigate the Lagunillas and Oklahoma oils, but this might be easier and done more quickly once the Kuwait oil had been fully studied.

133. Date of next meeting

It was agreed that the next meeting should be held at 11:15 a.m. on Friday, 23rd July, 1954.

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

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

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

July 13, 1954

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

Dear Dr. Saunders:

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

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

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

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

Very truly yours,

R. E. ECKARDT, M. D.

REE:ilk
Attachment

cc: Messrs. J. J. Fleig
A. Shelly Morton
R. A. Kehoe
D. V. Streep

API 05888

THE REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY

TO THE MEDICAL ADVISORY COMMITTEE OF THE API

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

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

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

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

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

1. The Chemical and Biological Work

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

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

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

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

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

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

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

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

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

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

2. Epidemiology

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

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

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

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

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

8

Expenditures of the Subcommittee on Carcinogenicity

1946	$ 6,000.00	
1947	0	
1948	65,000.00	(includes $40,000 grant for animal quarters)
1949	49,413.00	
1950	89,963.39	
1951	59,065.12	
to June 30, 1952	31,692.42	
July 1, 1952 to June 30, 1953	104,760.00	
July 1, 1953 to June 30, 1954	79,000.00	
	$484,893.93	
Budgeted July 1, 1954 to June 30, 1955	$ 72,250.00	

Future Work

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

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

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

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

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

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

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

3. Work on possible carcinogenic inhibitors.

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

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

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

Estimated Budget July 1, 1955 to June 30, 1956

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

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

Another breakdown of these figures can be given as follows:

Salaries

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

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

Composition of Subcommittee

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

E. W. Adams
Standard Oil Company (Indiana)

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

Allan E. Dooley
The Texas Company

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

L. M. Henderson
The Pure Oil Company

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

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

R. C. Mithoff
California Research Corporation

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

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

F. J. Sanders
Standard Oil Company (Ohio)

REE:ilk

June 21, 1954

Copy From D. V. Stroop For Information of Dr. R. E. Roberts - July 15, 1954

July 9, 1954

Dr. Robert A. Kehoe
University of Cincinnati
Kettering Laboratory of Applied Physiology
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Enclosed are two copies of a continuation agreement dated June 23, 1954, which have been signed on behalf of the American Petroleum Institute by President Frank H. Porter and Secretary Lenny Walker.

Also enclosed is a check in the amount of $36,125 to cover one-half of the maximum budget for the fiscal year ending June 30, 1955.

Very truly yours,

DVS:jn
Enclosures (3)
cc: Lenny Walker
George H. Gunsalus, M. D.

API 05897

File: Univ. of Cincinnati Expenditures

July 9, 1954

Dr. Robert A. Kehoe
University of Cincinnati
Kettering Laboratory of Applied Physiology
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Enclosed are two copies of a continuation agreement dated June 23, 1954, which have been signed on behalf of the American Petroleum Institute by President Frank M. Porter and Secretary Lenny Walker.

Also enclosed is a check in the amount of $36,125 to cover one-half of the minimum budget for the fiscal year ending June 30, 1955.

Very truly yours,

DVS:js
Enclosures (2)
cc: Lenny Walker
George H. Saunders, M. D.

P. S. on Lenny Walker's and file copies only.

Mr. Walker:-
Please draw and enclose check to order of University of Cincinnati and charge expenditure to Medical Advisory Fund.

DVS

API 05898

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

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

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

July 16, 1954

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

Dear Dr. Wade:

Your comments concerning the first paragraph of Dr. Horton's and Miss Dunnan's paper on "Carcinogenesis of the Skin I." has created a considerable amount of comment and discussion. There is apparently also some concern about how your comments can be resolved with the Kettering Laboratory.

One suggestion is that the last sentence of this paragraph have the phrase "to mice" added on the end of it. If this change would overcome the objections which you have to this paragraph, I am sure that the Kettering Laboratory would be amenable to this minor change.

If the above change does not satisfy the objections which you have to this paragraph, it would be my suggestion that you rewrite the first paragraph as you would wish to see it worded, and that you submit this rewriting to Dr. Saunders with a carbon copy to Dr. Kehoe (Dr. Horton) to see if the Kettering Laboratory would be agreeable to rewriting the first paragraph as you would wish it rewritten. In the event that the Kettering Laboratory would not agree to your rewrite, it would then appear to me that when this paper is forwarded to the Committee of the Board prior to publication, we could also recommend, as the Medical Advisory Committee, that your rewrite would be preferable to the one that the Kettering Laboratory proposes. The Board Committee would then be in a position to suggest either that the Kettering Laboratory wording or that your wording would be more preferable to them. Naturally, the Kettering Laboratory would be in a position not to concur with the recommendations of the Board Committee, but knowing Dr. Kehoe and others at the Kettering Laboratory, I believe that they would give considerable thought to this if they decided to publish their own wording instead of that preferred by the Board Committee and would undoubtedly have very strong reasons for adhering to their own wording.

I attempted to discuss this with you on the telephone today, but since you were out of your office I thought it could be handled by mail, since I am going on my vacation starting on the 17th and will be out of the office for two weeks. I would be happy to discuss this further if you feel it necessary after I return from my vacation and if it has not already been settled in the meantime.

Sincerely yours,

REE:ilk

R. E. ECKARDT, M. D.

cc: Dr. C. M. Saunders

API 05899

July 6, 1954

Dr. George Saunders, Chairman
Medical Advisory Committee
American Petroleum Institute
50 West 50th Street
New York, New York

Dear Doctor Saunders:

Dr. Eckardt sent us a copy of his letter to Mr. Stroop concerning the proposed publication by Mr. Horton and Miss Denham regarding carcinogenesis of the skin. Most of the suggestions we have made have been properly recognized. We are still of the opinion that the opening paragraph is misleading and not in strict keeping with the facts of the situation. Until such time as a definite clinical correlation has been established between exposure to high boiling aromatic fractions and the occurrence of skin cancer, I believe these animal data are only suggestive.

It is my understanding that Mr. Horton objects to any revision of this paragraph. If one could be sure that the manuscript will stay in strictly professional channels, his objections are well taken. From past experience, however, I feel reasonably sure that this assumption cannot be relied upon to protect us from unjustified employee relations problems.

Very truly yours,

LEO WADE, M. D.

LW:jmk
cc: Dr. R. E. Eckardt
Mr. William Haden
Mr. D. V. Stroop

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

July 21, 1954

AIR MAIL

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

Dear Dr. Eckardt:

I know that you, as chairman of the Subcommittee on Carcinogenicity, will be interested in this article on the effects of benzpyrene when applied to human skin. While the reproduction of the histologic sections leaves something to be desired, I think that you may wish to have it distributed to members of the Medical Advisory Committee because of its general interest.

Very truly yours,

ORIGINAL SIGNED BY

C. H. Hine, M.D., Ph.D.
Consulting Toxicologist

CHH/jck
Enclosure
bc: D.V. Stroop w/encl. ✓
A.W. Hort[illegible] Kettering Lab.
T.B. Albi[illegible]
R.A. Pratt

THE EFFECTS OF 3:4–BENZPYRENE ON HUMAN SKIN

PROF. GIAN BATTISTA COTTINI AND DR. GIAN BATTISTA MAZZONE

(From the Division of Dermatology and Syphilology of the University of Catania, Italy. Prof. F. Flarer, Director)

The carcinogenic potency of 3:4-benzpyrene and other hydrocarbons has been studied in the common laboratory animals, as the mouse, rat, rabbit, chicken, pigeon, and guinea-pig (1), but no attempts to ascertain the reactive capacity of human skin to the carcinogenic agents have been recorded. It was believed, therefore, that a study of this aspect of the problem would be of interest. Three considerations are of prime importance in this type of experiment: the extreme caution which must be exercised, the correlation with established clinical concepts, and the evaluation of the data obtained.

Regarding the safety of the treated individuals, possible complications may be forestalled by daily observation. As circumscribed and readily accessible areas of the body are utilized, the potential danger is minimized by the ease with which the area can subsequently be excised if necessary.

The approach to the experiment as a problem in clinical dermatology is different from that of the experimental investigator. Tar is one of the most commonly employed remedies in such skin conditions as psoriasis, lichenoid eruptions, kraurosis, and prurigo, and is frequently applied for long periods and not rarely in a concentrated form. Neoplasia as a result of such applications has never been observed.

Related to the purely experimental aspect of the problem are the investigations of Haddow and Robinson (2) and of Morelli and Gaastalla (3). These authors described an inhibitory effect of benzpyrene on the growth of transplanted tumors. Injections of the hydrocarbon caused diminution of the rate of tumor growth or regression of established tumors. Regressive phenomena also occurred after local applications to proliferating external neoplasms. Such observations suggest the possibility of therapeutic application of the hydrocarbons in malignant disease.

Although in view of the considerations enumerated above the treatment appeared relatively harmless, it was thought advisable for the early experiments to select adults or those of advanced age affected with such serious or fatal disorders as pemphigus or mycosis fungoides, or patients with advanced neoplastic disease, as squamous cell or basal-cell cancer, melanoma, or xeroderma pigmentosum, or with eruptions known as being amenable to tar therapy, as psoriasis or porokeratosis. When the action of benzpyrene in this group was ascertained, the observations were extended to younger individuals with less serious conditions. The resulting data are necessarily commensurate with the limited scope of the experiment, which sought to disclose the following:

1. The gross changes produced by benzpyrene in normal human skin.
2. The possible relation of the changes to the type of skin or the age of the subject.

3. The histologic changes in the treated areas.
4. The effect on various spontaneous lesions involving the skin.

Classification of Patients

The following conditions were represented in the 26 patients treated with benzpyrene: pemphigus vulgaris, 2; mycosis fungoides, 1; porokeratosis, 1; xeroderma pigmentosum, 1; basal-cell cancer, 2; squamous-cell cancer, 5; lupus erythematosus, 2; psoriasis, 3; syphilis in various stages, 7; ringworm, 2.

According to age, the patients were distributed as follows: less than twenty-five years, 5; between twenty-five and fifty, 12; more than fifty, 9.

Procedure

A 1 per cent solution of synthetic benzpyrene (Roche) in benzol was applied to protected and unprotected surfaces of the skin, generally the thigh and the upper extremity. In isolated instances slight friction was utilized in a circumscribed zone after application of a 1 per cent solution in olive oil. The diameter of the treated area did not exceed 2 cm., and care was exercised to [illegible] successive applications to the original site. At the conclusion of this treatment a fragment of skin was excised and examined histologically; the remainder was observed for possible late effects. Practically all patients received daily applications, a maximum of 120 being given in a period of four months. All patients were hospitalized. In several instances treatment was administered on alternate days. The carcinogenic potency of the benzpyrene was ascertained by means of skin paintings in the mouse.

Effect on Normal Skin

A progressive, relatively constant series of alterations developed in normal skin following applications of benzpyrene. In chronological order they were: erythema, pigmentation, desquamation, formation of verrucae, and infiltration.

Erythema: Clinically perceptible erythema occurred in only 2 patients with basal-cell cancer, who were more than fifty years of age. In the vast majority any erythematous reaction was either transitory, ill-defined, or obscured by the residue of yellow benzpyrene crystals deposited after evaporation of the solv[illegible]

Pigmentation: This occurred in all patients. It was strictly limited to the treated area, but was more evident in the central than in the peripheral zone. The time of appearance was variable. The earliest observation was after the twentieth application in unprotected normal skin of patients more than sixty years old with basal-cell or squamous-cell cancer. In patients between twenty-five and fifty years, with syphilis, mycosis fungoides, lupus erythematosus or porokeratosis it developed after the thirtieth application and in the youngest patient, with ringworm, after the forty-fifth. The change consisted in an increase in melanin in the basal layer of the epidermis. Rarely, small masses of pigment granules were found in the more superficial layers.

A number of factors appeared to be of importance in this respect. Pig-

FIG. 1. EFFECT PRODUCED BY 56 DAILY APPLICATIONS OF BENZPYRENE TO THE UNPROTECTED SKIN OF THE FOREARM IN A MAN OF SEVENTY YEARS

Note the pigmentation, accentuated skin markings, and beginning desquamation.

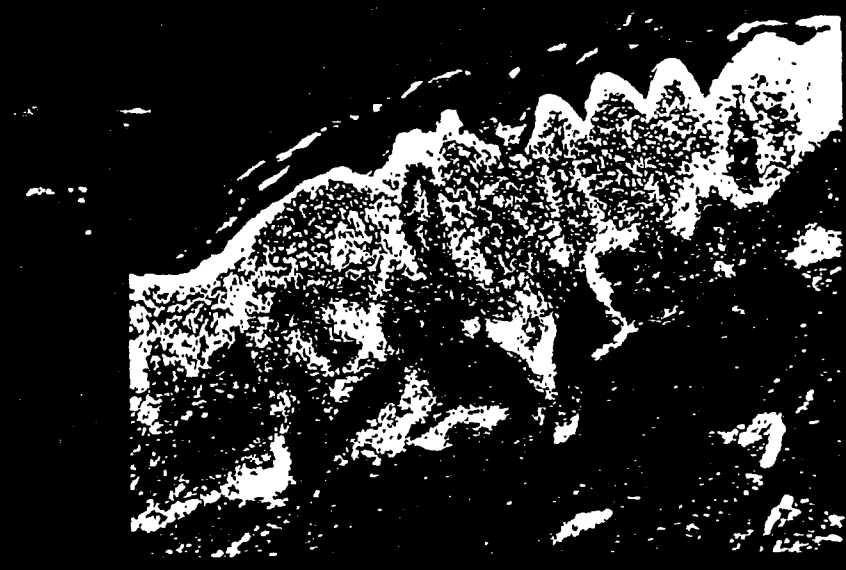

FIG. [illegible] POWER VIEW OF REGION ON THE DORSUM OF THE HAND IN A MAN OF SEVENTY YEARS AFTER 56 DAILY APPLICATIONS OF BENZPYRENE

mentation appeared earlier and was more evident in unprotected portions of the skin surface, as the dorsum of the hand or the face, where the effect of light rays, mechanical stimuli, and irritation was associated with the specific action of benzpyrene. It developed more readily in the skin of senile individuals, especially if atrophic changes were present, than in younger subjects, in whom the skin appears more capable of elaborating neutralizing mecha-

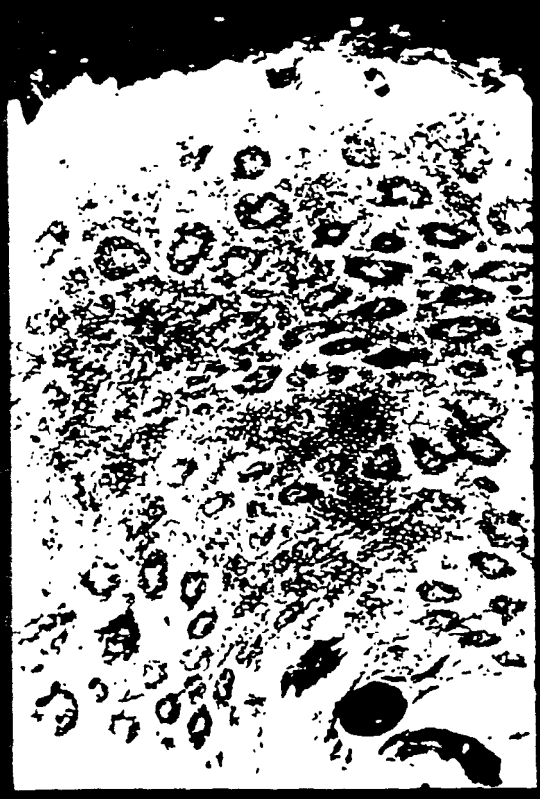

FIG. 3. HIGHER MAGNIFICATION OF FIG. 2, SHOWING PROLIFERATION IN THE EPIDERMIS

nisms. It was more pronounced in dark-skinned than in light-skinned persons. The nature of the primary skin ailment was without significance.

Desquamation: Desquamation, when it occurred, was slight in amount and resembled that of pityriasis. It was proportional in extent to the erythema of the first stage and generally more conspicuous on the unprotected skin. In one patient of advanced age with porokeratosis and a second with basal-cell cancer, desquamation manifested itself by the formation of superficial but adherent scales which, when detached, left a bleeding surface. In some instances desquamation was accompanied by pruritus.

Formation of Verrucae:[1] This was the most constant manifestation produced by benzpyrene. Verrucae developed late and disappeared rapidly after cessation of treatment. They occurred in practically all patients, either accompanying or directly succeeding the stage of pigmentation. Verrucous lesions were observed earliest in older individuals, but no relationship between the time of their appearance and the primary skin condition was detected. Of special interest was the occurrence of a network of papilliform elevations in a young, dark-skinned patient. The lesions, comparable with those of verruca

[1] Although clinically the lesions were not true verrucae, they are for convenience considered as such. It would be more accurate to describe the alteration as an accentuation of the relief pattern of the skin secondary to a deepening of the sulci.

vulgaris, regressed rapidly and disappeared completely one month after treatment was suspended.

Infiltration: In 2 patients of advanced age with cutaneous cancer and in one with porokeratosis signs of infiltration were perceptible on unprotected skin surfaces or in parts affected by senile atrophy after eighteen treatments. Infiltration did not occur in other subjects despite intensive treatment with the hydrocarbon.

In one patient in whom evidence of infiltration was observed, benzpyrene was applied to the thin, dry, atrophic and pigmented skin on the dorsal surface of the fourth interosseous space of the left hand. Erythema, pigmentation and verrucae developed after eight, twenty, and thirty days respectively. The lesion which ultimately resulted was a well defined, superficial and indolent

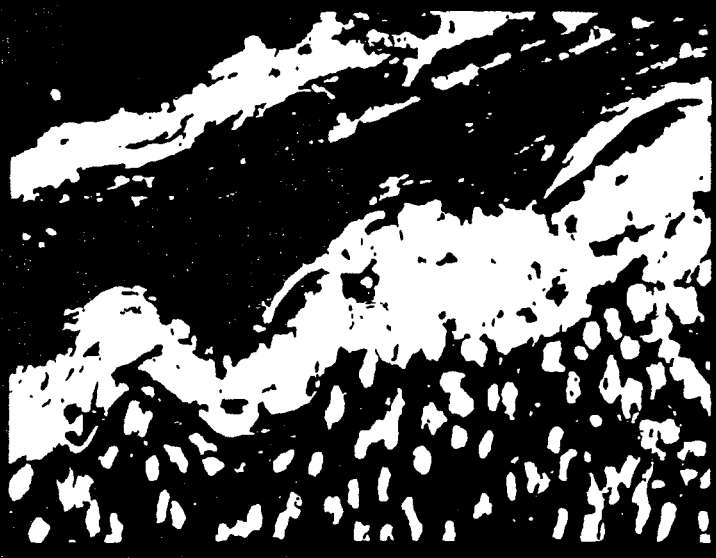

FIG. 4. DETAIL OF FIG. 2. PROLIFERATION IN THE STRATUM GRANULOSUM WITH BEGINNING DYSKERATOSIS.

placque resembling a strip of parchment, without adhesion to the deeper layer of the corium.

The histologic nature of the process at the cessation of treatment and fifteen days later was identical. Essential changes were limited to the epidermis. In the superficial layer of the dermis there was infiltration with polymorphonuclear leukocytes, chiefly about the dilated and tortuous blood vessels, sweat and sebaceous glands and hair follicles (Fig. 2). The epidermis showed evidence of acanthosis (Fig. 3), and the rete formed an irregular succession of prolongations into the corium. The stratum corneum was widened and contained zones of parakeratosis. Cellular proliferation was present in the stratum granulosum, rendering this layer more conspicuous than normally (Fig. 4). The cells of the stratum spinosum were enlarged and vesicular, the intercellular bridges widened and the intercellular spaces clearly demarcated.

Enlarged vacuolated cells were common. The basal layer of cells, however, was unaffected. No evidence of nuclear abnormalities nor of an absence of the clear demarcation of epidermis and derma was observed. In some areas the products of inflammation in the corium extended into the surface layer.

The pronounced acanthosis and the potential invasive power of the lesion made further application of benzpyrene hazardous. The benign course of the process in the following eight months, however, substantiated its non-malignant character.

Comparable early infiltrative lesions with subsequent regression were observed in 2 additional patients, but more complete observations were rendered difficult by local phenomena of intolerance and hypersensitivity.

