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

DATE: 1948 Nov 12

DOC#: API010

DOCUMENT DESCRIPTION: Meeting Minutes & Attendee List - API Medical Advisory Committee

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AMERICAN PETRCLEUM INSTITUTE
MEDICAL ADVISORY COMMITTEE

EIGHTH MEETING

Minutes of Meeting
November 12, 1948
Stevens Hotel
Chicago, Illinois

MEMBERS PRESENT

M. N. Newquist - Chairman
J. P. Holt - Secretary

V. C. Baird
F. F. Boys
W. W. Brooks
L. E. Curtis
Kieffer Davis
T. M. Frank
A. E. Hoag
T. J. Kelly
W. R. Levis
E. K. Linder
B. B. Reeve
C. A. Swan
McIver Woody

ASSOCIATES PRESENT

E. W. Adams
L. C. Beard, Jr.
R. C. Cole
A. E. Dooley
H. G. M. Fischer
N. J. Gothard
H. R. Warrick
F. M. Watkins
H. H. Zuidema

GUEST

A. O. Seeler

ADVISOR

D. V. Stroop - API

Total in Attendance - 26

MEMBERS ABSENT

W. O. Armstrong
D. M. English
H. E. Fraser
E. P. Luongo
W. A. Morrison
R. C. Page

ASSOCIATES ABSENT

R. S. Bonsib
C. R. Brown
R. S. Driver
H. W. Field
E. W. Isom
A. J. Koewing, Jr.
H. P. Lankelma
D. W. Larmer
C. R. McKay
R. B. Roaper
H. D. Wilde

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I

## INTRODUCTION OF GUEST AND NEW MEMBERS

The guest, Dr. A. C. Seeler, and new members, Dr. C. A. Swan and Dr. L. E. Curtis, were recognized. The Chairman pointed out that R. S. Bonsib, who had been instrumental in the establishment of the Committee, had recently been ill and recommended that an appropriate telegram be sent to Mr. Bonsib.

Action — The Committee was in unanimous agreement; thereupon a telegram was sent to Mr. Bonsib.

II

## MINUTES OF PREVIOUS MEETING

Action — The minutes of the previous meeting, April 2, 1948, were approved as circularized.

III

## REPORT OF SUBCOMMITTEE ON FLUORIDES - DR. A. E. HOAG, CHAIRMAN

The Subcommittee on Fluorides reported progress and recommended continued financial support of work at Kettering Laboratory. (Copy of report is attached as Appendix A.)

Action — The Committee voted unanimously to receive the report of the Subcommittee on Fluorides and to recommend that the API continue to support this program at the University of Cincinnati with a grant of $2,500 for the year 1949.

IV

## REPORT OF SUBCOMMITTEE ON CARCINOGENICITY - DR. McIVER WOODY, CHAIRMAN

The Subcommittee on Carcinogenicity reported a number of recommendations. (Copy of the report is attached as Appendix B.)

Action — The Committee voted unanimously to accept the report of the Subcommittee on Carcinogenicity and to adopt the Subcommittee's recommendations as follows:

1. That the selection of Dr. A. W. Horton for Dr. Kehoe's staff at the University of Cincinnati is acceptable to the Committee.

2. That the selection of an epidemiologist for Dr. Kehoe's staff is acceptable to the Committee.

3. That an additional $25,000 will be necessary to continue the program at the University of Cincinnati during 1949; to be followed by another $25,000 for the first six months of 1950.

4. That the fundamental chemical and physical studies which are indicated to investigate the operational technical aspects of this problem may require considerable more money than anticipated, and it is recommended that the technical advisory group consider the problem again and present its recommendations to the Subcommittee on Carcinogenicity.

5. That the carcinogenic program which the API is sponsoring at the University of Cincinnati should include:

   a. Biological or other experimental studies for the purpose of developing quicker techniques for determining the carcinogenicity of these materials.

   b. Biological testing program to determine the carcinogenicity of various samples.

   c. Experimentation directed toward defining protection procedures which might be used to protect individuals who may come in contact with these oils.

   d. Epidemiological studies of this problem in the industry.

   e. Investigation of solid and semi-solid natural petroleum constituents such as rod wax.

