

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

API 05912

EB 005657

SC-API-2566

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.

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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.

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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.

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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

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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:

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Biological Work	\$20,000
Technical Work	32,250
Epidemiological Work	<u>12,750</u>
	\$65,000

Another breakdown of these figures can be given as follows:

Salaries

Direct	\$22,000
Indirect	
Histopathology	2,000
Others	<u>20,000</u>

\$44,000

Miscellaneous Exp.

Animals	\$ 1,250
Supplies	5,000
Travel	4,000
Overhead	<u>10,750</u>

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. Cassaway, M. D.
Gulf Oil Corporation

L. M. Henderson
The Pure Oil Company

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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)

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June 21, 1954

API 05919

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