The average time required for complete regression of the manifestations

FIG. 5. BULLOUS LESIONS IN A PATIENT WITH PEMPHIGUS, PRODUCED BY 20 APPLICATIONS OF BENZPYRENE IN TWENTY THREE DAYS

produced by benzpyrene was two months. The lesions generally disappeared in the reverse order of their appearance.

In summarizing the effects of benzpyrene on the normal skin, it may be said that the two most constant alterations were pigmentation and the formation of verrucae. Erythema, desquamation, and infiltration, although rare, were most common in unprotected areas of atrophic senile skin. Sex was of no consequence.

EFFECT ON ABNORMAL SKIN

The effects of benzpyrene in several patients with pemphigus vulgaris and in one with xeroderma pigmentosum differed from those described in the previous section. It is perhaps logical to assume that the uninvolved skin in pemphigus or xeroderma is potentially the site of future manifestations of the disorders.

In the 2 cases of pemphigus, benzpyrene, after 20 applications, precipitated a local bullous eruption (Fig. 5) comparable in appearance and course with the eruption of the spontaneous disease. The bullae were preceded by slight pigmentation and pruritus. The specific effect produced by benzpyrene probably is related to a characteristic sensitivity of the skin in pemphigus (Nikolsky's sign). Pure benzol produced no reaction.

Of special interest are the observations in a child of four years, in good general condition but having xeroderma pigmentosum, multiple squamous-cell cancers of the face, and a melanoma of the right cheek. After 85 applications of a solution of benzpyrene to the deltoid and abdominal regions, and to the unprotected skin of the dorsum of the hand, where the symptomatic triad of xeroderma was evident, only pigmentary and minimal verrucous manifestations developed. The induced lesions regressed, and the parts were unchanged after two years.

In contrast to the relative innocuousness of benzpyrene was the more intense reaction following exposure of the lumbar region to ultraviolet irradiation for two minutes at a distance of 0.5 meter. Intense erythema developed, following which there appeared raised pigmented patches alternating with flat

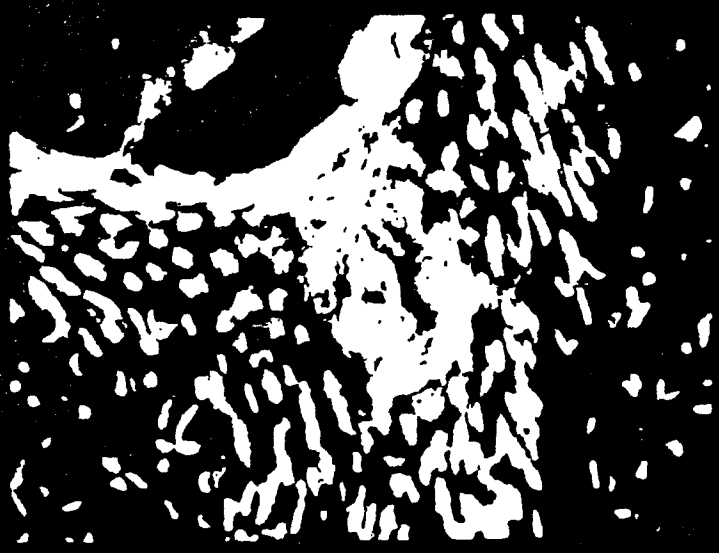

FIG. 6. UNUSUAL TYPE OF GIANT-CELL FORMATION IN THE REGION OF A HAIR FOLLICLE IN A PATIENT OF TWENTY-EIGHT YEARS WITH RINGWORM, AFTER 44 APPLICATIONS OF BENZPYRENE. UNPROTECTED SKIN OF FOREARM.

depigmented zones. The skin became dry and scaly. The intensity of this reaction did not diminish after two months. Corresponding with the grossly perceptible papular lesions, hyperplasia with hyperkeratosis, parakeratosis, and dyskeratosis, and hyperpigmentation were visible microscopically. Less advanced changes, without dyskeratosis, were observed in areas treated with benzpyrene.

It is difficult to ascribe the difference in reaction to ultraviolet light and benzpyrene in xeroderma to any known factor or specific change in the disease. Theoretically it is possible that some metabolic disturbance (porphyrin) may be responsible for a relative resistance to one agent and a hypersensitivity to the other. The effect of ultraviolet light on skin previously treated with benzpyrene was not investigated, as dangerous complications were feared. The two irritants, however, were combined inadvertently, since benzpyrene

was applied to exposed skin surfaces. No significant differences from the effect of benzpyrene in other portions of the body were observed.

The histologic changes, like the gross lesions, were closely related to the age of the patients rather than to the nature of their skin disorders, their general condition or sex, as follows:

I. In patients less than twenty-five years of age:

(1) Minimal irregularities in the superficial strata of the epidermis, with a tendency to the formation of epithelial outgrowths in the region of the hair follicles.

(2) Hyperkeratosis with occasional formation of small cornified masses at the openings of the hair follicles.

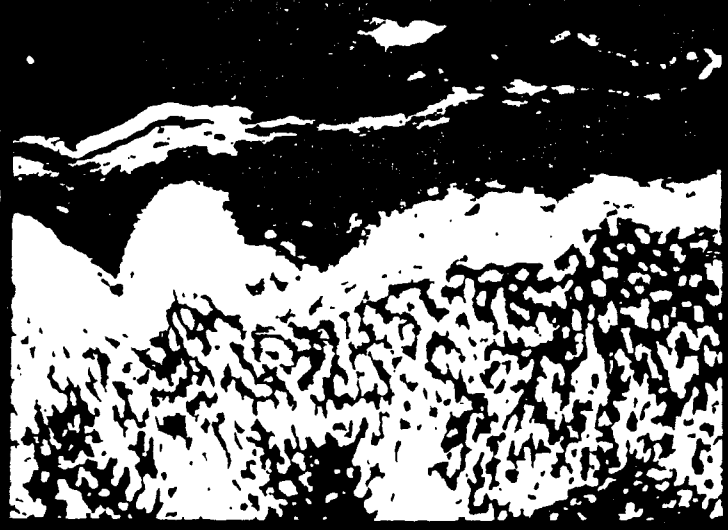

FIG. 7. CHANGES IN THE STRATUM GRANULOSUM OF UNPROTECTED SKIN SURFACE IN A PATIENT OF TWENTY NINE YEARS, WITH ACTIVE GUMMA, AFTER 40 APPLICATIONS OF BENZPYRENE IN FORTY TWO DAYS

(3) Inconstant vacuolization of cells in the stratum spinosum.

(4) Increase in melanin in the basal layer.

(5) Inflammatory changes in the papillary portion of the corium about the hair follicles and sebaceous glands.

(6) Occasional cellular irregularities and giant-cell formation at the openings of the hair follicles (Fig. 6).

II. In patients between twenty-five and fifty years of age: Variations from the changes in the younger group were minimal. In patients with active gummatous lesions of the skin more accentuated manifestations were observed:

(1) Focal proliferative lesions in the stratum granulosum. The width, however, did not exceed that of five layers of cells (Fig. 7). Nuclear abnormalities were not observed, but there was acanthosis.

(2) More intense inflammation in the derma.

III. In patients older than fifty years: All changes were more intense. Advanced lesions in several cases have been described.

Special studies of the cutaneous nerves were not made. Basophilic infiltration was not encountered.

Effect of Benzpyrene on Active Skin Lesions

The action of benzpyrene on the following processes involving the skin was observed: ulcerated squamous-cell cancer, basal-cell cancer, tumor manifestations of mycosis fungoides, desquamating form of psoriasis and porokeratosis.

Ulcerated Squamous-cell Cancer: An ointment containing 1 per cent benzpyrene was applied daily to an ulcerated growth in the case of multiple tumors associated with xeroderma. The initial effect appeared to be favorable, but treatment was discontinued after 30 applications, when no definite retardation in growth was evident. The hydrocarbon did not accentuate the malignant nature of the process. Similar results were obtained in a case of roentgen-ray cancer in a man of sixty years. The benzpyrene in addition exerted a prolonged analgesic effect. The destructive action of tar on nervous tissue in animals may be a related phenomenon.

Basal-cell Cancer: No gross or histologic changes were observed in several cases of basal-cell cancer after 87 treatments with benzpyrene.

Mycosis Fungoides: Lesions in the tumor stage in the iliac, thoracic and brachial regions regressed incompletely after daily applications of benzpyrene for two months. The treated areas appeared less cyanotic, and the external surface less irregular. Further regression did not occur with continued treatment. Associated with the changes were the pigmentary and verrucous manifestations commonly produced by the hydrocarbon. Non-treated areas of mycosis fungoides in other portions of body progressed and ulcerated extensively. Biopsies unfortunately were not available.

Desquamating Psoriasis and Porokeratosis: Desquamation appeared to be hastened after 15 treatments. The residual erythematous lesions, however, remained unaffected, and the exfoliative manifestations of the primary eruptions recurred. Histologic evidence of complicating processes was not evident after 50 applications of the hydrocarbon.

Syphilis: The accentuation of the skin reactions in patients with gummatous lesions has been described above. This phenomenon may bear a relationship to the assumption, frequently expressed, that syphilis acts as a predisposing factor in the spontaneous development of neoplasia.

Conclusions

1. Daily skin applications of a 1 per cent solution of benzpyrene in benzol in 26 human subjects for variable periods, not exceeding four months, resulted in definite manifestations localized to the treated areas. Erythema, pigmentation, desquamation, the formation of verrucae and infiltration developed in chronological order. Pigmentary and verrucous lesions were the most commonly observed changes. The gross and microscopic characteristics of each stage are described.

2. Following the suspension of treatment after a maximum of 120 applications or when evidence of infiltration appeared, the manifestations regressed completely within two to three months. Although reversible and apparently benign, the changes undoubtedly represented early stages of a process which would have ultimately gone on to neoplastic proliferation. In a broad sense they may be designated as prototypes of a precancerous process.

3. The alterations were more pronounced in older than in younger individuals, and on the unprotected skin surfaces. The reaction of young patients with active gummatous lesions was comparable to that observed in the older group.

4. In patients with pemphigus vulgaris benzpyrene produced a bullous eruption comparable in appearance and course to the spontaneous disease. The protected and unprotected skin of a patient with xeroderma pigmentosum, while extraordinarily sensitive to ultraviolet irradiation, did not react characteristically to benzpyrene.

5. Treatment with benzpyrene of ulcerated squamous-cell cancer of the skin was followed by temporary amelioration. In one instance an analgesic effect was observed. Limited retardation of the progress of mycosis fungoides lesions in the tumor stage occurred in one case after local application of benzpyrene. Basal-cell cancer and desquamating lesions of psoriasis or porokeratosis were unaffected.

6. The assumption appears warranted that benzpyrene, if applied to human skin for protracted periods, would be carcinogenic as it is in animals.

NOTE: All patients were seen by the authors at the end of April 1939. In none were changes found at the site of the benzpyrene applications.

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2. HADDOW, A.: Nature 136: 868, 1935.
HADDOW, A., AND ROBINSON, A. M.: Proc. Roy. Soc. ser. B 122: 442, 1937.
3. MORELLI, E., AND GUASTALLA, A.: Boll. lega ital. p. l. lotta contro il cancro 14 (10): 110, 1936.

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee July 21, 1954

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

July 13, 1954

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

Dear Dr. Saunders:

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

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

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

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

Very truly yours,

R. E. ECKARDT, M. D.

REE:ilk
Attachment
cc: Messrs. J. J. Phair
A. Wesley Horton
R. A. Kehoe
D. V. Stroop

THE REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY

TO THE MEDICAL ADVISORY COMMITTEE OF THE API

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

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

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

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

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

1. The Chemical and Biological Work

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

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

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

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

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

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

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

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

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

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

2. Epidemiology

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

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

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

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

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

Expenditures of the Subcommittee on Carcinogenicity

1946	$ 6,000.00	
1947	0	
1948	65,000.00	(includes $40,000 grant for animal quarters)
1949	49,413.00	
1950	89,963.39	
1951	59,065.12	
to June 30, 1952	31,692.42	
July 1, 1952 to June 30, 1953	104,760.00	
July 1, 1953 to June 30, 1954	79,000.00	
	$484,893.93	
Budgeted July 1, 1954 to June 30, 1955	$ 72,250.00	

Future Work

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

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

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

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

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

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

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

3. Work on possible carcinogenic inhibitors.

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

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

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

Estimated Budget July 1, 1955 to June 30, 1956

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

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

Another breakdown of these figures can be given as follows:

Salaries

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

Miscellaneous Exp.

Animals	$ 1,250	
Supplies	5,000	
Travel	4,000	
Overhead	10,750	
		21,000
		$65,000

Composition of Subcommittee

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

E. W. Adams
Standard Oil Company (Indiana)

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

Allan E. Dooley
The Texas Company

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

L. M. Henderson
The Pure Oil Company

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

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

R. C. Mithoff
California Research Corporation

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

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

F. J. Sanders
Standard Oil Company (Ohio)

REE:ilk

June 21, 1954

APPENDIX A - 2

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

June 22, 1954

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 17, New York

Dear Mr. Stroop:

On June 19, 1954, the following members of the Subcommittee on Carcinogenicity met at the Kettering Laboratory in Cincinnati to discuss the manuscript by A. Wesley Horton and Dorothy T. Denman entitled "Carcinogenesis of the Skin, I."

R. E. Eckardt, M. D., Chairman
C. H. Hine, M. D.
W. E. Scovill, representing Dr. Osborn and Dr. Sanders
L. M. Henderson
A. E. Dooley, representing Dr. Newquist and himself
E. K. Linder

Prior to the meeting of this group, I had received communications from all the other representatives of the Subcommittee indicating no objection by any member of the Subcommittee to the publication of this manuscript from a policy standpoint. Individual members of the Subcommittee had submitted certain suggestions to Dr. Horton for his consideration, and the representatives of the Subcommittee were advised that he is taking these comments into consideration and introducing all of those with which he is in agreement, prior to submitting the paper to the publisher for publication.

The following changes were recommended by the Subcommittee and will be incorporated into the manuscript before submission:

(1) A footnote identical with that attached to the previous manuscript from Dr. Horton and his associates acknowledging support of the API will be attached to this paper.

(2) The word "experimental" will be inserted between the words "basic" and "methods" in the title of the paper.

(3) The second sentence of the second paragraph of the paper will be changed to read as follows:

"Certain materials, such as shale oil (1,2,3), which have induced an abnormally high incidence of cancer of the skin of men as a result of repeated exposure to their occupation, have been found capable of producing epitheliomas in the skin of mice."

(Continued)

As indicated, Dr. Horton will introduce an additional three literature references in the bibliography on page 29 of the manuscript.

(4) Dr. Horton was not agreeable to the rewriting of the first paragraph of this paper since it is the stated purpose of the Kettering Laboratory that their interest in this problem is only insofar as it will lead to the development of information which will be of help in the estimation of the extent of the potential hazard of skin cancer in certain industries, which include not only the petroleum industry but also the coal tar industry and others. The Kettering Laboratory quite clearly recognizes and so states in the first paragraph that the determination of the relative carcinogenic potencies of various materials is only part of the determination of the potential hazard. It is, however, their belief that in industries or segments of industries which do not have adequate medical and industrial hygiene facilities of their own to determine adequately the extent of exposure, the Kettering Laboratory will be requested to complete the picture and make a full estimation of the potential hazard. For this reason they feel that the first paragraph of this paper as written in the manuscript accurately states their position in regard to skin cancer and they are not, therefore, willing to change the wording of this opening paragraph.

By copy of this letter to each of the members of the Medical Advisory Committee, I am requesting that they be informed of the action of the Subcommittee and request that they indicate any objections to publication of this paper directly to Dr. Saunders so that he may express the opinions of the Medical Advisory Committee concerning this manuscript at the time that he submits it to the Medical and Health Committee of the Board for their review.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

cc: Members of the Medical Advisory Committee

APPENDIX A - 3

ESSO STANDARD OIL COMPANY
15 WEST 51ST STREET
NEW YORK 19, N. Y.

July 20, 1954

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

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

Dear Dr. Eckardt:

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

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

Sincerely yours,

/s/ Leo Wade

LEO WADE, M. D.

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

Copy From D. V. Stroop For Information of Members - Medical Advisory Committee July 21, 1954 APPENDIX B

15 July 1954

REPORT OF SUBCOMMITTEE ON FLUORIDES

G. M. Saunders, M. D. - Chairman
W. H. Barcus
L. E. Curtis, M. D.
A. C. Pabst

The introduction of HF alkylation caused the petroleum industry to be confronted with the question of health hazards arising from the operation of HF alkylation units as affecting man, animals, and plant life. In January, 1946, considerable hysteria arose among farmers and residents in the industrial regions of Southern New Jersey relative to potential and alleged crop damage. Prior to this and in the central part of the United States, the aluminum industries had experienced great difficulty with fluorosis of cattle grazing in the vicinity of aluminum plants. Accordingly, the A.P.I. Subcommittee on Fluorides was formed to study the matter from the standpoint of the petroleum industry.

One of the first efforts of the Subcommittee was to seek a scientific organization that would undertake such studies. After considerable investigation it was found that the Kettering Laboratory was already working on fluorides, the project being sponsored by five companies handling HF or fluorides to the extent of $17,000.00 per year. The five companies extended an invitation to A.P.I. to participate in the work and made available all previous data and reports on the project. A.P.I. agreed to contribute $2,500.00 per year (on a year-to-year basis) and thus received the benefit of an extensive investigation at a nominal cost. Payments of $2,500.00 per year started in 1947 and have been continued to the present time. During 1953-54 the fluoride project at Kettering Laboratory, University of Cincinnati, was sponsored by ten companies or organizations, total contributions amounting to $28,310.00. American Petroleum Institute yearly contributions amount to $2,500.00 and payment was made in June 1954 for the twelve-month period ending 30 June 1955.

Investigations carried out during the past year include:

1) Urinary excretion of fluorides by subjects exposed to HF laden air.

2) Urinary excretion of fluorides ingested as sodium fluoride. Two individuals with evidence of renal dysfunction stored 76-81% of ingested fluoride whereas three normal individuals stored only 30-35% fluoride.

3) Rabbit experiments to evaluate effectiveness of sodium pyruvate as an antidote for acute fluoride poisoning. Some inhibiting effects were noted.

4) Rabbit studies on intratracheal injections of aqueous suspensions of fluoride bearing dusts.

5) Radiological studies of 50 persons residing for 20 years or more in Lake Preston, South Dakota, where drinking water contains 6 ppm of fluoride. No increase was detected in radiopacity of the bones in 48 persons, and only very slight increase in remaining two.

The American Petroleum Institute has contributed to the above project for some seven years, and it is believed this has aided in the accumulation of useful knowledge on fluoride compounds. During this period, the petroleum industry has gained much practical experience in the use and handling of HF so that today studies on fluorides are of considerably less importance than they were seven years ago. In view of this, it is the recommendation of the Subcommittee that consideration be given to the termination of this activity at the close of the current period, June 1955.

/s/ G. M. Saunders

APPENDIX C

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee July 16, 1954

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

July 14, 1954

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

Dear Dr. Saunders:

I respectfully submit the report of the Subcommittee on the Physiology of the Skin to the Medical Advisory Committee. You will note that our Subcommittee recommends that the API solicit funds in the amount of $5,000 for the interval July 1, 1955 - June 30, 1956, in continuing support of this work by the Medical Advisory Committee.

Very truly yours,

R. E. ECKARDT, M. D.

REE:ilk
Attachment

cc: Messrs. R. A. Kehoe
D. V. Stroop

THE REPORT OF THE SUBCOMMITTEE ON THE PHYSIOLOGY OF THE SKIN

TO THE MEDICAL ADVISORY COMMITTEE OF THE API

The Subcommittee on the Physiology of the Skin was created at the 13th Meeting of the API Medical Advisory Committee in response to a request from Dr. Kehoe for support of work that his laboratory was performing on this basic problem. In the original letter from Dr. Kehoe, it was indicated that this work would require approximately $25,000 per year for its continuance, and that he was asking support only to the extent of $5,000, the remaining to be made up from contributions of other interested groups. A committee appointed by B. B. Reeve, M. D., the Chairman of the Medical Advisory Committee, recommended that the API support Dr. Kehoe's work to the amount of $5,000 per year. The first contribution of $2,500 supported this research until June 30, 1952. Since that time, $5,000 annually has been given to the Kettering Laboratory in support of this work.