In the discussion of the Subcommittee report, it was stated that a detailed report of the carcinogenic studies that have been carried out at the University of Cincinnati, under the auspices of the API, would be presented to the Committee by Dr. R. A. Kehoe within the next few months.

V

REPORT OF SUBCOMMITTEE ON CUTTING FLUIDS - DR. B. B. REEVE, CHAIRMAN

The Subcommittee on Cutting Fluids reported progress and recommendations. (Copy of the report is attached as Appendix C.)

Action

1. The Committee received the report and voted unanimously to accept the Subcommittee's recommendation, with regard to publication of the paper "The Cutting Oil Dermatoses - A Critical Review," that this paper carry the following notice: "This work was made possible by a grant from the American Petroleum Institute. The author wishes to express his thanks to the Institute for making this work possible."

2. The Committee also voted unanimously to defer publication by the Institute of the bulletin "Safeguarding the Use of Cutting Fluids and Coolants" pending further consideration as follows:

   a. That comments concerning technical aspects of this paper be sent by members and associate members of the API Medical Advisory Committee to Professor P. Drinker and Dr. A. O. Seeler of Harvard, and that Dr. Seeler review these comments and suggestions.

b. Following receipt of these comments, that Dr. Seeler prepare a condensed version of the bulletin "Safeguarding the Use of Cutting Fluids and Coolants" and submit this condensed version to the Subcommittee on Cutting Fluids for consideration sometime within the next six months.

VI

REPORT OF SUBCOMMITTEE ON MEDICAL POLICIES AND PRACTICES-DR. T.M. FRANK, CHAIRMAN

The Subcommittee on Medical Policies and Practices reported two recommendations which are reproduced in Appendix D to these minutes.

Action

1. The Committee received the report and voted to recommend to the members of the API the use of the International Certificate of Innoculation and Vaccination approved by the World Health Organization and distributed by the Federal Security Agency.

2. After considerable discussion the Committee voted against acceptance of the recommendation: "That employees be encouraged to take immunizations of proved effectiveness from their personal physicians. However, emergencies may arise when companies will find it advisable to offer such immunizations."

Note: In connection with the use of the International Certificate of Innoculation and Vaccination, it is possible to get authorization for key physicians of each organization to be appointed as certifying officers of U.S. Public Health Service without compensation by writing to Dr. G. L. Dunnahoo, Chief Quarantine Division, U.S. Public Health Service, Federal Security Building, South, Washington 25, D.C. Further information on immunization requirements in various countries may be secured from the same source.

VII

REPORT OF EDITORIAL SUBCOMMITTEE - DR. J. P. HOLT, CHAIRMAN

The Editorial Subcommittee reported recommendations which are stated in Appendix E to these minutes.

Action The Committee voted unanimously to receive the report of the Editorial Subcommittee and to accept the Subcommittee's recommendations as follows:

1. That the API publish the revised drafts of Toxicological Reviews on substances as follows:

Acetone
Carbon Monoxide
Hydrogen Fluoride
Phosphoric Acids

2. That the Toxicological Review on Silica be submitted to Dr. Seeler of Harvard for rewriting.

3. That the bulletin "Safeguarding the Use of Cutting Fluids and Coolants" be referred to Dr. Seeler of Harvard for rewriting in a condensed form. Following this, the report will be submitted to the Subcommittee on Cutting Fluids for reconsideration.

VIII

REPORT OF SUBCOMMITTEE ON PERMISSIBLE CONCENTRATIONS - DR. V. C. BAIRD, CHAIRMAN

The Subcommittee on Permissible Concentrations reported progress and recommendations (see Appendix F for complete copy of report as amended at meeting).