To date, the Kettering Laboratory has worked on the following projects in connection with this work:

(1) The influence of surface active agents on skin reactions produced in experimental animals by primary irritants and sensitizers.

It is believed that this work may be of value to the petroleum industry since it may suggest certain surface active agents which will be useful in the petroleum industry without increasing the effect of primary irritants or sensitizers on the skin, or, conversely, may point out certain surface active agents which should be avoided by the petroleum industry since they will enhance these primary irritating or sensitizing actions.

(2) Occupational acne.

It is known that occupational skin diseases constitute approximately 13% of all occupational diseases. The factors which influence the production of occupational skin diseases, including occupational acne, may furnish leads to the petroleum industry for their adequate control. This information may be helpful to the study of oil dermatitis proposed by the Lubrication Committee of the API, if and when such a study is undertaken.

(3) Changes in the sweating mechanism in psoriasis and other skin diseases.

The wide geological distribution of the petroleum industry, from the tropics to the arctic, suggests that an understanding of the contribution of the sweating mechanism to skin disease may see wide application in the control of such diseases in the petroleum industry.

(4) Work on evaluation of protective creams.

A portion of this work has already been published by Dr. Suskind in the Archives of Industrial Hygiene and Occupational Medicine. It represents the most scientific work that has ever been performed on protective creams, and has already found applications within the petroleum industry.

(5) Cooperative work of the API carcinogenicity project.

This naturally has direct potential benefits to the petroleum industry. This cooperative work includes the effect of variables on the absorption of materials applied to the skin and the interpretation of microscopic changes produced by co-carcinogens and carcinogens.

It is the recommendation of the Subcommittee on the Physiology of the Skin that the API, through the Medical Advisory Committee, continue to support the basic skin physiology work being performed at the Kettering Laboratory in the amount of $5,000 for the interval July 1, 1955-June 30, 1956. The actual budget for 1954 for this work is $33,000, contributed by 5 other parties in addition to the API. The API contribution is therefore less than 1/6 of the total budget, and the API is one of 6 contributors.

Composition of the Subcommittee on the Physiology of the Skin

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

F. F. Boys, M. D.
Sinclair Refining Company

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

REE:ilk

July 14, 1954

September 14, 1954

Mr. M. J. Rathbone, Chairman
API Medical and Health Committee
c/o Standard Oil Company (New Jersey)
30 Rockefeller Plaza
New York 20, New York

Dear Mr. Rathbone:

As requested in your letter of August 17 to David V. Stroop, the Medical Advisory Committee on September 9 reviewed, discussed, and offered comments on the project proposed and described in R. Cubicciotti's letter of July 19.

The stated purpose of the proposal has been the subject of repeated discussions notably at the joint meeting of representatives in New York on July 16, 1953, when members of the Subcommittee on Cutting Fluids failed to persuade the members of the Lubrication Committee panel that a search for causative agents might be unduly costly and lead to no practical results, from a medical viewpoint.

This led to a tacit agreement on the compromise proposal for the modified project at an arbitrary maximum cost of $20,000.

The Medical Advisory Committee concurred in the compromise agreement despite its persistent belief that the estimated cost of the modified proposal was high in the light of the meager results which could be anticipated on the medical aspects of the dermatoses problem.

During the past year nothing has developed to change the views of the Medical Advisory Committee members. They now reiterate their belief that the project will probably contribute little or nothing to the fund of knowledge on the medical aspects of the dermatoses problem, although we are not in a position to assess any public relations value. However, it is the wish of the Medical Advisory Committee not to obstruct the project, if the Division of Marketing desires to proceed with the work.

Very truly yours,

SIGNED BY George M. Saunders, M. D.
Chairman
Medical Advisory Committee

A REVIEW OF MEDICAL ADVISORY COMMITTEE STUDIES RELATING TO CUTTING FLUIDS

General - The Medical Advisory Committee throughout the ten years of its existence has recognized the prevalence of dermatitus incidental to exposure to oil and products containing oil. Morbidity figures show that 10-15 percent of all industrial disease cases involve dermatitus following such exposures.

1945 - At its organization meeting on May 7 and 8, 1945, the Medical Advisory Committee recommended a study on chlorinated compounds, particularly chlorinated cutting oils. This study resulted in tentative conclusions (November 1945) that:

> "1. Chlorinated paraffins appear to be relatively free from condemnation due to either systemic or dermatological effects.
>
> "2. The likelihood of systemic effects by the use of chlorinated aromatics in cutting oils is remote. There are claims in the literature of adverse dermatological effects.
>
> "3. Suitable precautions should be taken in the selection of workers, the working conditions and hygiene.
>
> "4. The toxicity of carbon tetrachloride is well recognized and therefore should not be used as a cutting oil additive."

1946 - The conclusions reached in 1945 were confirmed and the Medical Advisory Committee expanded its study to include all cutting fluids.

1949 - "For information only - Not for publication" the Medical Advisory Committee had prepared two mimeographed bulletins:

1. "The Cutting Oil Dermatoses - A Critical Review" By Bertrand C. Kriete - Harvard University School of Public Health.

2. "Safeguarding the Use of Cutting Fluids and Coolants" By Roy S. Bonsib - Standard Oil Company (N. J.)

1950-1954 - Medical Advisory Committee studies on cutting fluids were suspended awaiting the development of recommendations under consideration by the Lubrication Committee, Division of Marketing.

---ooOoo---

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee July 16, 1954

SHELL DEVELOPMENT COMPANY
Emeryville, California

July 9, 1954

AIR MAIL

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

Dear Dr. Saunders:

Enclosed you will find reports of the Subcommittees on Economic Poisons and C_9- C_{12} Aromatics. These reports are submitted in accordance with the request of Mr. D. V. Stroop, as outlined in his letter of May 5, 1954.

I have the concurrence of Dr. Curtis with the form and content of the report on economic poisons. Unfortunately, the Subcommittee on C_9- C_{12} Aromatics has had only one meeting, and the report reflects rather arbitrarily my conclusions as to the activities of this subcommittee. I have as of this date submitted the report to the other members of the subcommittee. If these members have serious objections to the contents, I will review them and perhaps modify the report. I trust that this will not be necessary, but I would like to reserve the right to alter this second report in some measure, if necessary.

Very truly yours,

/s/ C. H. Hine

C. H. Hine, M. D., Ph.D.
Consulting Toxicologist

CHH/jck
Enclosures

Report of the Subcommittee on C_9- C_{12} Aromatics
to the Medical Advisory Committee of
the American Petroleum Institute

July 1954

I. Objectives

1. To assess the potential health problems associated with C_9- C_{12} aromatics.

2. To investigate the desirability of conducting industrial hygiene and toxicological studies concerning C_9- C_{12} aromatics.

II. Scope and Accomplishment

1. Past Accomplishments

Consideration of possible health problems associated with the C_9- C_{12} aromatic fractions from petroleum solvents was first given by the Subcommittee on Permissible Concentrations at the seventh meeting (1948) of the Medical Advisory Committee. At that time it was pointed out that there was a paucity of data concerning the industrial hygiene and toxicology of these compounds that it would not be possible to prepare suitable toxicological reviews. The Medical Advisory Committee therefore agreed to sponsor a toxicological investigation of representative compounds in this group. A sum of $10,000 was voted to support these studies, and preliminary arrangements were made with the Department of Pharmacology at the Baylor University School of Medicine in Houston, Texas.

However, at the ninth meeting of the Medical Advisory Committee, the funds allotted for this study were diverted to support of the more pressing problems of the study of carcinogenicity. It was the feeling of some members of the Medical Advisory Committee that the potential problem presented by these compounds did not warrant investigation. No further action was taken on this problem until 1952, when a survey of Committee members, conducted by Dr. R. E. Eckardt of the Standard Oil Development Company, indicated that eight members showed an active interest in re-examining this problem. Further interest was elicited at the seventh meeting of the Medical Advisory Committee, when several case reports of injury and death following exposure to C_9- C_{12} aromatics were presented. Subsequently, a subcommittee was appointed to study and report recommendations on this problem.

2. Present Activities

The first meeting of the Subcommittee on C_9- C_{12} Aromatics was held on April 26, 1954. The subcommittee decided that in order to assess potential health problems, a review should be made of the incidence of undue exposure and intoxication allegedly caused by both individual compounds and mixtures of C_9- C_{12} aromatics. A questionnaire was prepared and sent to medical officers of petroleum companies in the API in order to develop this information. The results of this survey are not yet available.

III. Future Plans and Recommendations

1. The subcommittee reports that at this time it does not have in its possession sufficient data to adequately attain its objectives. Consequently, it recommends that it continue its effort to develop additional information.

2. Should the subcommittee uncover sufficient evidence to recommend that the Medical Advisory Committee support experimental studies, it will submit a budget requirement for the year 1955-56 in the amount of approximately $20,000.

IV. Benefits to the Petroleum Industry

It is the subcommittee's opinion that investigation of this problem will more adequately assess the potential health problems associated with C_9- C_{12} aromatics. The increased use of these solvents and the proportionately greater quantities of varied constituents make it highly desirable for the petroleum industry to be cognizant of the problems associated with their use.

V. Members of the Subcommittee

C. H. Hine, M.D. (Chairman)
Shell Development Company

R. D. Bent
Atlantic Refining Company

J. W. Crookshank, M.D.
Cities Service Refining Company

Kieffer Davis, M.D.
Phillips Petroleum Company

A. E. Dooley
The Texas Company

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

C_9 - C_{12} AROMATICS COMMITTEE REPORT

A review was made of the incidence of undue exposure and intoxication allegedly caused by both individual compounds and mixtures of C_9 - C_{12} aromatics. A questionnaire was sent to the medical officers of the petroleum companies in the API and the opinions of experts in the field of industrial health were solicited in order to develop this information.

On the basis of fragmentary and inconclusive evidence that was obtained, it became necessary to classify the hazard associated with C_9 - C_{12} aromatics as similar to that of benzene.

However, it is the feeling of the subcommittee that the actual hazard is probably of a lower order than that of benzene, and it is therefore the recommendation of this subcommittee that the Medical Advisory Committee sponsor a research program to establish the magnitude of this hazard in comparison to benzene or n-hexane.

It is further recommended that monies in the amount of $20,000 be appropriated for support of this program for a period of one year. It is finally recommended that other interested groups be contacted to determine the desirability of entering a joint research program in this matter.

SHELL DEVELOPMENT COMPANY

EMERYVILLE, CALIFORNIA

August 9, 1954

TELEPHONE OLYMPIC 3-2100

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

Gentlemen:

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

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

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

Very truly yours,

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

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

API 05934

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

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

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

August 18, 1954

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

Dear Mr. Stroop:

I am sending you a copy of a letter which I would appreciate your attaching as a cover letter to Dr. Horton's and Mrs. Denman's manuscript, the stencils for which you have recently received from Dr. Kehoe. Would you please see that this letter and the manuscript are distributed to each of the members of the Subcommittee on Carcinogenicity and also to each of the members of the Medical Advisory Committee. Thank you for your cooperation.

Sincerely yours,

R. E. Eckardt.

R. E. ECKARDT, M. D.

REE:ilk

Encl.

P.S. I am also enclosing 10 copies of the revised manuscript with the alternate page 1.

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

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F. J. Sanders

Gentlemen:

Attached to this letter is the revised manuscript of the paper by Dr. Horton and Mrs. Denman entitled: CARCINOGENESIS OF THE SKIN. I. Basic Experimental Methods Employed in Testing Complex Hydrocarbon-Type Tars and Oils, and the Development of a Quantitative Scale to Express Their Relative Potencies for Mice.

You will note that Dr. Kehoe has suggested an alternate page 1 for this manuscript. I would greatly appreciate it if each of you would communicate with Dr. Hine and express your preference either for the original page 1 or the alternate, which is attached. With your information, Dr. Hine will then be in a position to recommend to the Medical Advisory Committee that our subcommittee approves this paper for publication, either with the original page 1 or with the alternate page 1, depending upon the preferences which each of you expresses to Dr. Hine. Since the meeting of the Medical Advisory Committee is to be held one day prior to the meeting of the Subcommittee, Dr. Hine will need your expressions as to preference for page 1 prior to the 9th of September, 1954. It is my understanding that the paper as a whole has the approval of the Subcommittee for publication and that we will so recommend to the Medical Advisory Committee. It is then assumed that the Medical Advisory Committee will go along with our recommendation and recommend to the Medical and Health Committee of the Board that the paper be published, and that the Medical and Health Committee of the Board will review the paper at its next meeting and indicate whether or not it has any objections to the publication of the manuscript.

Very truly yours,

R. E. Eckardt.

R. E. ECKARDT, M. D.

REE:ilk
Attachment

cc with attachment: Members of the Medical Advisory Committee

API 05936

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

August 18, 1954

Messrs. E. W. Adams
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Very truly yours,

R. E. Eckardt ss

R. E. ECKARDT, M. D.

REE:ilk
Attachment

cc with attachment: Members of the Medical Advisory Committee

Alternate Page One

CARCINOGENESIS OF THE SKIN. I. Basic Experimental Methods Employed in Testing Complex Hydrocarbon-type Tars and Oils, and the Development of a Quantitative Scale to Express Their Relative Potencies for Mice.[1]

by A. Wesley Horton and Dorothy Templeton Denman

The investigation of skin cancer in this Laboratory has been directed toward the appraisal of the potential hazards which arise in industry out of the handling of chemical substances which are known to have, or suspected of having, carcinogenic properties under appropriate conditions. The experiments which have provided the background for this paper have been concerned with the relative carcinogenic potency, for experimental animals, of hydrocarbon-type oils and tars. The data of these experiments are employed herein to the extent that they have contributed to the development of reproducible methods for measuring and expressing such potencies.

Mice were chosen as the primary test species since neoplasms of the skin, comparable in certain respects to those of man in the same tissue, can be reproduced in these animals under suitable experimental conditions (1). Certain materials such as shale oil, which have induced an abnormally high incidence of cancer of the skin of men as a result of repeated exposure in their

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[1] The majority of this work was carried out as part of the American Petroleum Institute Research Project MC-1.

CARCINOGENESIS OF THE SKIN. I. Basic Experimental Methods Employed in Testing Complex Hydrocarbon-type Tars and Oils, and the Development of a Quantitative Scale to Express Their Relative Potencies for Mice.[1]

by A. Wesley Horton and Dorothy Templeton Denman

The investigation of skin cancer in this Laboratory has been concerned with the estimation of the extent of the potential hazard of this disease in certain industries. As in any other aspect of the general field of toxicology, it must be recognized that a specific hazard is the product of several variables, two of which assume dominant importance. These may be termed conveniently the physiological activity of the material or mixture in question, and the conditions of exposure. The latter aspect involves the practices of personal and industrial hygiene. This paper will be devoted primarily to the development of reproducible methods of determining the first variable, the level of activity, or relative carcinogenic potency, of hydrocarbon-type oils and tars.

Mice were chosen as the primary test species since neoplasms of the skin, comparable in certain respects to those of man in the same tissue, can be reproduced in these animals under suitable experimental conditions(1). Certain materials such as shale oil, which have induced an abnormally high incidence of cancer of the skin of men as a result of repeated exposure in their

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occupation (2,3), have been found capable of producing epitheliomas in the skin of mice (4,5). Conversely, in our experience, certain inbred mice, such as the C3H strain, have rarely developed "spontaneous" skin tumors, and have not reacted by skin tumor formation to repeated application of a number of materials, including benzene and white mineral oil, which are presumed to be non-carcinogenic to the skin of man on the basis of extensive practical experience.

The specification, "suitable experimental conditions", in the previous paragraph, was used advisedly. It has become evident that the problem of excessive mortality among the experimental animals, due to the toxicity of the material under examination as well as to the occurrence of incidental disease, cannot be met simply by increasing the number of animals on test. Such an approach ignores the probability that the survivors of these conditions are not at all representative of the population involved, with respect to their susceptibility to carcinogenesis. Hence, stress will be laid upon the necessity for standards of selection and care of the experimental animals which will maintain their health at as high a level as possible.

EXPERIMENTAL METHODS

Most of our work has been carried out with male mice of the C3H strain, purchased from the Jackson Memorial Laboratory, Bar Harbor, Maine. A number of experiments have also been carried out with male mice of the CFW strain obtained from Carworth Farms, but the results were not as reproducible as those derived from the C3H strain. Although the difference in genetic homogeneity

is undoubtedly a factor, the fact that the C3H mice are more docile probably contributes to the reproducibility of experiments in which they are employed. The frequent occurrence of bites and scratches of the skin of the CFW mice, inflicted by their companions, probably results in occasional direct intraepithelial introduction of carcinogens. Added to this complication is the possibility that wound-healing may play an accelerating role in carcinogenesis (6). Current experimentation with Swiss mice from Jackson Memorial Laboratory indicates that, for similar reasons, the males are unsatisfactory animals for quantitative tests. The females of this stock, on the other hand, do not seem particularly pugnacious and, hence, should prove quite useful for this purpose.

The mice were received at six to eight weeks of age and placed under observation for approximately four weeks before use in any experiment. To control infestation of the animals with mites or lice (which when uncontrolled affects adversely their health), the mice were dusted routinely with Aramite[2] by the supplier prior to shipment and then twice again with the same miticide during the period of observation in this Laboratory. Any group in which there was evidence of poor health during this period was withheld from use in tests in which quantitative results were needed.

In all experiments described herein, the mice were fed on Purina Laboratory Chow and water without restriction. At six months of age, C3H mice fed on this diet and subjected to no adverse experimental procedure reach an average weight of about 29 to 31 g., while corresponding CFW mice weigh about 33 to 35 g.

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[2] Aramite - 15W, U. S. Rubber Company, Naugatuck, Conn.

Since growth of both the hosts and their tumors might vary with the temperature of their surroundings, an effort has been made to maintain a relatively constant temperature of 75±2°F. in the animal rooms.

For a given experiment, a group of 20 to 30 mice was divided into three to five cages. The animals were assigned individual numbers for identification and marked by clipping their toes.

The contact of the mice with any given material involved its repeated application upon the interscapular region of their skin. When dosages of 100 mg. of a material were to be applied, the fur was left intact, but when the dosage was to be less than 100 mg., the fur was removed by means of electric clippers. A small camel-hair brush of a selected size to deliver the desired dosage was used to apply the material, which was then simply allowed to spread according to its individual physical characteristics. Applications were repeated in accordance with a predetermined schedule (one, two, or three times each week) until the animals died. Care was taken to keep the dosage and the location of each application as constant as possible throughout the experiment.

Normal growth of the mice could not be maintained in testing certain of the materials, particularly those of high potency, when the experiment involved three applications of the material per week in the dosage of 100 mg. Hence, when there was some physicochemical or biological evidence that a given sample was likely to have a relatively high carcinogenic potency to the

mice (equivalent to that of a solution of 0.15 percent, or greater, of methylcholanthrene in benzene), the material was applied at a lower frequency, usually once each week. In the case of materials of lower potency, more frequent applications were required to obtain tumors in a reasonable length of time. Hence, when the toxicity of such samples proved to be a serious problem at the 100 mg. level, the dose was reduced, in some cases to as low as 5 to 10 mg. per application.

Experience has shown that, even when the mortality among an experimental group was low, the time of appearance of tumors was sometimes delayed seriously by conditions of variable or uncertain origin which also interrupted the normal growth of the animals. As a measure of such conditions, therefore, the mice were weighed at frequent intervals throughout the experiments. Since early observations gave evidence that interruptions of growth were usually the result of intercurrent infections of low severity affecting most of the animals in a given cage, the weighing of individual animals was discontinued in favor of determining the average weight of the survivors in each group. Various precautions, such as regular cleaning and sterilization of cages, feeders and water bottles, decontamination (with a bacteriostatic agent) of gloves used to handle animals from one cage before proceeding to another, and isolation of sick mice, were taken to minimize infections and to prevent their spread from one group to another.

Throughout each experiment, the animals were examined at least once each week by one of us (D.T.D.), and the presence and time of appearance of any abnormal gross changes in the skin were recorded. Epilation and crusting of small areas were frequently

noted and, in the early stages of tests on solutions of greater than 0.2 percent of methylcholanthrene or benzpyrene in benzene, large swellings, of the type previously described by Cramer (7), and small ulcerated areas, were occasionally observed. In response to the application of solutions of these synthetic carcinogens, papillomas eventually developed on the skin of practically all of the surviving animals except when the lowest level of concentration was being tested (0.01 percent). In general, the induced neoplasms progressed through the familiar pattern from papilloma to squamous cell carcinoma, with gross evidence of invasion. In the first test of a given material, sections of all epidermal tumors produced were prepared for microscopic examination.

The date on which each typical papilloma was found to have reached the arbitrary size of 1 mm. in diameter and elevation was recorded as the "time of appearance" of the papilloma. In addition, the date on which it was grossly apparent that the tumor was invading the subcutaneous tissues was noted (rolled border, generally accompanied by cratering necrosis of the center). When a mouse developed such an apparently malignant tumor, it was killed. Usually, the others were maintained on test until death from "natural causes" occurred. The data, thus obtained, were recorded on graphs such as those shown in Figures 1 through 4.

As experience was gained in associating the physical and chemical characteristics of various types of complex materials with their relative toxicity and with their ability to induce tumors of the skin in C3H mice, certain criteria were developed for selecting optimum conditions for any given biological test.

The interpretation of the results of the different experiments was made possible by comparison with external standards of reference, discussed in a later section of this paper. As a general practice, a schedule of application was chosen which would lead to induction of papillomas in an average time of not less than 12 weeks. This restriction was based on repeated observations that the mean time of appearance of tumors was unduly variable in experiments in which the severity of exposure resulted in more rapid induction of tumors. On the other hand, experimental conditions which involved very long periods of time before the appearance of tumors sometimes proved to be even more unsatisfactory than those associated with very short latent periods. The longer the experiment, the greater was the possibility of the occurrence of infection or other unidentified interference with the normal growth of the mice. Even when these interruptions resulted in little or no loss of animals, the irregular effects on the growth of the induced tumors made it very difficult to interpret the results of the experiment. Therefore, as a general rule the frequency and severity of the applications were scheduled to produce an average latent period as close to 15 weeks as possible. When the materials were low in potency, this obviously meant the use of as severe conditions as were compatible with the normal growth and survival of the mice.

INTERPRETATION OF DATA OBTAINED

In general, under the conditions of these experiments one of two results has been obtained in response to the applications of any one of a series of materials, i.e., most of the animals which lived long enough developed tumors of the skin at the site

of the application, or none of them did so. The outcome of the experiments, therefore, has been essentially unequivocal, and the relative potencies of the different active materials could be expressed in terms of the relative rates of induction of tumors.

The calculation of the "mean time of appearance of tumors" involved the determination, by the method of least squares, of the linear function which best fitted the plot of the cumulative frequency of tumor response (in probits) versus the time (in weeks) after the first application. The latter coordinate is equivalent to cumulative dosage. Typical plots of such data are shown on the right side of Figures 1 through 4. It is to be noted that, for these experiments involving repeated applications of carcinogenic materials to the skin, the response varied linearly with time, and not with the logarithm of time. It is assumed that the exponentially decreasing rate of appearance of tumors usually observed following single or limited numbers of subcutaneous injections of carcinogens (8) was not seen in these experiments because the more resistant animals in any given group were given a larger effective dosage than were the more susceptible.

CALCULATION OF CUMULATIVE FREQUENCIES OF RESPONSE

The convention is adopted (after Bliss, 9) that, at the midpoint of the period between two given observations, the number of mice bearing tumors is equal to the average of the numbers at the times of the observations. At the midpoint of each period during which one or more mice develop their first papilloma, a calculation is made of

the cumulative percentage of the "effective group of mice" which bear tumors on that date. The "effective group" at a given time is defined as the sum of the number of survivors plus the number of mice which died previously after developing tumors of the skin, except that after the appearance of a tumor in the "average" mouse this sum is held constant. The "average" mouse is designated by the median in a simple arithmetic array of the times of appearance of the first tumor in each animal.

As an example, the calculations used to obtain the cumulative frequencies of tumor response from the data of Figure 2 are shown in Table I.

CALCULATION OF MEAN TIME OF APPEARANCE OF TUMORS, $\bar{x}$

Experience has shown that, if the frequency of response, r (in probits), is plotted against the time, x, a linear relationship is obtained, e.g., Figures 1 through 4. Therefore, the mean time of appearance of tumors, $\bar{x}$, may be obtained graphically from the best straight line fitted by eye to such a plot. However, we have found that $\bar{x}$ may be obtained by algebraic methods more rapidly and without the subjective aspects inherent in graphical analysis, so long as a suitable calculator is available. The following example shows the calculation of the mean time, $\bar{x}$, from the data of Table I.

TABLE I

TIME[1] OF OBSERVATION OF NEW POSITIVES	MIDPOINT[1] OF PERIOD BETWEEN OBSERVATIONS, x	NUMBER OF NEW POSITIVES, R'	TOTAL NUMBER OF MICE BEARING TUMORS, $R' + \Sigma R^2$	CUMULATIVE RESPONSE, $\frac{\Sigma R + (\Sigma R + R')}{2}$	EFFECTIVE NUMBER OF MICE	FREQUENCY OF RESPONSE, r (probits)
	12.5			0.5	19	3.06 (2.6%)
13		1	1			
	14.5			2.0	19	3.75
15		2	3			
	15.5			3.5	19	4.10
16		1	4			
	16.5			4.5	19	4.28
17		1	5			
	17.5			7.5	19	4.73
18		5	10			
	18.5			11.5	19	5.27
19		3	13			
	19.5			15.0	19	5.81
20		4	17			
	20.5			18.0	19	6.62
21		2	19			

[1] Number of weeks after first application. [2] ΣR is the total number of mice with tumors at the time of previous observation.

1. $r = mx + b$

Determine constants, m and b, by method of least squares (10). Normal equations:

$$\Sigma rx = m\Sigma x^2 + b\Sigma x$$

$$\Sigma r = m\Sigma x + 8b$$ (note that the coefficient of b equals the number of points used)

(Values of x and r are underlined in Table I)

$$656.07 = 2328.0m + 135.0b$$

$$37.62 = 135.0m + 8b$$

$$b = -2.520$$

$$m = 0.428 = \text{slope of dose-response relationship}$$

$$\therefore r = .428x + -2.52$$

2. $\bar{x}$ = time when r equals 5

= 17.6 weeks

s, standard deviation of mean,

= $\bar{x}$ minus time of 4-probit response

= 2.3 weeks.

CLASSIFICATION OF EXPERIMENTAL RESULTS ON THE BASIS OF THE HEALTH OF THE ANIMALS

In the appraisal of data derived from these experiments, consideration has been given to the following apparent relationships between the average growth and survival of the mice and the mean time of appearance of their epidermal tumors.

1. If, in the course of an experiment, an intercurrent infection overtakes a group of mice at about the time when papillomas would be expected to appear (on the basis of other comparable experiments), there is usually a delay in the mean time of appearance of

tumors. The infection need not be lethal to any of the mice, a change in sign of the slope of the average growth curve frequently being an indication of such a condition. It is believed that, in many such instances, the mice would probably be unaffected were their resistance not diminished somewhat by systemic toxic effects induced by the hydrocarbons being applied upon their skin. Thus, untreated controls may not show any symptoms of the infection.

Not infrequently, as the animals recover from such disturbances, tumors grow to measurable size in a large proportion of the animals in a relatively short time. The slope of the plot of the frequency of response versus time is then exceedingly steep (see Figure 2). In other words, the standard deviation of the mean time of appearance of tumors in the group is smaller than the normal range, 3 to 5.5 weeks, for such experiments using C3H mice. Thus, it could be assumed mistakenly, if it were not for the evidence from the weight curves of the presence of uncontrolled variables, that such an experiment had defined the fiducial limits of the mean, calculated from the standard deviation, better than another in which such disturbances had not occurred.

2. In some experiments the cumulative toxic effects of the material applied, or chronic infections, or a combination of both, result in prolonged inhibition of the growth of the mice. A number of examples have been observed in which the average weights have increased for a few weeks, became stationary at a point 10 percent or more below that of adult controls, and then, in many instances, gradually declined (see Figure 3). Whether or not these conditions influence the timing of the initial changes resulting

in the neoplasms, they may retard the growth of the induced tumors to visibly discernible size and, accordingly, lengthen the apparent average period of time required for the induction of tumors by the material under test. In such experiments, the standard deviation of this mean time is frequently much greater than normal.

This somewhat extended discussion of the apparent relationships between the irregularities in growth due to the toxicity of applied materials and to intercurrent infections, and the rate of induction of tumors, does not derive from the originality of this observation but rather from our recognition of its importance in experiments in which various materials are being compared. Occasional mention of the phenomenon has appeared in the literature on experimental carcinogenesis (e.g., 11, 12) and, in the field of chemotherapy of cancer, recognition has been given to the necessity of considering the systemic toxicity of a material in evaluating the specificity of its apparent "anticarcinogenic" effects (e.g., 13). Hence, it is believed that, in the experimental assay of the relative potencies of various materials or of the susceptibility of various species or strains of one species to a given material, information on the health and survival of the groups of animals being compared is essential to any quantitative interpretation of the data.

The results of all experiments described herein have been examined, therefore, in the light of these relationships. Each one has been classified according to the estimated significance of such effects in the following manner.

Class A. Those characterized by normal growth and survival of the mice at least until the time when most of the animals have developed papillomas (see Figure 4).

Class B. Those in which all or most of the mice lived long enough to develop tumors, but in which there was evidence (from average weights) of intercurrent infection at times during the period when the new growths were appearing. So long as recovery from the infection was prompt, and no obvious skewing of the distribution of the times of appearance of tumors occurred, it was felt that reliable estimates of the mean time of appearance could reasonably be made (see Figure 1). However, when no tumors had appeared prior to the onset of an infection, and when, with recovery, tumors developed somewhat precipitously, the reliability of the apparent mean time of appearance was not determinable, and therefore such tests were classified X (see Figure 2).

Class X. Those characterized by poor growth (see Section 2 above and Figure 3) or high rate of mortality. The confidence limits of the apparent mean time for the induction of tumors could not be calculated by standard statistical methods, because of inability to assign proper weight to the effects of the uncontrolled variables.

Experiments involving the application of moderately toxic materials frequently failed to meet the requirements of the Class A category. On the other hand, results of the frankly unsatisfactory type (Class X) were usually found to be avoidable through the exercise of appropriate care in the initial choice and the subsequent handling of the mice.

REFERENCE STANDARDS

To provide a background of reference which might permit a more nearly quantitative interpretation of the mean time of appearance of tumors induced in C3H mice by complex oils and tars under various experimental conditions, a number of experiments have been carried out over the past five years employing solutions of the synthetic carcinogens, 3-methylcholanthrene (MC), benzo[a]-pyrene (BP), and 7,12-dimethylbenz[a]anthracene (DMBA), in various solvents. It has been found that one of the essential requirements for obtaining reproducible and logically consistent results is the maintenance of the animals in a good state of health as measured by growth curves. Thus, in Table II, the results of Experiments 204 show the precision of the determination of the mean time, $\bar{x}$, when Class B experiments are involved. In using volatile materials such as benzene as solvents, occasional checks on concentration of the carcinogens are necessary, with appropriate corrections for evaporation. Similarly, it has been found that even in the case of a complex material, so long as the conditions of the experiments permitted reasonably normal growth of the animals, the repeatability of the determination of the mean time, $\bar{x}$, has been quite satisfactory (within ±10 percent).

To determine the effect on the rate of induction of tumors of variations in the level of concentration and in the frequency of exposure, comparable experiments were conducted with other solutions of MC in benzene, shown in Table II. From certain of these results (Experiments 204, 209, 238, and 243) it is apparent that variation in the quantity of solution used for each application from 20 to 100 mg., other factors remaining constant, had no significant effect on the rate of induction of tumors. Similar results have been observed when solutions of BP in benzene were used as the carcinogenic stimulus. This constancy of potency with variation in the quantity of material applied (or area of skin exposed) also holds for some complex oils and tars, but for others there is significant change of potency with changes in the quantity used for each application. The chemical basis for these differences will be discussed in a later paper.

It has been determined experimentally that variations in the concentration of MC over the range, 0.05 to 0.35 percent, did not affect the average area covered by a given weight of its solutions in benzene. It was further assumed on the basis of the results of experiments 204, 209, 238, and 243 that the dosage of MC per unit area of the skin was not significantly different when 20 or 100 mg. of the same solution were applied. Therefore, the values in column 5, Table II, were calculated directly from the concentration of MC in the solutions and the number of applications per week. Since the amount of MC, in mg., in 100 mg. of solution is equal to the concentration, in percent by weight, the values in column 5 are equal to the products of the values in columns 2 and 4.

TABLE II

EXPERIMENTS INVOLVING THE APPLICATION OF SOLUTIONS OF METHYLCHOLANTHRENE IN BENZENE UPON THE SKIN OF C3H MICE

EXPERIMENT NUMBER	CONCENTRATION OF METHYLCHOLANTHRENE IN SOLUTION (% by weight)	DOSAGE OF SOLUTION PER APPLICATION (mg.)	NUMBER OF APPLICATIONS PER WEEK	DOSAGE OF METHYLCHOLANTHRENE PER UNIT AREA[1] PER WEEK (mg.)	MEAN TIME OF APPEARANCE OF TUMORS, $\bar{x}$ (weeks)	PERCENT OF MICE WITH TUMORS	CLASSIFICATION
206B	0.69	100	3	1.98	6.9 ± 4.2[2]	100	B
205A	0.345	100	3	1.035	11.1 ± 2.0	100	B
204A	0.172	100	3	0.516	16.0 ± 1.7	100	B
204B	0.172	20	3	0.516	16.4 ± 1.1	100	B
204C	0.172	20	3	0.516	16.6 ± 1.2	100	B
204D	0.172	20	3	0.516	15.7 ± 1.1	100	B
243A	0.15	100	3	0.45	18.1 ± 1.8	100	A
243B	0.15	20	3	0.45	18.7 ± 2.0	100	B
203A	0.086	100	3	0.258	30.0 ± 2.3	90	B
203B	0.086	100	3	0.258	26.3 ± 3.4	100	B
205B	0.345	100	2	0.69	15.1 ± 1.5	100	B
238A	0.23	20	2	0.46	18.7 ± 2.3	100	B
238B	0.23	100	2	0.46	16.4 ± 2.0	85	B

[1] Area of skin covered by 100 mg. of solution of methylcholanthrene in benzene.

[2] 5% fiducial limits (14).

TABLE II (page 2)

EXPERIMENTS INVOLVING THE APPLICATION OF SOLUTIONS OF METHYLCHOLANTHRENE IN BENZENE UPON THE SKIN OF C3H MICE

EXPERIMENT NUMBER	CONCENTRATION OF METHYLCHOLANTHRENE IN SOLUTION (% by weight)	DOSAGE OF SOLUTION PER APPLICATION (mg.)	NUMBER OF APPLICATIONS PER WEEK	DOSAGE OF METHYLCHOLANTHRENE PER UNIT AREA[1] PER WEEK (mg.)	MEAN TIME OF APPEARANCE OF TUMORS, $\bar{x}$ (weeks)	PERCENT OF MICE WITH TUMORS	CLASSIFICATION
220	1.034	100	1	1.034	10.1 ± 1.6[2]	100	B
209A	0.517	20	1	0.517	18.7 ± 2.0	100	B
209B	0.517	100	1	0.517	16.2 ± 2.7	100	B
205C	0.345	100	1	0.345	22.4 ± 2.7	100	B
207	1.15	100	3	3.45	9.1	100	X
209C	0.517	100	3	1.551	10.4	100	X
205D	0.345	100	3	1.035	14.8	100	X
219	0.115	100	3	0.345	24.2	96	X
201	0.012	100	3	0.036	72.6	44	X
268	0.287	20	2	0.574	17.6	100	X
206A	0.69	100	1	0.69	17.1	100	X
205E	0.345[3]	100	1	0.345	12.9	100	Z[3]
238C	0.23[3]	100	1	0.23	14.4	100	Z[3]

[1] Area of skin covered by 100 mg. of solution of methylcholanthrene in benzene.
[2] 5% fiducial limits.
[3] Sample of methylcholanthrene used in these experiments contained undesirable impurity (see p.19).

Comparison of the data in columns 5 and 6 for Class A and B experiments shows a consistent inverse relationship between the dosage of carcinogen per unit area per week and the mean time of appearance of tumors. The data are plotted in Figure 5 together with the curve of the corresponding hyperbolic function (calculated by the method of least squares from the data on Class A and B experiments),

$$(\bar{x} - 3.7)(d + 0.10) = 8.2$$

$$\text{or,} \qquad \bar{x} = \frac{8.2}{(d + 0.10)} + 3.7 \quad .$$

It is interesting to note the similarity between this equation and that calculated from the theoretical considerations of the mechanism of carcinogenesis by Iversen and Arley (15),

$\overline{t_{ap}} = \frac{1}{kc_o} + T$, where $\overline{t_{ap}}$ is the mean time of appearance of tumors and c_o the concentration of the carcinogen, k and T being constants.

The constant, 0.10, in the experimental equation might be interpreted as a correction required by the definite, though very small, probability of the "spontaneous" excitation of a cell of the dorsal skin of a C3H mouse to the rate of proliferation necessary for the development of a new growth.

The purity of the polycyclic hydrocarbon is obviously an important consideration in obtaining consistent results. The usual chemical criteria are necessary, but not always sufficient, requirements. In one case in particular, the MC, as received, had a sharp melting point, 176-7°C.(uncorr.).

Yet, on repeated bioassay, it proved to be excessively irritating and much more rapidly carcinogenic than the normal material. The results of Experiments 205E and 238C, using this sample, indicate that the impurity had active carcinogenic or accelerating properties. Tumors developed at a rate expected only with solutions containing 2 to 3 times the concentrations of MC employed.

Unfortunately the quantity of this particular sample available did not permit the determination of the structure of the particular impurity responsible for this effect. The compound apparently constituted less than 0.5 percent of the sample. Therefore, both recrystallization and chromatography on activated alumina have been used in combination in an attempt to guard against this contamination. Bioassay has remained the only sure way of ascertaining that the purified MC is free of significant concentrations of this material.

Similar experiments have been carried out with solutions of two other commonly used carcinogenic hydrocarbons, BP and DMBA (see Table III). As is evident from the data, it has been difficult to obtain satisfactory experiments with BP on C3H mice. The growth of the animals has tended to be extremely erratic. Even in tests in which the average weight eventually reached 30 g., the curve was, more often than not, interrupted at critical times by sharp downward breaks. In these experiments, recovery from these periods of poor health was sometimes accompanied by the appearance of tumors in a large percentage of the animals in a

TABLE III

EXPERIMENTS INVOLVING THE APPLICATION OF SOLUTIONS OF SYNTHETIC CARCINOGENS IN VARIOUS SOLVENTS UPON THE SKIN OF C3H MICE

EXPERIMENT NUMBER	CARCINOGEN	SOLVENT	CONCENTRATION OF CARCINOGEN IN SOLUTION (% by weight)	DOSAGE OF SOLUTION PER APPLICATION (mg.)	NUMBER OF APPLICATIONS PER WEEK	DOSAGE OF CARCINOGEN PER UNIT AREA[1] PER WEEK (mg.)	MEAN TIME OF APPEARANCE OF TUMORS, $\bar{x}$ (weeks)	CLASSIFICATION	RELATIVE CARCINOGENIC POTENCY, P_{MC}
215	DMBA	Benzene	0.115	100	3	0.345	15.6 ± 3.3[2]	B	0.19
214	DMBA	Benzene	0.345	100	3	1.035	7.5 ± 1.1	B	0.73
244A	BP	Benzene	0.172	100	3	0.516	25.2 ± 2.6	B	0.09
244B	BP	Benzene	0.172	20	3	0.516	28.6	X	(0.08)
252A	BP	Benzene	0.322	20	1	0.322	35.3	X	(0.16)
252B	BP	Benzene	0.322	20	3	0.966	23.0	X	(0.11)
252C	BP	Benzene	0.322	100	3	0.966	20.4	X	(0.13)
264A	BP	White mineral oil	0.175	20	3	0.525	25.4	X	(0.09)
264B	BP	White mineral oil	0.175	100	3	0.525	25.5	X	(0.09)
270	BP	White mineral oil	0.35	20	3	1.05	21.6	X	(0.12)

[1] Area of skin covered by 100 mg. of solution of methylcholanthrene in benzene.