Action 1. The Committee received the amended report and accepted its recommendations as follows:

a. That the toxicological surveys under way at Harvard should be continued.

b. That the silica-alumina catalyst experimental-biological studies under way at Harvard University should be continued.

c. That a report of the present status on the treatment of burns with a recommendation for procedure for treatment should be prepared by Dr. Seeler of Harvard.

d. That Dr. Seeler should prepare a review of the available information on the toxicity of $C_4$ to $C_{12}$ aldehydes with recommendations for further investigations needed.

e. That toxicological experimental studies on $C_9$ to $C_{12}$ aromatics should be carried out at Baylor University College of Medicine with an appropriation of $15,000 as recommended by the Subcommittee.

f. That the data concerning the silica catalyst problem should be summarized by Dr. Seeler for the Committee at its Spring meeting. These data should be collected from and circularized to the petroleum industry.

g. That the work at Harvard University be supported by annual grants of $10,000 per year.

h. That the Institute should be authorized to raise an unassigned sum of $15,000 to use on emergency problems, subject to approval by the Safety Committee of the Board of Directors.

2. The Committee voted against the acceptance of the Subcommittee's recommendation that Professor Drinker and associates at Harvard University be authorized to add an industrial hygiene engineer to their staff to work full time for one year with Dr. Seeler on the environmental aspects of toxic hazards relating to the petroleum industry.

## IX

## NEW BUSINESS

A. Distribution of Publications and Circulars

The Committee discussed policies and procedures governing the distribution of Medical Advisory Committee publications and circulars to interested agencies and individuals outside of the petroleum industry.

Action

1. The Committee voted in favor of sending complimentary copies of API Toxicological Reviews to those State health departments and to class A medical schools as may be included on complimentary mailing list to be prepared by the Editorial Subcommittee.

2. There was a consensus that it would be impracticable to establish general mailing lists for committee circulars and other unpublished information and that individuals requesting such information, if necessary, should be referred to members of the Medical Advisory Committee who might be in position to assist.

B. Atmospheric Pollution

The Committee discussed the publicity which had been given to atmospheric-pollution problems at Donora, Pennsylvania, and Los Angeles, California.

Action

1. The Committee requested Dr. Curtis to secure and to supply the Committee, in summarized form, such information as may be available on the California problem in advance of the April 1949 meeting. Dr. Curtis was empowered to organize a special subcommittee to assist in this work if he found the need for such assistance.

2. The Committee discussed but voted not to adopt a motion stated as follows:

> "In view of the Donora incident, and other similar problems possibly related to the petroleum industry, it is recommended that an outstanding authority in the field of atmospheric pollution health problems be employed to survey the question of atmospheric-pollution problems related to the petroleum industry and report to the Committee six months from now, giving recommendations for what action the petroleum industry should take; the cost of this survey to be no more than $5,000."

3. There was a consensus that the problem of atmospheric pollution justified active consideration by the API Committee on Disposal of Refinery Wastes, particularly with respect to the elements which might adversely affect health. The Committee recommended that this consensus should be transmitted to the Committee on Disposal of Refinery Wastes and requested a joint meeting with that Committee, or of representatives of the two Committees, at some convenient time and place.

C. Proposed Uniform Industrial Hygiene Code

The Committee discussed but did not take any action with respect to this matter.

D. Industrial Hygiene Foundation of America

Dr. J. P. Holt and Dr. W. R. Levis were appointed as a committee to render a report on the Industrial Hygiene Foundation, with respect to membership, its functions, services available, dues, etc., at the next meeting.

E. Ninth Meeting

The Committee voted to hold its ninth meeting in Detroit, Michigan, April 1 and 2, 1949.

X

ADJOURNMENT

There being no further business to be considered, the meeting was adjourned.

J. P. Holt, M.D.
Secretary

Approved:
M. N. Newquist, M.D.
Chairman

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APPENDIX A

REPORT TO THE API MEDICAL ADVISORY COMMITTEE

BY THE SUBCOMMITTEE ON FLUORIDES

Dr. A. E. Hoag - Chairman

November 11, 1948

Since the distribution of the reprints on Fluorides last Spring, no further report has been received from the Kettering Laboratory until just recently. A letter was received from Dr. Robert A. Kehoe in which he stated that the plan of the University of Cincinnati is to prepare a detailed annual report for all of the sponsors. This report will be put together as carefully as though it were to be published. It will be mimeographed for distribution to the several representatives of each of the sponsors of the work.