[2] 5% fiducial limits.

relatively short time (relationship exemplified in Figure 2). It will also be noted that, even at high levels of concentration, the mean time of appearance of tumors induced by solutions of BP in "non-accelerating" solvents, such as benzene and white mineral oil, in the skin of C3H mice was in no case less than 20 weeks.

USE OF REFERENCE STANDARDS AS A SCALE OF RELATIVE POTENCY OF COMPLEX TARS AND OILS

Various methods of expressing the relative potencies of the pure polycyclic carcinogens and complex materials have been reviewed by Badger (16). Many of these are simply rough classifications based upon a particular investigator's personal experience. The Iball index (17) and a recent technique (18) attempted a more quantitative approach, involving the use of the reciprocal of the mean time of appearance of tumors. Such methods are useful in comparing results obtained in a given laboratory using a standardized and inflexible schedule of application of various materials. However, experimental techniques and other factors differ significantly from one research organization to the next, thus rendering the comparison of data on this basis rather difficult. Further, it is sometimes necessary to alter either or both the frequency of application and the quantity of material applied to obtain satisfactory conditions for the measurement of the potency of a sample while minimizing its toxic side effects. Hence, a scale of relative potencies which would permit such flexibility in experimental design was needed.

The use of the data on relative rates of induction of tumors by various levels of concentration of solutions of synthetic carcinogen, MC, as external standards of reference, provided a practical solution to this problem. Although this hydrocarbon has not been identified as such in complex tars and oils, it might be regarded as representative of the 4- and 5-ringed carcinogens present (19, 20, 21). By use of Figure 5, the mean time of appearance of tumors induced by some complex tar or oil may be translated into a value of Relative Carcinogenic Potency, P_{MC} (potency as compared to MC). The dosage of MC corresponding to the given mean time is either read off the graph or calculated from the equation,

$$d = \frac{8.2}{\bar{x} - 3.7} - 0.10 \quad .$$

Then, the value of the relative potency, P_{MC}, for the complex material in question is

$P_{MC} = d$, for an experiment involving one application each week,

$= \frac{d}{2}$, for an experiment involving two applications each week,

$= \frac{d}{3}$, for an experiment involving three applications each week.

Thus, by comparing the results of tests on complex materials with those involving MC as an external standard of reference, one may obtain the relative carcinogenic potencies of the different materials, even though the experiments may have involved differing frequencies of applications. For example, if the application of two 20 mg. doses of oil A each week to a group of C3H mice results

in the induction of skin tumors in an average time of 20 weeks, the relative potency, P_{MC}, of oil A at the 20 mg. level of dosage is 0.40/2, or 0.20. It should be noted, however, that the potency of some complex oils varies significantly with the quantity used in each application. Hence the description of the potency of a given material cannot be considered complete until it has been tested at two appreciably different dosages, e.g., 20 mg. and 100 mg. per application, unless negative results were obtained at the higher level of dosage in a test in which the mice survived and grew at a normal rate. Because of certain differences in composition, a given oil may be much more potent than another under severe conditions of exposure, but the former may actually have a lower potency than the latter if the comparison is carried out under mild conditions. Chemical research on such oils has led to an understanding of this apparent paradox, and the matter will be dealt with in a later publication.

The technique of relating results on complex materials to those on standard synthetic carcinogens should facilitate comparison of results from different laboratories. The synthetic compound chosen should, of course, be comparable to the type of carcinogens supposed to be present in the complex mixtures. Under appropriate conditions of dosage and frequency of application, it must be capable of inducing tumors at least as rapidly as the most potent of the samples to be tested. For this reason, BP has not proved to be a suitable standard for work with C3H mice, since its solutions in non-accelerating solvents will not induce tumors sufficiently rapidly even at high levels of concentration. On the

other hand, DMBA is very satisfactory from this standpoint, but has the disadvantage of requiring special care in handling to prevent it oxidation to the non-carcinogenic 7,12-photooxide (12).

It should be reemphasized that this consideration of a quantitative scale of potencies applies only to the results of experiments which may be classified as satisfactory from the standpoint of the growth and survival of the mice (A and B by our criteria). Those in our Class X have only a limited value. If positive results are obtained, the material may be classified qualitatively as carcinogenic; if survival is good and most of the mice eventually develop tumors (X classification based on certain irregularities in growth) the estimation of the apparent potency may be useful as a minimum value.

RELATIVE POTENCIES OF POLYCYCLIC AROMATIC COMPOUNDS

Arbitrarily, the relative potency of MC on the P_{MC} scale is 100. By comparing data on the rate of induction of tumors by solutions of known concentration of other aromatic hydrocarbons in benzene under suitable experimental conditions, with data on MC, such as those shown in Table II and Figure 5, it should be possible to arrive at logical estimates of the relative carcinogenic potencies of the different compounds. Numerical values for BP and DMBA may thus be derived from the data of Table III. For example since the P_{MC} for Experiment 214 was 0.62, i.e., 0.345 percent DMBA produced tumors at the same rate as 0.62 percent MC under comparable conditions, the relative potency of the former is

$$P_{MC}^{\circ} = \frac{100}{0.345} \times 0.62 = 180 .$$

From Experiment 215, the relative potency, P_{MC}^{o}, for DMBA is 165. The higher value, 180, is preferred at the present time, since, if autoxidation of the hydrocarbon caused any reduction in activity, it might reasonably be assumed that the effect would have been greater in Experiment 215.

Similarly, the relative potency of BP on this scale is 57 to 65 (Experiments 244A and 252A). The data from Experiment 252B and 252C involving three applications each week cannot be used since apparently the maximum effective dosage of this carcinogen had been reached at a lower level. Thus, as a general rule the determination of the relative potency of any given compound should be based upon the results of experiments at at least two different concentrations, which differed significantly with respect to the mean time of appearance of tumors under otherwise comparable conditions. At least one and preferably both of these should meet our classification A or B from the standpoint of growth and survival.

SUMMARY

Repeated applications of solutions of highly carcinogenic hydrocarbons upon the dorsal skin of male mice of the C3H strain under suitable experimental conditions result in the induction of epitheliomas in essentially all of the exposed animals. Such experiments, involving solutions of 3-methylcholanthrene in benzene, show a consistent inverse relationship between the mean time of appearance of tumors ($\bar{x}$) and the dosage (d) of the carcinogen per unit area of the skin per week.

$$\bar{x} = \frac{8.2}{d + 0.10} + 3.7 \quad .$$

For experiments involving synthetic carcinogens in non-accelerating solvents, such as benzene and white mineral oil, the mean time of induction of tumors is independent of the quantity of solution employed in each application, in the range 20 to 100 mg. The good health of the mice, as measured by their growth, has proved to be an essential factor in obtaining reproducible results.

A quantitative scale for expressing the relative carcinogenic potencies of various synthetic carcinogens and complex tars and oils has been derived, using the experiments on solutions of methylcholanthrene in benzene as reference standards. Utilizing the relationship between the dosage of methylcholanthrene and the rate of induction of tumors shown above, a value for the relative potency, P_{MC}, is obtained. The numerical value of the P_{MC} of a tar or oil is equal to the level of concentration, in percent by weight, of the solution of methylcholanthrene in benzene which would induce papillomas at the same rate as the material in question under comparable experimental conditions. The potencies, P_{MC}^{o}, of pure compounds, relative to that of methylcholanthrene, taken as 100, may be derived in a similar manner. From the data in this paper, the relative potencies of 7,12-dimethylbenz[a]anthracene and benzo[a]pyrene are 180 and 60 respectively.

ACKNOWLEDGEMENTS

The authors are indebted to their associates in the Kettering Laboratory and in the petroleum industry for their many constructive suggestions. Particular thanks are due to Dr. F. F. Heyroth and Dr. R. A. Kehoe for their valued counsel in the planning of the program, to Miss M. J. Graf for the tabulation and statistical analyses of the data, and to Drs. Frank Cleveland and Frank Dutra, who have been responsible for the pathology.

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EXPERIMENTS INVOLVING THE APPLICATION OF MATERIALS UPON THE SKIN OF C3H MICE

LEGEND

Symbols used in connection with average weight curves:

$\overline{\triangledown i}$ Time of death (from disease) of ith tumor-free mouse.

i Time of death (from disease) of ith tumor-bearing mouse.

$\overline{\overline{\triangledown i}}$ or $\overline{i}$ Time mouse killed.

Gross and microscopic pathology:

$\boxed{i}$ Time of appearance of first papilloma in ith mouse. When this symbol is first used for a given mouse after its death, the presence of non-invading carcinoma (intra-epithelial) or small areas of benign neoplasm was determinable only by histopathology.

$\textcircled{i}$ Time of appearance of gross changes indicative of malignancy in tumor of ith mouse. Diagnosis confirmed except in cases where no tissue section available. When this symbol is first used for a given mouse after its death, the invasive malignancy of the tumor was determinable only by histopathology.

$\overset{NS}{\boxed{i}}$ or $\overset{NS}{\textcircled{i}}$ No tissue section available for histopathology.

FIGURE 1

EXPERIMENT 220, SOLUTION OF METHYLCHOLANTHRENE, 1.034 PERCENT BY WEIGHT IN BENZENE

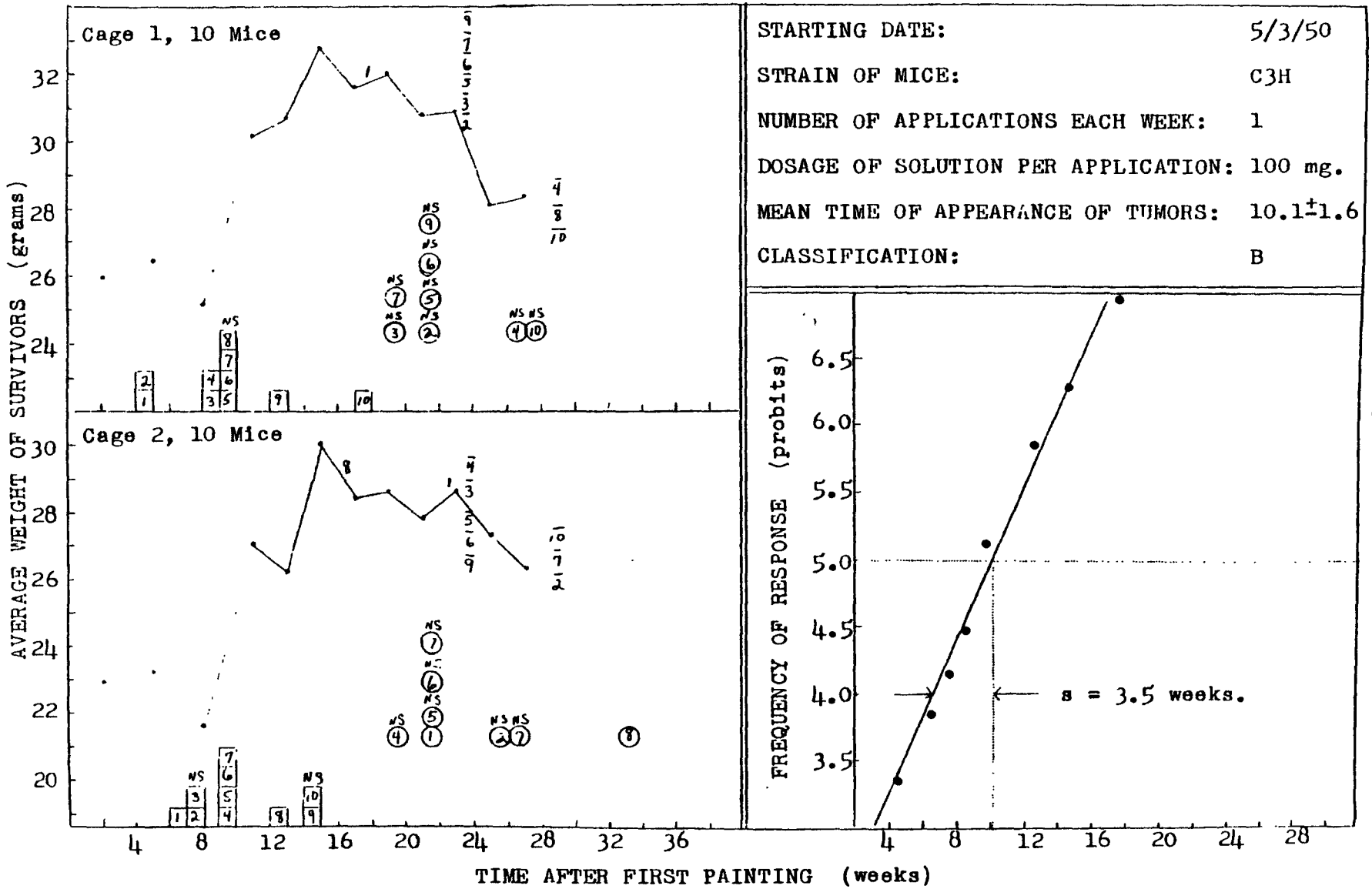


FIGURE 2

EXPERIMENT 268, SOLUTION OF METHYLCHOLANTHRENE, 0.287 PERCENT BY WEIGHT IN BENZENE

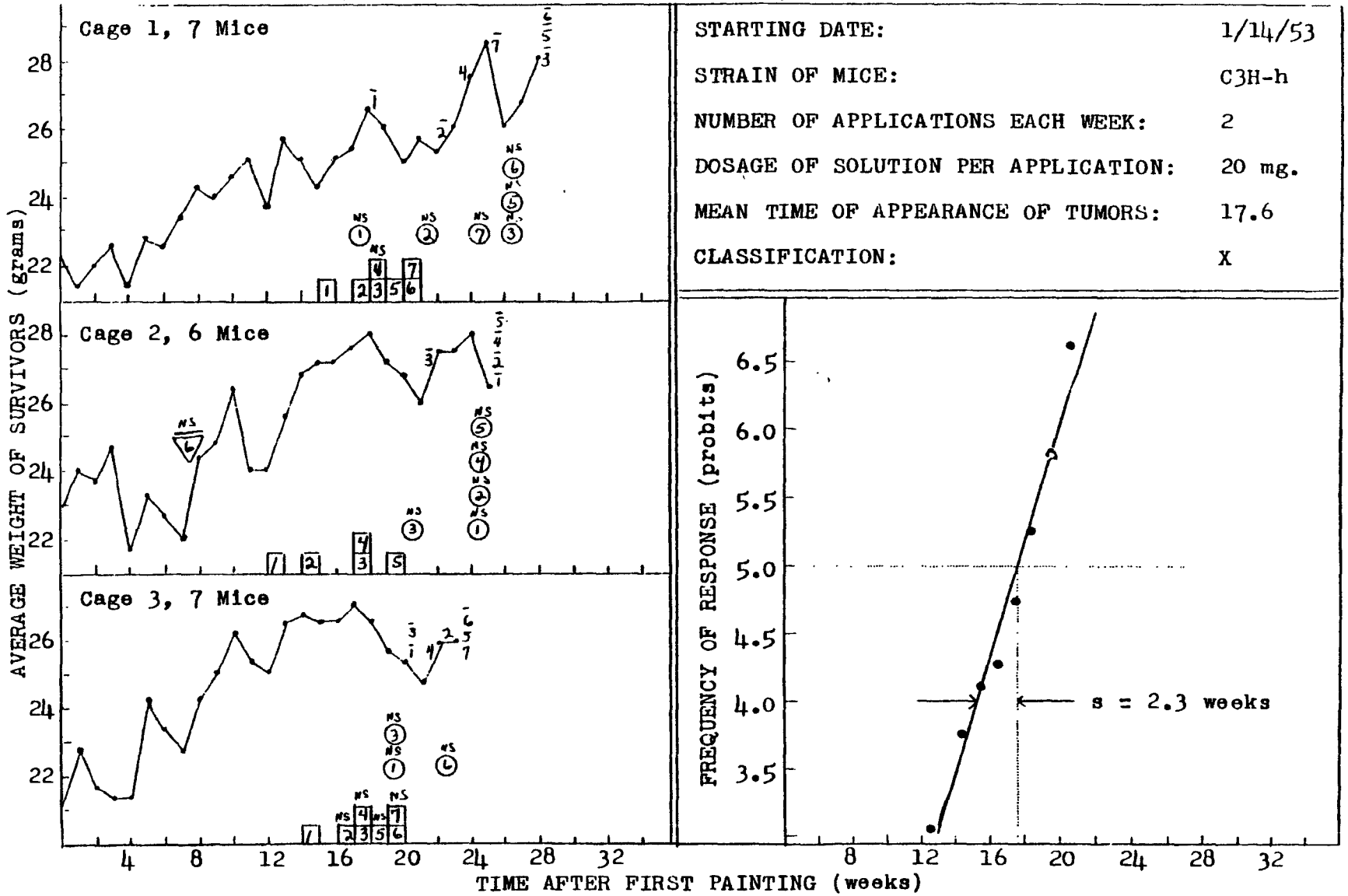


FIGURE 3

EXPERIMENT 284, SOLUTION OF METHYLCHOLANTHRENE, 0.50 PERCENT BY WEIGHT IN BENZENE

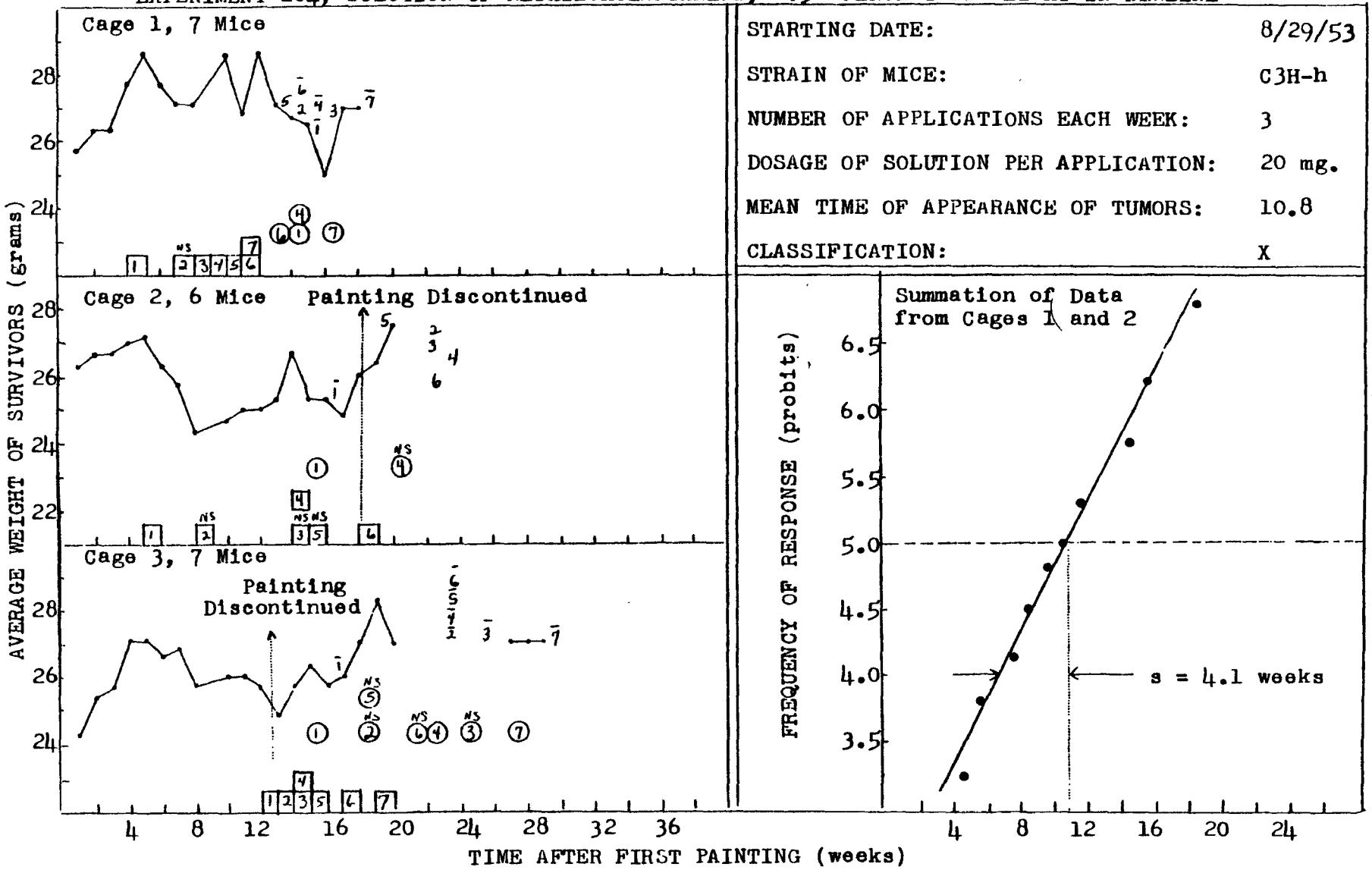


FIGURE 4

EXPERIMENT 243, SOLUTION OF METHYLCHOLANTHRENE, 0.15 PERCENT BY WEIGHT IN BENZENE

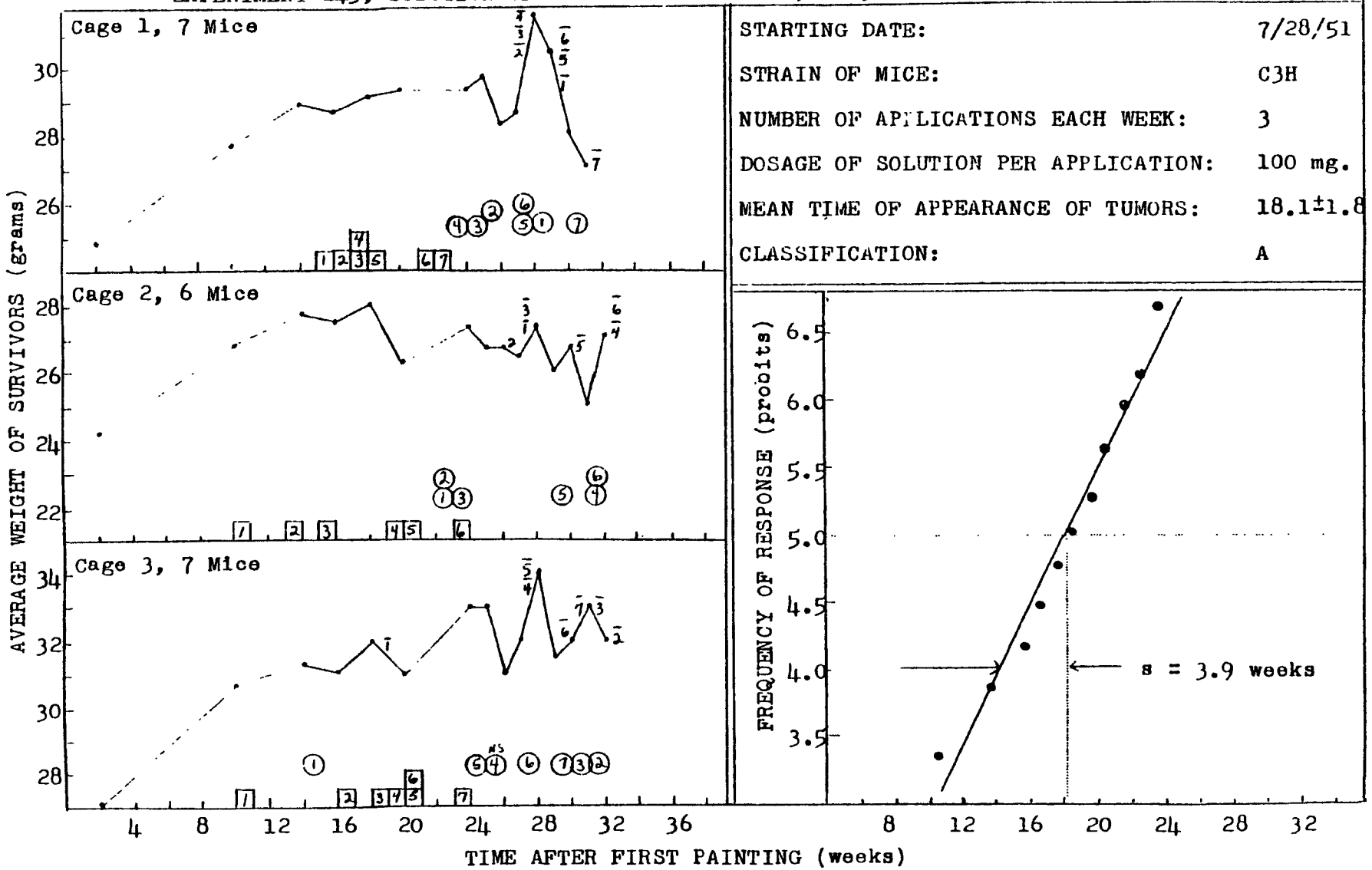
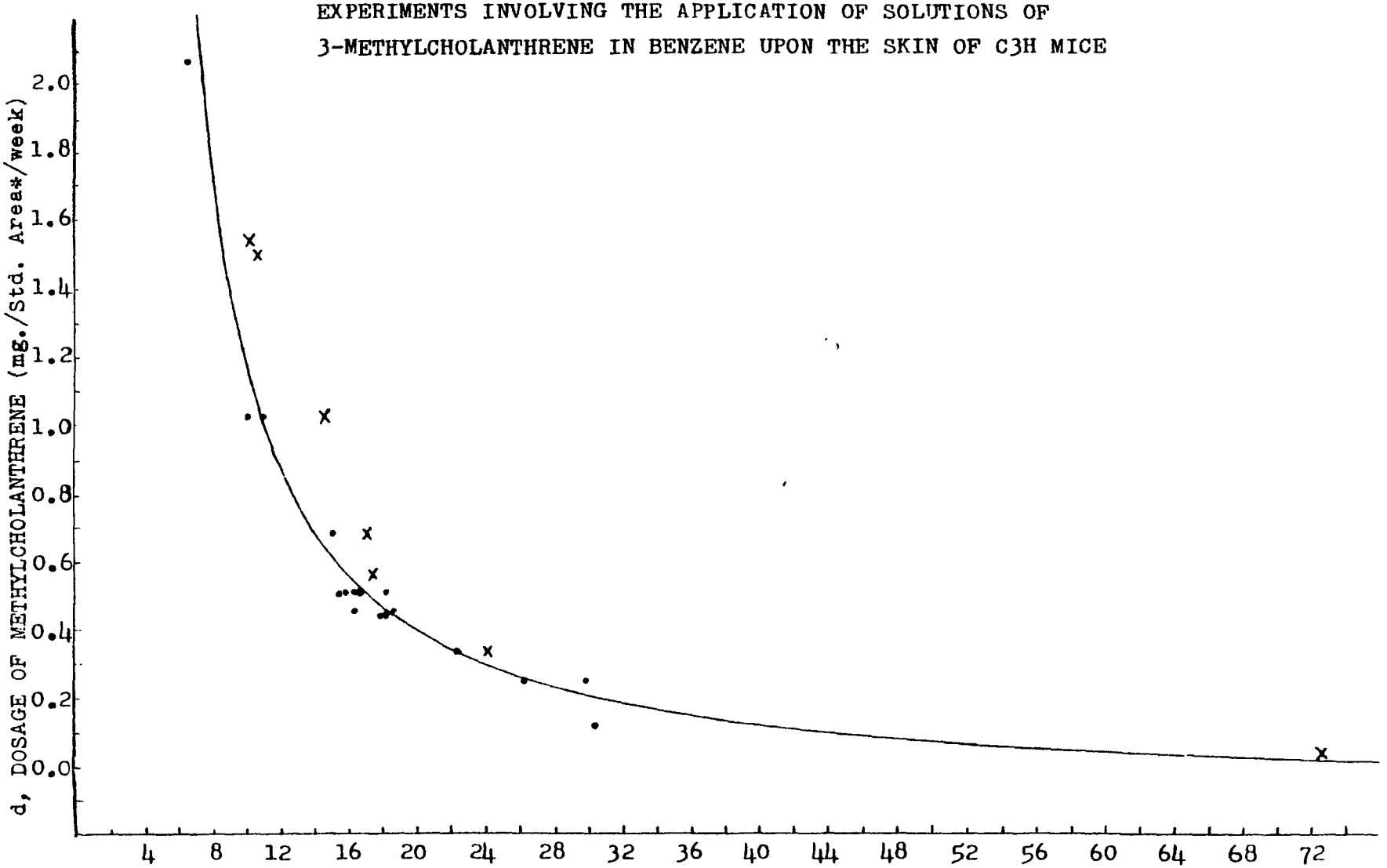


FIGURE 5

EXPERIMENTS INVOLVING THE APPLICATION OF SOLUTIONS OF
3-METHYLCHOLANTHRENE IN BENZENE UPON THE SKIN OF C3H MICE



*Area of skin covered by 100 mg. of solution.

Copy from D. V. Stroop for information of Members of Medical Advisory Committee. August 23, 1954

ESSO LABORATORIES
STANDARD OIL DEVELOPMENT COMPANY
P. O. Box 51
Linden, N. J.

MEDICAL RESEARCH DIVISION
Robert E. Eckardt, PH.D., M.D., Director

August 12, 1954

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

Dear Mr. Stroop:

I have reviewed the information which was forwarded from England and I am sending to you the material which I think should be duplicated for distribution to the members of the Subcommittee on Carcinogenicity.

Of particular importance I believe is item 4 on the Agenda. This suggested that the British may be taking cognizance of the diesel engine exhaust potential problem. It will be interesting to follow their approach to this problem.

I would appreciate it if you would have the attached material duplicated for distribution not only to the members of the Subcommittee on Carcinogenicity but to all members of the Medical Advisory Committee.

Very truly yours,

/s/ R. E. Eckardt

R. E. Eckardt, M. D.

REE:ilk

Encls. Committee on the Carcinogenic Action of Mineral Oils
MRC.54/527, CAMO. Ag. 16
MRC.54/528, CAMO.54/4
MRC.54/529, CAMO.54/5
MRC.54/542, CAMO.54/6
MRC.54/547, CAMO.54/9

MEDICAL RESEARCH COUNCIL

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(Committee members)

MRC.54/527
CAMO.Ag.16

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

A G E N D A

for the Sixteenth Meeting to be held at
11.15 a.m. on Friday, 23rd July, 1954 at
38 Old Queen Street, London, S.W.1.

1. Minutes of previous meeting. (MRC.54/454 - already circulated)

2. Progress Reports.

   Progress report by Dr. W. Carruthers and Professor J. W. Cook. (CAMO.54/4 - Enclosure A)

   Progress report by Professor H. N. Green and Dr. M. J. Redcliffe. (CAMO.54/5 - Enclosure B)

3. Future Plans.

4. Possible Carcinogenicity of Diesel exhaust fumes.

   There is a continuing and growing interest in the possible carcinogenicity of diesel exhaust fumes and it would be of assistance to the Council to have an authoritative statement on the subject. The Committee might also wish to make recommendations about possible future research.

5. Any other business.

6. Date of next meeting.

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MRC.54/528
CAMO.54/4

Committee on the Carcinogenic Action of Mineral Oils

PROGRESS REPORT BY DR. W. CARRUTHERS AND PROFESSOR J. W. COOK

We have continued our examination of the aromatic extracts of the two Kuwait fractions K_4S_2b (b.p. 357½ - 360°) and K_4S_6b (b.p. 377½ - 380°).

As mentioned in the last Report, anthracene hydrocarbons were removed from these fractions by treatment with maleic anhydride, and the recovered 'anthracene-free' oil separated into 'picrate-forming' and 'non-picrate-forming' parts with picric acid in alcohol. The 'picrate-forming' parts, recovered from the crystalline picrates by decomposing them with alkali, have now been further subdivided by chromatography on silica gel and on alumina. From several of the small fractions thus produced small amounts of crystalline substances have been isolated. One of these compounds, from K_4S_2b, has been identified as 1:8-dimethylphenanthrene. Another substance, from the same fraction, has been shown to be a derivative of fluorene, probably a tetramethylfluorene or its equivalent. From fraction K_4S_6b a polycyclic sulphur-containing compound has been obtained. Elementary analysis indicates the molecular formula $C_{15}H_{14}S$, and the ultraviolet absorption spectrum suggests that it is a derivative of the tricyclic condensed thiophene compound 6:7-benzothionaphthene, $C_{12}H_8S$. Further investigation of these and other compounds is in progress.

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Members of Committee)

MRC.54/529
CAMO.54/5

Committee on the Carcinogenic Action of Mineral Oils

PROGRESS REPORT BY PROFESSOR H. N. GREEN AND DR. M. J. REDCLIFFE

Mouse Experiment

This is now in its 25th week.

A large number of tumours have been obtained with 0.2% and 0.05% dimethylbenzanthracene in liquid paraffin, (see mouse life sheets), but of all the oil fractions, f ($K_{4.4}$) alone has produced two definited tumours.

An epidemic of haemolytic streptococcal septicaemia in May was responsible for the death of 60 mice.

As the mice on e (K_4S_8b) were more affected by this than any other group a second series of 50 mice was started on e on 11th June, 1954.

Survivors to date in the various groups are as follows:

a (K_4S_3a) : 34	b (K_4S_3b) : 23	c (K_4S_6) : 29
d (K_4S_6a) : 27	e (K_4S_8b) : 19	f ($K_{4.4}$) : 25
g ($K_{4.4\frac{1}{4}}$) : 46	h ($D\frac{1}{2}$) : 39	i (K_4S_4R) : 31
j (D_2) : 13	k (K_4S_2) : 34	

Rabbit Experiment

This is in its 18th week.

One rabbit died at the 10th week.

So far 5 tumours have been produced.

e (K_4S_8b) has produced 2 tumours, both at site II (R ear) at 12 and 16 weeks; d (K_4S_6a) has produced 1 tumour at site I (L ear) at 15 weeks; c (K_4S_6) has produced 1 tumour at site II (R ear) at 15 weeks; h ($D\frac{1}{2}$) has produced 1 tumour at site VII (Interscapular) at 16 weeks.

MOUSE LIFE SHEETS

SAMPLE J. (0.2% DMB in Liq. Paraffin)

Time in Weeks	No. Surviving	No. with Tumours	
8	46	2	
9	46	3	
10	46	4	
11	45	8	
12	45	8	
13	45	10	
14	44	19	
15	44	35	
16	44	41	
17	40	38	
18	35	33	
19	30	29	
20	28	28	(100%)
21	23	23	
22	23	23	
23	19	19	
24	15	15	
25	13	13	

SAMPLE H. (0.05% DMB in Liq. Paraffin)

11	49	2
12	48	3
13	45	13
14	45	14
15	45	14
16	45	16
17	45	17
18	45	20
19	43	23
20	43	24
21	43	24
22	42	33
23	41	31
24	40	32
25	39	32

SAMPLE F. ($K_{4.4}$)

12	46	0
13	46	0
14	46	0
15	46	1
16	46	0
17	46	0
18	40	0
19	35	0
20	31	1
21	30	1
22	30	1
23	28	1
24	27	2
25	25	2

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee members)

MRC.54/542
CAMO.54/6

Committee on the Carcinogenic Action of Mineral Oils

PROGRESS REPORT NO. XI. (JULY 1954)

by

D. L. Woodhouse

The general observations on the tests at this centre after 44 weeks do not differ materially from those given in the previous report of April 1954 - 30 weeks.

Rabbit Tests

The tumours now present on the rabbits are indicated in Table 1. It will be seen that

(1) Some of the fractions which previously had produced only a few papillomas have now shown some "long term" activity e.g. K4S3A (7 cf. 1) and K4S3 (6 cf. 2).

(2) The paraffinic fraction K4SP has not produced any further papillomas in this period.

(3) On the contrary in one instance some small papillomas which appeared early have not developed or have actually regressed cf. K4S4A and K_4^4.

(4) The number of tumours produced by the Aromatic (SA) series still exceeds that in the (S) series.

(5) The response to the 0.2% 9:10-dimethyl-1:2-benzanthracene is now practically equal to that of the active mineral oil fractions K4S6A and K4S8A with 16 positive sites each.

Comparison of the type, size and rate of growth of papillomas in the standard carcinogens and in the oil fractions gives the impression that the former are usually more fleshy and spreading. In all cases multiple papillomas often appear on the sites of application.

Mouse Tests

The tumours on the mice treated with the mineral oils are still fewer than in the rabbit series, the differences being specially observed in K4S6A. The most active fraction is K4S8A with 7 small but definite papillomas. In many instances, papillomas about 2mm in diameter appear to remain unchanged for long periods.

The tumours present at 44 weeks are given in Table 2.

Table 1. Rabbit Experiments 1953-54 (after 44 weeks)

Sites and Time of Appearance of Tumours

K4S1A		K4S2A		K4S3A		K4S4A		K4S5A		K4S6A		K4S7A		K4S8A	
Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site
20	II	18	III	13	II	13	III	13	III	11	VII	10	VII	11	IV
20	IV	25	VII	27	VII	13	IV	13	II	12	IV	11	VII	11	IV
22	I	27	I	33	IV	17	II	13	VII	13	III	17	III	11	IV
30	III	30	IV	37	I	22	I	14	VII	17	IV	17	IV	11	VII
35	I	33	I	37	III	28	I	18	I	17	IV	18	III	11	VII
35	III	35	VII	37	VII	35	I	18	II	18	II	20	I	13	III
37	VII	6 tumours		42	III	35	I	20	I	18	II	25	IV	17	II
42	I			7 tumours		37	II	20	IV	20	I	27	I	18	III
8 tumours						8 tumours		22	III	20	I	35	III	20	III
								22	IV	20	VII	9 tumours		22	VII
								27	I	22	IV			27	VII
								29	I	22	II			28	I
								35	IV	22	VII			28	I
								42	III	27	II			35	IV
								14 tumors		40	III			37	II
										42	VII			42	III
										16 tumors				16 tumours	

Table 1 cont.

Rabbit Experiments 1953-54

(after 44 weeks)

Site and Time of Appearance of Tumours

K4S1A		K4S2A		K4S3A		K4S4A		K4S5A		K4S6A		K4S7A		K4S8A	
Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site	Weeks	Site
25	I	18	I	18	II	11	I	30	I	18	VII	17	III	10	IV
42	III	20	VII	25	III	13	VII	35	II	20	VII	18	VII	11	II
2 tumours		22	I	33	VII	25	IV	37	II	22	II	18	VII	30	VII
		22	II	35	IV	35	VII	37	IV	33	III	37	I	3 tumours	
		35	II	37	II	35	VII	40	II	40	II	37	VII		
		37	VII	37	VII	37	VII	5 tumours		40	IV	42	IV		
		6 tumours		6 tumours		42	IV			6 tumours		6 tumours			
						7 tumours									

Table 1 cont.

Rabbit Experiments 1953-54

(after 44 weeks)

Site and Time of Appearance of Tumours

D(2) Weeks	Site	D($\frac{1}{2}$) Weeks	Site	$K_4$4 Weeks	Site	$K_4$4($\frac{1}{4}$) Weeks	Site	K4SP Weeks	Site
17	I	22	VII	10	II	-	-	20	VII
17	II	27	II	27	III			25	II
18	II	30	VII	30	III			2 tumours	
18	VII	35	I	33	IV				
22	I	35	IV	42	I				
22	II	35	IV	5 tumours					
22	VII	6 tumours							
25	IV								
27	VII								
33	III								
35	I								
37	III								
42	III								
42	III								
42	VII								
15 tumours									

Table 2. Mouse Experiments 1953-54 (after 44 weeks)

Oil Fraction	No. of tumours/time in weeks	Total Tumours
K_4S1A	1/22, 1/24	2
K4S3A	1/35, 1/44	2
K4S4A	1/9, 1/30, 1/34, 1/35	4
K4S5A	1/24, 1/35, 1/44	3
K4S6A	1/20, 1/40	2
K4S7A	1/23, 1/32, 2/44	4
K4S8A	1/22, 1/23, 2/28, 1/30, 2/40	7
K_44	1/22, 1/35	2
K4S4	1/30, 1/40	2
K4S5	1/34	1
K4S8	1/36	1

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Members of Committee)

Copied as:
MRC.54/547
CAMO.54/9

Committee on the Carcinogenic Action of Mineral Oils

COPY OF A LETTER FROM DR. W. K. TAYLOR
TO MR. J. C. R. HUDSON

GODALMING GROUP LABORATORY

Group Laboratory
c/o St. Thomas's Hospital,
Godalming, Surrey.