Dr. Kehoe stated that it will not be possible to make this report available in time for our meeting in Chicago because it would not be a complete report of the year's work. However, Dr. Kehoe stated that he would try to send us a summary of the work to date so that we could use this information at our meeting.

Dr. Kehoe said also that this year they expect to call a meeting of the representatives of several of the sponsors to review the work in some detail and to consider certain aspects of the future program.

The recent happenings at Donora, Pennsylvania, make it imperative that we keep up our research work on Fluorides.

It is suggested that the committee ask for a continuation of the research work at the Kettering Laboratory on Fluorides and that the amount of $2,500 be expended toward this research.

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## APPENDIX B

### REPORT TO THE API MEDICAL ADVISORY COMMITTEE

### BY THE SUBCOMMITTEE ON CARCINOGENICITY

Dr. McIver Woody - Chairman

November 11, 1948

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

1. That the selection of Dr. A. Wesley Horton for Dr. Kehoe's staff is acceptable to us.

2. That the selection of the epidemiologist for Dr. Kehoe's staff is acceptable to us.

3. That an additional $25,000 will be necessary to continue the program at the University of Cincinnati during 1949, to be followed by another $25,000 for the first six months of 1950.

4. That the fundamental chemical and physical studies which are indicated to investigate the operational technical aspects of this problem may require considerably more money than anticipated; and it is recommended that the technical advisory group consider the problem again and present its recommendations to the Subcommittee on Carcinogenicity.

5. That the carcinogenic program which the API is sponsoring at the University of Cincinnati should include:

   a. Biological or other experimental studies for the purpose of developing quicker techniques for determining the carcinogenicity of these materials.

   b. Biological testing program to determine the carcinogenicity of various samples.

   c. Experimentation directed toward defining protection procedures which might be used to protect individuals who may come in contact with these oils.

   d. Epidemiological studies of the problem in the industry.

   e. Investigation of solid and semi-solid natural petroleum constituents such as rod wax.

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APPENDIX C

REPORT TO THE API MEDICAL ADVISORY COMMITTEE

BY THE SUBCOMMITTEE ON CUTTING FLUIDS

Dr. B. B. Reeve - Chairman

November 11, 1948

We have reviewed the final draft of the bulletin "Safeguarding the Use of Cutting Fluids and Coolants." All of the suggested changes received have been considered and revisions made where justified. We have returned the corrected draft to the Editorial Committee for final approval.

With regard to the publication of the paper "The Cutting Oil Dermatoses - A Critical Review," which has been prepared by Mr. Kriete of Harvard University School of Medicine, it is recommended that this paper contain a statement as follows:

> "This work was made possible by a grant from the American Petroleum Institute. The author wishes to express his thanks to the Medical Advisory Committee of the American Petroleum Institute and to the American Petroleum Institute for cooperation and support for this work."

It is recommended that the review on cutting oil dermatoses be kept up-to-date.

It is still recommended by this committee that emphasis be placed on prevention rather than the research approach of cutting oil dermatitis.

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APPENDIX D

REPORT TO THE API MEDICAL ADVISORY COMMITTEE

BY THE SUBCOMMITTEE ON MEDICAL POLICIES AND PRACTICES

Dr. T. M. Frank - Chairman

November 11, 1948

1. That we recommend to the members of the API the use of the International Certificate of Innoculation and Vaccination as approved by the World Health Organization and distributed by the Federal Security Agency.
   In line with its use it is possible to get authorization for key physicians of each organization appointed as certifying officers of U.S. Public Health Service without componsation, by writing to Dr. G. L. Dunnahoo, Chief Quarantine Division, U.S. Public Health Service, Federal Security Building, South, Washington 25, D.C. Further information on immunization requirements in various countries may be secured from the same source.