WKT/MPS.

19th July, 1954.

Dear Mr. Hudson,

As the Pathologist of a large group of Chest Hospitals, I am naturally very interested in the question of squamous metaplasia and bronchial carcinoma, particularly so in the relationship between this disease and the inhalation of oil and its combustion products. I feel, personally, and various items of research tend to support the view, that there is a relationship and it seems very regrettable that just at the time when large scale research on the subject is being initiated, London Transport should seek to introduce 1,700 additional oil driven vehicles on the streets of London in place of electric trolley buses. It seems to be a pity that no influential group of doctors can persuade London Transport to postpone this step until more is known of the aetiology not only of carcinoma of the lung but other respiratory diseases and particularly squamous metaplasia.

One important point is very clear and that is that a considerable amount of oil is to be found in suspension in the air over our roads, as evidenced by the greasy state of the average car windscreen. It would be of interest to determine the origin of this oil -- i.e., diesel exhaust or lubricating oil and whether it is associated with substances which are likely to potentiate any carcinogenic effect. It would be of interest to examine air collected through the intake fan of a car heater and compare the findings in a centre like central London with its numerous diesel vehicles and an equally industrialised area such as might be found in Wolverhampton where passenger diesel vehicles are in the minority. A further point which should be considered is whether first class maintenance of diesel engines is likely to produce finer oil covered carbon particles which are more likely to remain in suspension in the air. The large particles in the black exhaust from badly maintained engines rapidly sink to the ground.

Whilst on the question of possible toxicity of exhaust gases, attention might be paid to the desirability of using the present type of air intake for car heaters where air is collected in a vent at the front of the car about one foot from the ground. Another important factor is the increasing use of small portable 1 h.p. engines using petrol -- oil mixture, many of which are used under cover. I personally find the fumes from my rotary hoe extremely irritant.

However, the problem daily becomes more confused and it may well be that many factors are responsible and that the cause of squamous carcinoma is not that of the columnar cell type. I should be delighted to place the facilities of this department at your disposal, if required, now that we have a certain amount of research capacity available following the completion of work which we have been carrying out for the Tuberculosis Research Unit.

Yours sincerely,

/s/ W. K. Taylor

Group Pathologist

Mr. J. C. R. Hudson,
Medical Research Council,
38 Old Queen Street,
London, S.W.1.

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

September 14, 1954

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Sbeeet
New York 20, New York

Dear Mr. Stroop:

I am sending you herewith a statement of expenditures made on behalf of American Petroleum Institute during the second quarter of 1954. I believe you will find this statement self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

E R Fortlage

E. R. Fortlage,
Secretary to
Dr. Kehoe

is

API 05986

Cut: R. E. Eckardt, M.D.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR 2nd Quarter 1954

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

Direct Salaries	3923.33	
Indirect Salaries		
Histopathological Preparation	400.50	
Other Services	6634.43	10,958.26

MISCELLANEOUS EXPENSE

Purchase of Animals	367.20	
Special Laboratory Supplies	188.47	
Travel	1191.42	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	2189.63	3,936.72
TOTAL		14,894.98

Balance Available for Further Work at End of 1st Quarter 1954		15,752.82
Balance Due Kettering Laboratory at End of		
Receipts		
Expenditures 2nd Quarter 1954		14,894.98
Balance Available for Further Work at End of 2nd Quarter 1954		857.84
Balance Due Kettering Laboratory at End of		

FORM 1220 KET. LAB. 3M—11-53

API 05987

Copy From D. V. Str[illegible] For Information of George M. [illegible]anders, M. D. and R. E. Eckardt, M. D. September 16, 1954

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR 2nd Quarter 1954

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

Direct Salaries	3923.33	
Indirect Salaries		
Histopathological Preparation	400.90	
Other Services	6634.43	10,958.26

MISCELLANEOUS EXPENSE

Purchase of Animals	367.20	
Special Laboratory Supplies	188.47	
Travel	1191.42	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Amenities, Pensions, Maintenance, etc.	2189.63	3,936.72
TOTAL		14,894.98

Balance Available for Further Work at End of 1st Quarter 1954	15,752.82	
Balance Due Kettering Laboratory at End of _____		
Receipts _____		
Expenditures 2nd Quarter 1954	14,894.98	
Balance Available for Further Work at End of 2nd Quarter 1954	857.84	
Balance Due Kettering Laboratory at End of _____		

API 05988

Copy From D. V. Stroop to Members of Medical Advisory Committee and Subcommittee on Carcinogenicity October 19, 1954

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

October 15, 1954

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

Dear Mr. Stroop:

I am attaching recent minutes of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council of Great Britain. These have been forwarded through Dr. Newquist's office, and after reviewing them I believe it would be of interest to the members of the Medical Advisory Committee to review these minutes. I would appreciate it, therefore, if you would arrange to have these minutes duplicated and distributed to all the members of the Medical Advisory Committee and, in addition, to the Kettering Laboratory group.

Sincerely yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Encl.

MEDICAL RESEARCH COUNCIL

For Specified (Normal Committee) Circulation

MRC. 54/606
Camo.Min.16.

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the Sixteenth Meeting, held at 38 Old Queen Street, London, S.W.1., on Friday, 23rd July, 1954, at 11:15 a.m.

Present: Professor T. Ferguson (Chairman), Colonel S.J.M. Auld, Professor J.W. Cook, Professor H.N.Green, Dr. I. Hieger, Dr. J.O.Irwin, Professor F.Morton, Professor R.D.Passey, Professor J.R.Squire, Dr. D.L.Woodhouse, and Mr.J.C.R. Hudson (Secretary).

Attended: Dr. W.Carruthers, Dr. J.Faulkner and Dr. B.S.Lush.

134. Minutes.

After making the following amendments the Minutes of the previous meeting were approved and signed:

(i) Minute 129, second paragraph; "originally thought that the Lagunillas" to read "originally found that the Lagunillas";

(ii) Minute 129, second paragraph; "approximately 210°C" to read "approximately 310°C";

(iii) Minute 130, second sentence to read: "It was noteworthy, he said, that the potencies of the fractions relative to the standard carcinogens as judged by mice and rabbits were different, but the response of the various fractions among themselves was similar in both types of experiment".

135. Progress Reports

(i) In amplification of his report (CAMO. 54/4) Professor Cook said that some of the compounds isolated were in minute quantities and it was accordingly difficult to analyse and identify them. Of the three compounds reported he thought that the isolation of a fluorene derivative from a mineral oil had not previously been recorded.

(ii) Professor Green had nothing to add to his report (CAMO.54/5) although he hoped to be able to develop a test for carcinogenicity by tumour inhibition.

(iii) The present report by Dr. Woodhouse (CAMO.54/6) showed that the results quoted in the previous report (CAMO.54/3) based on thirty weeks. trial gave a sufficiently close indication of levels of biological activity for the purpose of deciding on subsequent experiments although there might be inaccuracies of detail. The results indicated that the carcinogenicity

occurred mainly in the higher (347-390°C) boiling fractions of the aromatic portion. From this it appeared that the tests should be extended to even higher boiling fractions in order to make certain that no appreciable degree of carcinogenicity remained in the residue.

(iv) Professor Morton reported that he had now completed the distillation of Lagunillas up to 295°C, and that modification of the Steadman still to operate under a higher vacuum would be necessary before any higher boiling fractions could be obtained.

136. Nomenclature.

It was suggested that the fractions now being produced might be re-classified under single letters or figures for convenience. However, the general feeling was that the present nomenclature was known by all the people concerned and that the title of each fraction epitomised its life history.

It was agreed to maintain the present nomenclature for all purposes.

For convenience, the present system of nomenclature is summarised below.

Three original crude oils, Kuwait (K), Lagunillas (L), and Oklahoma (O), were distilled each into four fractions and a residue, i.e. K1-5 etc. Fractions distilled on the Steadman still (S) into 2½°C cuts, were designated lower and upper boiling fractions (a & b), which were then mixed to give eight 5°C cuts, for convenience in the biological tests. The 5°C cuts, which were given numerical suffixes, i.e. K_{1-5} S_{1-8}, were split into aromatic (A) and raffinate (R) portions. Subsequent chemical treatment of the aromatic extract gave a maleic anhydride reactive portion (m), i.e. an anthracene; a picrate forming portion (p) and a residue (r).

Thus, K_4S_6aAm would be the anthracene portion of the aromatic extract from the lower boiling fraction of the sixth 5°C cut in the Steadman still of the fourth fraction of the original Kuwait crude oil. The term $K_{4.6}$ represents the sixth cut of a laboratory distillation of K_4 and is equivalent to K_4S_6.

137. Future Plans for the year 1954-1955

It was agreed that the biological tests to be carried out at Birmingham during the next year should be on the m, p, and r extracts of the fractions K_4S_4A to K_4S_8A. The detailed plans for these tests were to be decided between Professor Squire and Professor Cook (circulated subsequently as CAMO.54/9). The previous proposal, recorded in Minute 131, was not to be undertaken at present.

It was also agreed that Professor Morton should undertake the fractionation of another batch of Kuwait oil, and that, if possible, the aromatic portion should be separated before distillation.

138. Possible Carcinogenicity of Diesel Exhaust Fumes.

At the Chairman's request Dr. Faulkner gave a brief account of the Council's position with regard to this matter. Numerous inquiries had been received and the answer given to date had been that the Council were supporting research on atmospheric pollution in general both from the point of view of its chemical and physical characteristics and of its effect on health but that apart from the work on the benz-phrene content of diesel exhaust by Mr. R.L. Cooper (in receipt of a personal grant from the Council) no specific investigation was being undertaken on the possible effect of these fumes on health. The Council would welcome the guidance of the Committee on the matter. It was then discussed and the following points raised:-

(i) It was noted that visible fumes were emitted from diesel engines only if the engines were improperly maintained. The Committee felt that it would be desirable to obtain information about the nature of the pollution produced under different working conditions.

(ii) In this regard Colonel Auld said that Research Group No. 2 of the Institute of Petroleum will be reviewing all the current information on this problem and he agreed to make the Group's report available to the Committee: he thought this review would be available by the end of 1954.

(iii) It was noted that Professor D.H. Hey of King's College, London, who had expressed interest in the problem and who had diesel engines available in his laboratory for experimental work, should be invited to attend the meeting at which the above report would be discussed.

(iv) Professor Morton said that he also had diesel engines in his laboratory and that he would be prepared to use them under varying working conditions so that the fumes produced under these conditions could be studied.

(v) It was the general view of the Committee that, on the face of it, the question of diesel exhausts was one which seemed likely to repay study; but it was felt that the line of approach should await study of the review of existing knowledge likely to be available in time for the next meeting of the Committee.

139. Date of Next Meeting

It was agreed that the next meeting should be held on Friday, 17th December, 1954 at 2.30 p.m.

MEDICAL RESEARCH COUNCIL

MRC. 54/607
CAMO. 54/10

Committee on the Carcinogenic Action of Mineral Oils

PLANS FOR BIOLOGICAL EXPERIMENTS AT BIRMINGHAM 1954-5

Basis

The 1953-4 experiments at Birmingham, as reported in CAMO. 54/6 and CAMO. 54/3, were carried out with fractions of Kuwait 4 (Boiling Range 350-390°C) separated in Professor Morton's Steadman Still (K_4S_1-8) and by subsequent extraction of aromatic-containing fractions with acetone solvent extraction (K_4S_1A-8A). These experiments showed that even with the Steadman apparatus little further separation was being achieved by distillation, due presumably to the formation of azeotropic mixtures of carcinogen(s) with paraffinic compounds. (Better separations might be achieved by distillation of the separated aromatic-containing material, but this would require an even higher vacuum to keep the still temperature down to acceptable levels.) The maximum difference in concentration within the series K_4S_1-8 is of the order of 2x - 3x. On the other hand, solvent extraction with acetone was shown to concentrate the carcinogen into the aromatic-containing fraction. As acetone extraction removed only 16 -22% of K_4S_2-8 and 32% of K_4S_1 (cf. CAMO. 53/5), this effected considerable concentration, the biological results showing effects 2x - 10x greater with each K_4SA fraction when compared with the corresponding K_4S fraction.

Concurrent chemical work at Glasgow (CAMO. 54/1, CAMO. 54/4) has shown the feasability of separating each aromatic-containing extract into three main classes of compound:-

(i) "m" - maleic anhydride adduct-formers containing mainly anthracene derivatives.

(ii) "p" - substances forming picrates from anthracene-free oils, including phenanthrenes, etc.

(iii) "r" - remaining substances in these oils.

It was agreed therefore at the Committee meetings held on 23rd July, 1954, and 29th April, 1954, that the biological testing at Birmingham for 1954-55 should be carried out with "m", "p" and "r" fractions derived from K_4S_4A - K4S8A (the most potent fractions so far obtained from Kuwait oil). As the quantity of material obtainable in this way was in some instances likely to be only 1/10 or 1/20 of the corresponding K_4S-A fraction, it was further agreed that these materials should be diluted for biological testing with liquid paraffin to the same volume as that of the K4S-A fraction from which it had been derived. 250 ml. amounts of each test material would be required for this purpose.

Details of blending, etc.

Some complication arose from the fact that each K_4S_1-8 fraction covering 5°C boiling ranges which were previously tested was derived by admixture of $2\frac{1}{2}$°C cuts kept separate for chemical work e.g. K_4S_8 boiling range 385°-390°C was derived from K_4S_8a 385°-$387\frac{1}{2}$°C and K_4S_8b $387\frac{1}{2}$°-390°C. (In each case the subscript "a" referred to the lower boiling range subfraction.) The details of fractions to be used were therefore left to Dr. Carruthers and Proffessor Squire to work out. It is suggested that the following 18 fractions should be used:-

K_4S_8A	m	K_4S_8A	p	K_4S_8A	r
K_4S_7A	m	K_4S_7A	p	K_4S_7A	r
K_4S_6Aa	m	K_4S_6Aa	p	K_4S_6Aa	r
K_4S_6Ab	m	$K_4S_6A_b$	p	$K_4S_6A_b$	r
K_4S_5A	m	K_4S_5A	p	K_4S_5A	r
K_4S_4A	m	K_4S_4A	p	K_4S_4A	r

It will be noted that in the case of the K_4S_6 fractions, those derived from K_4S_6Aa and K_4S_6Ab have been kept separate. In the other instances blending will be used so as to maintain the same ration of a/b as in the original oil. Thus to prepare the K_4S_8A tests the following calculation is used :-

	Volume in Original Distillation	% in 'Aromatic' Extract.	Vol. aromatics	Volume of Aromatic Fraction in 250 ml. of Blend with Same Proportion of Aromatics as in Original Oil.
K_4S_{8a}	10.28 l.	21.2	2179 ml. ($K_4S_8A_a$)	$250 \times \frac{2179}{3785} = 144$ ml.
K_4S_{8b}	9.13 l.	17.6	1606 ml. ($K_4S_8A_b$)	$250 \times \frac{1606}{3785} = 106$ ml.
Total K_4S_8	19.41 litres		Total Volume (K_4S_8a) = 3785 ml.	= 250 ml.

Thus for K_4S_8A m, K_4S_8A p and K_4S_8A r, Dr. Carruthers will supply m, p and r compounds equivalent to 144 ml. of K_4S_8Aa, admixed with m, p and r compounds equivalent to 106 ml. of K_4S_8Ab. Each of these three will then be made up to 250 ml. at Birmingham with liquid paraffin for biological testing. Analogous procedures will be used for the K_4S_7A, K_4S_5A and K_4S_4A subfractions a and b. In the case of $K_4S_6A_a$ and $K_4S_6A_b$, the amounts of m, p and r compounds equivalent to 250 ml. of each of these fractions will be supplied for biological testing separately.

Remainder of 21 fractions for biological testing

The three remaining fractions tested will be D(2) and D($\frac{1}{2}$) standards as before (i.e. 0.2% and 0.05% 9:10 dimethyl 1:2 benzanthracene in liquid paraffin). In addition Professor Morton will supply K_4S_{1-8}, a fraction boiling just above 390° C prepared from the residue left after distillation of K_4S_{1-8} in order to see whether appreciable further amounts of carcinogen remain in this residue.

Possible results to be anticipated from "m" "p" "r" tests

1. If complete separation of carcinogen occurs, one of the "m", "p" or "r" fractions diluted in liquid paraffin should have the same potency as the corresponding K_4S_{-A} fraction in the 1953-4 tests, while the remaining two should be free from activity (e.g. in the 44 week results of CAMO. 54/6 the K_4S_8A m might show about 16/25 rabbit sites affected while K_4S_8A p and K_4S_8A r showed none).

2. If no separation occurs, each test substance should have 1/3 the activity of the corresponding K_4S_{-A} fraction in the 1953-4 test, (e.g. in the 44 week results the K_4S_8A m, K_4S_8A p and K_4S_8A r fractions might each show about 8/25 rabbit sites affected).

3. A result intermediate between 1. and 2. is perhaps the most likely. Anomalous results can also be envisaged.

These examples are given to show that the biological tests are feasible and likely to give constructive information.

Proposed date for starting 1954-5 biological testing at Birmingham.

This to be 1st October. If delay in supply fractions turns out to be inevitable, Dr. Carruthers undertook to warn Dr. Woodhouse at least by 7th September. Dr. Irwin also undertook to suggest suitable allocation of 21 fractions to rabbit sites as before.

5th August, 1954

File: ~~MAS-General; Issues~~

Copy From D. V. Stroop to George M. Saunders, M.D. and R. E. Eckardt, M.D.

UNIVERSITY OF CINCINNATI

Department of Preventive Medicine and Industrial Health

November 5, 1954

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am sending you herewith, for your information, a statement of expenditures made on behalf of American Petroleum Institute during the third quarter of 1954. I believe you will find this statement self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

/s/ E. R. Portlage

E. R. Portlage, Secretary to
Dr. Kehoe

cf

Enc.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR THIRD QUARTER OF 1954

SALARIES (Based on Proportion of Time Actually Spent on Project)			
Direct Salaries		$4862.79	
Indirect Salaries			
Histopathological Preparation		648.50	
Other Services		5266.35	$10,777.64
MISCELLANEOUS EXPENSE			
Purchase of Animals		210.32	
Special Laboratory Supplies		842.23	
Travel		1043.47	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.		3485.21	5,581.23
	TOTAL		$16,358.87
Balance Available for Further Work at End of 2nd Quarter 1954		857.84	
Receipts July 1954		36125.00	
Sum Available		36,982.84	
Expenditures 3rd Quarter 1954		16,358.87	
Balance Available for Further Work at End of 3rd Quarter 1954		20,623.97	

INSTITUTE OF PETROLEUM

RESEARCH GROUP No. 2.

Minutes of Meeting No.14, held at 26 Portland Place, 29.9.54.

ATTENDANCE

IN THE CHAIR:	F. Morton
GUESTS:	W. M. Catchpole, P. J. M. Trollope, R. B. Killingsworth, A. T. Wilford, C. S. Windebank
MEMBERS:	S. J. M. Auld, J. W. Cook, W. S. Ault, E. J. Dunstan, E. J. Boorman, A. McLean, W. Pohl
APOLOGIES FOR ABSENCE:	J. N. Haresnape
SECRETARY:	E. Herbert

1. MINUTES OF MEETING No. 13, 4.11.53

These were signed as correct. It was noted that in Minute 4 on Page 2, line 5, "only two years ago" should read "nearly two years ago".

2. REPORT ON WORK AT BIRMINGHAM UNIVERSITY AND ON M.R.C. COMMITTEE

The Chairman described the work which had been done at the Birmingham University on carcinogenicity of mineral oils, and the progress which had been made; he referred also to the MRC Committee interested in this subject. He indicated the programme of future work and mentioned that a full report would shortly be circulated to members. Professor Cook added some technical details. The meeting noted the position with approval.

Colonel Auld, having thanked Professor Morton for taking over the Chair of the Committee during his period of office as President, expressed the desire that there should be placed on record the high value of the work being done at Birmingham under Professor Morton's control, and a strong recommendation that this work should be carried on and should continue to receive the necessary financial support. This was duly moved and seconded, and unanimously agreed.