2. That employees be encouraged to take immunizations of proved effectiveness from their personal physicians. However, emergencies may arise when companies will find it advisable to offer such immunizations.

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APPENDIX E

REPORT TO THE API MEDICAL ADVISORY COMMITTEE

BY THE EDITORIAL SUBCOMMITTEE

Dr. J. P. Holt - Chairman

November 11, 1948

The Committee recommends that the toxicological reviews on the following compounds be published by the API:

Acetone
Carbon Monoxide
Hydrogen Fluoride
Phosphoric Acids

In view of the additional data and contemplated studies, it is recommended that the Toxicological Review on Silica be submitted to Dr. A. O. Seeler of Harvard for rewriting. A review on Silica should be prepared that contains no information on silica catalyst and at an appropriate time, a review on silica catalyst should be prepared.

In view of numerous comments received concerning various points in the review on "Safeguarding the Use of Cutting Fluids and Coolants," and especially in view of the criticism offered by Mr. W. L. Stewart that the recommendations contained were not applicable to both large and small industries, and in view of the considerable work carried out by Harvard University on this question, it is recommended that the proposed API publication be referred to Harvard for revision into a condensed form and resubmitted to the Subcommittee on Cutting Fluids.

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APPENDIX F

REPORT TO THE API MEDICAL ADVISORY COMMITTEE

BY THE SUBCOMMITTEE ON PERMISSIBLE CONCENTRATIONS

Dr. V. C. Baird - Chairman

November 11, 1948

I. Progress Report: Activities at Harvard University

HARVARD UNIVERSITY
School of Public Health

Department of Industrial Hygiene

55 Shattuck Street
Boston 15, Massachusetts

October 15, 1948

Dr. V. C. Baird
Humble Oil and Refining Company
P.O. Box 2280
Houston 1, Texas

Dear Doctor Baird:

I am enclosing a report of our activities for the past six months.

PROGRESS REPORT

Toxicological Reviews

During the past six months, tentative drafts of toxicological reviews of ammonium molybdate, acetic acid, hydroquinone, butyl acetate, mesitylene, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$ aromatics, and ammonium nitrate have been prepared. The toxicological survey on maleic anhydride has been revised. An extensive review of the literature on BAL has been prepared. Since it was felt that information concerning BAL would be of importance to the practicing physician as well as to the physicians of the petroleum industry, the Editorial Committee gave permission for the publication of the review in a journal with a general medical circulation. The review on BAL has been accepted for publication by the New England Journal of Medicine and will probably be published late this year.

We have been unable to find a competent bibliographical research assistant who can read foreign languages. This has hampered the work as much of the toxicological literature is in German and we cannot disregard this material. Bibliographic material has been collected on the following compounds:

acetylene
alkyl nitrates
alkyl peroxides
alkyl thioethers
alkyl sulfuric acids
ammonium acetate
ammonium chloride
ammonium hydroxide
amyl acetate
amyl alcohol
anthracene
arsine
barium chloride
barium hydroxide
barium nitrate
benzaldehyde
bromine
butadiene
calcium chloride
calcium hypochloride
calcium hydroxide and oxide
carbon black
chromate salts
copper napthenate
di alkyl sulfates
ethylene dichloride
hydrocyanic acid
naphthalene
a-naphthol
nickel carbonyl
potassium bromide
potassium chloride
potassium chromate
potassium hydroxide
potassium iodine
potassium nitrate
potassium permanganate
pyridine
sulfur trioxide
tributyl phosphite
trichlorethylene
tricresyl phosphate
triphenyl phosphate