3. HEALTH HAZARDS ASSOCIATED WITH DIESEL EXHAUST FUMES

The Chairman explained that the Minister of Health and the Minister of Fuel and Power, having made a joint approach to M.R.C. on the subject of health hazards associated with diesel exhaust fumes, the M.R.C. had asked its sub-committee for a report. He read Minute 138 of this sub-committee which, although its terms of reference covered skin cancer, and it was not anxious for additional work, evidently felt that it could not divest itself of responsibility towards this problem.

The M.R.C. committee had asked for information on two main points. Firstly, if any information was available from organizations using diesel transport concerning health studies of employees over a sufficiently long period to enable

statistical analyses to be made. Secondly, did the IP. Committee consider that research into the composition of diesel exhaust fumes was desirable and if so, by what organization might it be initiated.

I. Information concerning health records of Diesel Engine Users.

Mr. Wilford, (London Transport Executive) said that such records were available in London Transport and extended over the period (about 25 years) during which diesel-engined vehicles had been in use. Since the records covered a number of garages and depots, some operating internal combustion-engined vehicles, others concerned with trolleybuses, they would be expected to provide useful data of the type required. He suggested that the M.R.C. Committee should make a direct approach to the Executive's Chief Medical Officer.

Mr. Ault stated that the Shell-B.P. Marketing Organizations would also have health records concerning workers in garages using diesel transport. He believed that a study of these records would be of value but agreed with Mr. Wilford that direct contact between the M.R.C. and the Medical Officers should be established.

It was also suggested that approach should be made by M.R.C. to the Medical Officers of other transport organizations, particularly the Manchester Corporation Transport Department, known to have been operating diesel fleets for some 25 years.

It was agreed to recommend to the M.R.C. Committee that they should seek information from the Medical Officers of the L.T.E., Shell-Mex and B.P. Ltd., Esso Petroleum and possibly M.C.T.D.

II. Information concerning investigation of composition of diesel exhaust fumes.

Several members drew attention to the desirability of considering atmospheric pollution in general and regretted the tendency to over-emphasize the contribution made to the general problem by the diesel engine. Professor Cook gave an account of the Committees of the M.R.C. concerned with atmospheric pollution, and suggested that if an investigation into fuel combustion was found to be desirable the assistance of Research Committee No. 2 of the IP. would be of the greatest value.

Colonel Auld said that at the moment the Committee could be of the greatest help if the members would use their American and Continental contacts to ascertain what views were held in other countries. In particular the M.R.C. Committee would welcome guidance as to the desirability of setting up research work in this country.

It was generally agreed that at this stage the examination of exhausts of individual engines, as suggested in the M.R.C. Committee Minute was not recommended. Before any experimental work was commenced, it would be desirable to plan the investigation on a broad basis and participants in initial discussions should include representatives of engine users and manufacturers, the Motor Industry Research Association, British Internal Combustion Engine Research Association, and the Petroleum Industry.

Dr. Killingsworth asked if investigations should be confined to diesel fuel. It was suggested that diesel fuels had been considered, because their fumes could be absorbed at mouth level. Dr. Killingsworth enquired also whether information had been sought from America, and offered to check with his American colleagues if and where in America there was information on this subject. Mr. Ault felt that it would be premature to approach A.P.I. at this stage, and that it was doubtful if there was much published information in America although some medical officers might have some interesting data. Mr. Boorman drew attention to two reports in the National Petroleum News regarding Smog in Los Angeles. (See pages 23 and 20 of N.P. News, August 4th and 18th respectively). It was suggested that M.R.C. be referred to these articles.

It was agreed that, if, as a result of their contacts with the Medical Officers of the interested oil and transport companies, the M.R.C. Committee wish to put any questions to the IP. Committee, then the Committee would attempt to provide the answers. In the meanwhile all members were asked to trace pertinent information on both diesel fuels and petrol, not only from America but also from the Continent of Europe.

The question of the competency of Research Committee 2 to handle this matter was raised. It was pointed out that the problem would eventually have to be submitted to the Research Committee for report to Council. It was considered that the most appropriate IP. body to deal with the subject at this stage was Committee 2, particularly as the M.R.C. regard its opinions as unbiased and valuable.

4. DATE OF NEXT MEETING

To be arranged by the Chairman.

18.10.54.PMA

ADDITION TO THE MINUTES by Professor F. Morton.

A Committee has recently been established in the U.S.A. under the Co-ordinating Research Council, Inc., and sponsored by the American Petroleum Institute and the Automobile Manufacturers Association, to study the composition of exhaust gases from internal combustion automotive engines. This committee is composed of several panels, one of which will study engine variation in relation to its effect upon the composition of exhaust gases. Another panel will develop means of sampling and analyzing exhaust gases, and a third panel is interested in uncovering all possible sources of information relating to the proper technique for sampling such gases and for obtaining accurate analyses.

I have been asked by H. M. Smith of the U.S. Bureau of Mines to co-operate with this committee and to send details of a new sampling valve and techniques which have been developed at Birmingham, but which have not yet been described in literature. In return the committee will send to me all the details of their work and keep me informed of progress.

Do the members of IP. Committee No. 2 feel that I should ask H.M. Smith in confidence if the American Committee is in any way concerned with the health hazards associated with diesel exhaust?

Various agencies studying the smog problem already have agreed that ozone is linked to smog and is present in the Los Angeles atmosphere in excessive amounts.

But the district report is the first flat statement that the substance can be traced to vehicle exhaust gases.

---oOo---

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

MINUTES OF THE MEDICAL RESEARCH COUNCIL

138. Possible Carcinogenicity of Diesel Exhaust Fumes.

At the Chairman's request Dr. Faulkner gave a brief account of the Council's position with regard to this matter. Numerous enquiries had been received and the answer given to date had been that the Council were supporting research on atmospheric pollution in general both from the point of view of its chemical and physical characteristics and of its effect on health but that apart from the work on the benz-pyrene content of diesel exhaust by Mr. R.L. Cooper (in receipt of a personal grant from the Council) no speeific investigation was being undertaken on the possible effect of these fumes on health. The Council would welcome the guidance of the Committee in the matter. It was then discussed and the following points raised:

i) It was noted that visible fumes were emitted from diesel engines only if the engines were improperly maintained. The Committee felt that it would be desirable to obtain information about the nature of the pollution produced under different working conditions.

ii) In this regard Colonel Auld said that Research Group No. 2 of the Institute of Petroleum will be reviewing all the current information on this problem and he agreed to make the Group's report available to the Committee: he thought this review would be available by the end of 1954.

iii) It was noted that Professor D. H. Hey of King's College, London, who had expressed interest in the problem and who had diesel engines available in his laboratory for experimental work, should be invited to attend the meeting at which the above report would be discussed.

iv) Professor Morton said that he also had diesel engines in his laboratory and that he would be prepared to use them under varying working conditions so that the fumes produced under these conditions could be studied.

v) It was the general view of the Committee that, on the face of it, the question of diesel exhausts was one which seemed likely to repay study but it was felt that the line of appraoch should await study of the review of existing knowledge likely to be available in time for the next meeting of the Committee.

NATIONAL PETROLEUM NEWS. AUGUST 4, 1954. Page 23.

MOTOR VEHICLE EXHAUST CALLED TOP SMOG CAUSE

Stanford Research Institute has branded motor vehicle exhaust as a major smog contributor in its report summarizing six years of smog study.

The Institute's 134-page report, released by Western Oil and Gas Assn., estimates 3,100 tons of pollutants are emitted daily into the Los Angeles Basin atmosphere, of which 1,500 tons are hydrocarbons.

Auto exhaust heads the list with 1,016 tons, followed by:

* Evaporation from automobile tanks and carburetors - 164 tons
* Refining - 155 tons
* Marketing - 37 tons
* Production - 32 tons
* Filling automobile tanks - 28 tons
* Filling service station tanks - 24 tons

In short, exhaust gases take the blame for 81% of the total organic hydrocarbons emitted and nearly 95% of the active hydrocarbons.

The report notes in passing that backyard incinerators emit 400 tons of organic materials daily.

The researchers say the key to smog probably is ozone, since Los Angeles has the world's highest concentration of that oxidant. Moreover, ozone concentrations increase and diminish with the intensity of the smog.

"This ozone may react in the air with harmless materials such as hydrocarbons to form troublesome compounds that are responsible for many of the undesirable effects of smog", the report concludes.

Copies of the document are available from Western Oil and Gas Assn., at 510, W. 6th St., Los Angeles, 14.

NATIONAL PETROLEUM NEWS. August 18, 1954. Page 20.

AUTOMOBILE EXHAUST LINKED TO SMOG

Automobile exhausts are responsible for a considerable amount of ozone, the "silent partner" in Los Angeles' smog problem, says Gordon P. Larson, director of the Air Pollution Control District. Larson said three district scientists have established that unburned gasoline and nitrogen oxides emitted by exhausts create ozone in the presence of sunlight. Ozone, in turn, is believed to "trigger" other chemical reactions in the atmosphere, which causes smog's undesirable effects.

So, Larson emphasized, the district now can make formal scientific indictment against exhausts as a smog contributor. As he puts it, "We are on the same firm scientific ground in demanding that automobile exhausts be cleaned up as we were in demanding two years ago that refineries clean up."

G.K 12/14/54

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

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

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

November 22, 1954

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

Dear Mr. Stroop:

I am attaching some minutes received from the Institute of Petroleum's Research Group No. 2 meeting of September 29, 1954. In view of the discussion in paragraph 3 of these minutes, I believe it would be advisable to have these minutes reproduced and distributed to all of the members of the Medical Advisory Committee.

Very truly yours,

R.E. Eckardt.

R. E. ECKARDT, M. D.

REE:ilk

Encl. - Minutes of
Meeting No. 14

API 06020

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REE:ilk

Encl. - Minutes of
Meeting No. 14

INSTITUTE OF PETROLEUM RES-2-14

RESEARCH GROUP No. 2.

Minutes of Meeting No.14, held at 26 Portland Place, 29.9.54.

ATTENDANCE

IN THE CHAIR:	F. Morton	
GUESTS:	W.M. Catchpole	P.J.W. Trollope
	R.B. Killingsworth	A.T. Wilford
	C.E. Windebank	
MEMBERS:	S.J.M. Auld	J.W. Cook
	W.S. Ault	E.J. Dunstan
	E.J. Boorman	A. McLean
	W. Pohl	
APOLOGIES FOR ABSENCE:	J.N. Haresnape	
SECRETARY:	E. Herbert	

1. MINUTES OF MEETING No. 13, 4.11.53

These were signed as correct. It was noted that in Minute 4 on Page 2, line 5, "only two years ago" should read "nearly two years ago".

2. REPORT ON WORK AT BIRMINGHAM UNIVERSITY AND ON M.R.C. COMMITTEE

The Chairman described the work which had been done at the Birmingham University on carcinogenicity of mineral oils, and the progress which had been made; he referred also to the MRC Committee interested in this subject. He indicated the programme of future work and mentioned that a full report would shortly be circulated to members. Professor Cook added some technical details. The meeting noted the position with approval.

Colonel Auld, having thanked Professor Morton for taking over the Chair of the Committee during his period of office as President, expressed the desire that there should be placed on record the high value of the work being done at Birmingham under Professor Morton's control, and a strong recommendation that this work should be carried on and should continue to receive the necessary financial support. This was duly moved and seconded, and unanimously agreed.

3. HEALTH HAZARDS ASSOCIATED WITH DIESEL EXHAUST FUMES

The Chairman explained that the Minister of Health and the Minister of Fuel and Power, having made a joint approach to M.R.C. on the subject of health hazards associated with diesel exhaust fumes, the M.R.C. had asked its sub-committee for a report. He read Minute 138 of this sub-committee which, although its terms of reference covered skin cancer, and it was not anxious for additional work, evidently felt that it could not divest itself of responsibility towards this problem.

The M.R.C. committee had asked for information on two main points. Firstly, if any information was available from organisations using diesel transport concerning health studies of employees over a sufficiently long period to enable statistical analyses to be made. Secondly, did the IP. Committee consider that research into the composition of diesel exhaust fumes was desirable and if so, by what organisation might it be initiated.

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It was agreed to recommend to the M.R.C. Committee that they should seek information from the Medical Officers of the L.T.E., Shell-Mex and B.P. Ltd., Esso Petroleum and possibly M.C.T.D.

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18th respectively). It was suggested that I.R.C. be referred to these articles.

It was agreed that, if, as a result of their contacts with the Medical Officers of the interested oil and transport companies, the M.R.C. Committee wish to put any questions to the IP. Committee, then the Committee would attempt to provide the answers. In the meanwhile all members were asked to trace pertinent information on both diesel fuels and petrol, not only from America but also from the Continent of Europe.

The question of the competency of Research Committee 2 to handle this matter was raised. It was pointed out that the problem would eventually have to be submitted to the Research Committee for report to Council. It was considered that the most appropriate IP. body to deal with the subject at this stage was Committee 2, particularly as the M.R.C. regard its opinions as unbiased and valuable.

4. DATE OF NEXT MEETING

To be arranged by the Chairman.

18.10.54.PMA.

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A Committee has recently been established in the U.S.A. under the Coordinating Research Council, Inc., and sponsored by the American Petroleum Institute and the Automobile Manufacturers Association, to study the composition of exhaust gases from internal combustion automotive engines. This committee is composed of several panels, one of which will study engine variation in relation to its effect upon the composition of exhaust gases. Another panel will develop means of sampling and analyzing exhaust gases, and a third panel is interested in uncovering all possible sources of information relating to the proper technique for sampling such gases and for obtaining accurate analyses.

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Do the members of IP. Committee No.2 feel that I should ask H.M. Smith in confidence if the American Committee is in any way concerned with the health hazards associated with diesel exhaust?

CONFIDENTIAL

MINUTES OF THE MEDICAL RESEARCH COUNCIL

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So, Larson emphasized, the district now can make formal scientific indictment against exhausts as a smog contributor. As he puts it, "We are on the same firm scientific ground in demanding that automobile exhausts be cleaned up as we were in demanding two years ago that refineries clean up."

Various agencies studying the smog problem already have agreed that ozone is linked to smog and is present in the Los Angeles atmosphere in excessive amounts.

But the district report is the first flat statement that the substance can be traced to vehicle exhaust gases.

---oOo---

R. E. Eckardt M.D.

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

November 5, 1954

CABLE ADDRESS KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1810

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am sending you herewith, for your information, a statement of expenditures made on behalf of American Petroleum Institute during the third quarter of 1954. I believe you will find this statement self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

ef

Enc.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR Third Quarter of 1954

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

Direct Salaries	4862.79	
Indirect Salaries		
Histopathological Preparation	648.50	
Other Services	5266.35	10,777.64

MISCELLANEOUS EXPENSE

Purchase of Animals	210.32	
Special Laboratory Supplies	842.23	
Travel	1043.47	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	3485.21	5,581.23
TOTAL		16,358.87

Balance Available for Further Work at End of 2nd Quarter 1954	857.84	
Balance Due Kettering Laboratory at End of		
Receipts July 1954	36,125.00	
Sum Available	36,982.84	
Expenditures 3rd Quarter 1954	16,358.87	
Balance Available for Further Work at End of 3rd Quarter 1954	20,623.97	
Balance Due Kettering Laboratory at End of		

FORM 1230 KET. LAB. 3M—11-53

API 05999

Copy From D. V. Stroop to Members of Subcommittee on Carcinogenicity and Medical Advisory Committee December 1, 1954

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

November 19, 1954

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

Dear Mr. Stroop:

I am attaching a copy of the minutes of the meeting of the Subcommittee on Carcinogenicity held at the Conrad Hilton Hotel in Chicago on September 10, 1954. These minutes were prepared by Allan E. Dooley of the Texas Company and have been reviewed by Dr. Hine who was Acting Chairman at that meeting.

Since I was not in attendance at the meeting, I am not in a position to offer any comments other than that Dr. Hine believes that they are a satisfactory representation of the proceedings at the meeting. I would suggest, therefore, that these minutes be duplicated and forwarded to each of the members of the Subcommittee on Carcinogenicity and the Medical Advisory Committee.

Sincerely yours,

/s/ R. E. ECKARDT

R. E. ECKARDT, M.D.

REE:ilk

Attachment

For Information Only - Not for Publication

AMERICAN PETROLEUM INSTITUTE

SUBCOMMITTEE ON CARCINOGENICITY

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

Members Present or Represented:

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

Member Absent:

R. E. Eckardt, M. D.

Others Present:

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

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

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

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

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

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

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

4. No work is being done on inhibitors.

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

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

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

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

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

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

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

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

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

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

Mrs Downes

Please prepare & distribute mimeographed copies as indicated (2)

12/1/54

API 06004

Copy from DVS to Members of Subcommittee on Carcinogenicity Medical Advisory Committee

ESSO LABORATORIES

STANDARD OIL DEVELOPMENT COMPANY

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

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR

HORACE W. GERARDE PH.D., M.D
HEAD TOXICOLOGIST

INDUSTRIAL HYGIENE SECTION

NATHAN V. HENDRICKS, CH.E.
HEAD OF SECTION

FRANKLIN W. CHURCH, M.S.

GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

November 19, 1954

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

Dear Mr. Stroop:

I am attaching a copy of the minutes of the meeting of the Subcommittee on Carcinogenicity held at the Conrad Hilton Hotel in Chicago on September 10, 1954. These minutes were prepared by Allan E. Dooley of the Texas Company and have been reviewed by Dr. Hine who was Acting Chairman at that meeting.

Since I was not in attendance at the meeting, I am not in a position to offer any comments other than that Dr. Hine believes that they are a satisfactory representation of the proceedings at the meeting. I would suggest, therefore, that these minutes be duplicated and forwarded to each of the members of the Subcommittee on Carcinogenicity and the Medical Advisory Committee.

Sincerely yours,

R. E. Eckardt.

R. E. ECKARDT, M. D.

REE:ilk

Attachment

API 06005

[illegible]

[illegible] 9/20/54

Members Present or Represented:

D. H. [illegible] M. D. - Acting Chairman
[illegible] (By [illegible] Doane)
[illegible] Jr.
[illegible] E. Dooley
[illegible] D. [illegible], M. D.
[illegible] Henderson
[illegible] Linder, M. D.
R. C. [illegible]thoff
[illegible] Newquist, M. D.
J. [illegible] Osborn, M. D.
[illegible] (By [illegible])

Members Absent:

R. [illegible] Eckardt, M. D.

Others Present:

[illegible]	Shell Development
J. [illegible] Cruickshank, M.D.	Cities Service
[illegible] Frank, M.D.	Pan American Refinery
Paul D. Halley	Standard Oil, Indiana
[illegible] Horton	Kettering Laboratory
[illegible] Landon	Gulf Oil
[illegible]	Pure Oil
Clark P. Miller, M.D.	[illegible]
[illegible] Pabst	Socony-Vacuum
[illegible] Phair, M. D.	Kettering Laboratory
[illegible] Reeve, M. D.	Standard Oil, Indiana
[illegible] Ruddock, M.D.	Richfield Oil

The minutes of the Subcommittee meeting of June 19, 1954 [illegible] approved as circulated.

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

Dr. Horton discussed his progress report, dated September 1, 195[illegible] copies of which he had mailed to the Subcommittee at the end of August. In Dr. Horton's discussion he has brought out the following points:

1. [illegible]

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

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

4. No work is being done on inhibitors.

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

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

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

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

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

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

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

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

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

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

File: MAC Correspond ce

November 24, 1954

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

Dear Dr. Eckardt:

Your letter of November 19th has been received.

In view of the number of non-members of the Subcommittee on Carcinogenicity who attended the meeting held in Chicago September 18th, I wonder if it would be desirable to send copies of the minutes to all members of the Medical Advisory Committee.

Very truly yours,

DVB:ed

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

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

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

November 30, 1954

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

Dear Mr. Stroop:

In answer to your letter of November 24th, I am certainly in agreement with sending copies of the minutes of the Subcommittee on Carcinogenicity meeting to all members of the API Medical Advisory Committee.

Very truly yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee
December 14, 1954

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

November 22, 1954

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

Dear Mr. Stroop:

I am attaching some minutes received from the Institute of Petroleum's Research Group No. 2 meeting of September 29, 1954. In view of the discussion in paragraph 3 of these minutes, I believe it would be advisable to have these minutes reproduced and distributed to all of the members of the Medical Advisory Committee.

Very truly yours,

/s/ R. E. ECKARDT

R. E. ECKARDT, M.D.

REE:ilk

Encl. - Minutes of
Meeting No. 14