Animal Studies

A. Mineral Oil in Kerosine Poisoning

An experiment was undertaken to determine whether mineral oil might be an effective antidote against kerosine. Albino mice weighing about twenty grams were given various doses of kerosine by stomach tube. One-half of the mice were given mineral oil by stomach tube within fifteen minutes after the dose of kerosine. The following table summarizes the results of the experiment:

| No. of Mice | Kerosine cc per kgm P.O. | Mineral Oil cc per kgm P.O. | No. of Mice Surviving on 14th Day |
|---|---|---|---|
| 10 | 12.5 | 0 | 10 |
| 10 | 12.5 | 25 | 10 |
| 10 | 25 | 0 | 10 |
| 10 | 25 | 25 | 9 |
| 10 | 37.5 | 0 | 7 |
| 10 | 37.5 | 25 | 8 |
| 10 | 50 | 0 | 6 |
| 10 | 50 | 25 | 4 |
| 10 | 0 | 50 | 10 |

B. Silica-alumina Catalyst

Samples of fresh and equilibrium silica-alumina catalyst together with appropriate analytical data were kindly supplied by the Esso Laboratories. Saline suspensions of the catalyst samples have been injected intraperitoneally into guinea pigs. To control

the experiment, additional groups of pigs have been injected with material known to be inert and with material of established silicotic potency. Guinea pigs from each treatment group will be sacrificed at intervals up to a year, unless the animals receiving the catalyst samples show a positive reaction sooner. Unfortunately the more innocuous the samples prove to be the longer the experiment will last.

Proposed Future Work

Considerable time will be required for the completion of toxicological surveys on the compounds listed above, and new ones which are suggested from time to time. Furthermore, revision of the toxicological surveys will have to be undertaken as additional information becomes available. Dr. Baird has suggested that a review of the present concepts of the treatment of burns be prepared and this would certainly seem to be a desirable undertaking.

Recent studies suggest that inhalation of certain silica-alumina combinations may produce pulmonary pathology that differs from that of classical silicosis. We do not know whether a negative intraperitoneal test will rule out the possibility of this type of pathology. It will, therefore, be necessary to carry out inhalation studies if the intraperitoneal tests prove to be negative. In view of the importance of the problem, it would seem wise to begin chronic inhalation studies promptly rather than to delay until the intraperitoneal experiment has been completed. We can undertake chronic inhalation experiments if it is so desired, but additional funds will be needed.

October 22, 1948

In view of your letter of October 18, 1948, can the following paragraph be added to my report?

"Unfortunately information is not available as to the extent of exposure to certain of the agents for which toxicological reviews are being prepared. It has been suggested that the value of the reviews would be greatly increased if an industrial hygiene engineer associated with the Harvard project could visit representative plants and actually determine the extent of exposure to certain toxic agents. The value of such information to those responsible for the control of industrial hazards would, of course, be great. Furthermore, specific information as to the extent of exposure to a given agent together with a review of available toxicological data would indicate whether or not toxicological studies were urgently needed. The problems concerning the silica-alumina catalyst and the $C_9$, $C_{10}$ and $C_{11}$ aromatics which now confront the Medical Advisory Committee are examples of situations in which it would be of value to have data as to actual exposure. While we feel that this project represents a highly desirable extension of the present program for toxicological surveys, we must point out that even if the Committee should approve and tentatively make funds available for its support, our ability to undertake the project will be contingent on the finding of a qualified person to do the field work."

Sincerely yours,
/s/ Albert O. Seeler
Albert O. Seeler, M.D.
Assistant Professor of Industrial Medicine
Harvard University

A. Review of work in past 6 months:

1. Preparation of Article on BAL, to be published in New England Journal of Medicine; also to be issued as a unit in toxicological reviews.

2. Tentative drafts have been prepared on ammonium molybdate, acetic acid, hydroquinone, butyl acetate, mesitylene, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$ aromatics, and ammonium nitrate. The toxicological survey on maleic anhydride has been revised.

3. Compounds now under study are:

acetylene
alkyl nitrates
alkyl peroxides
alkyl thioethers
alkyl sulfuric acids
ammonium acetate
ammonium chloride
ammonium hydroxide
amyl acetate
amyl alcohol
anthracene
arsine
barium chloride
barium hydroxide
barium nitrate
benzaldehyde
bromine
butadiene
calcium chloride
calcium hypochloride
calcium hydroxide and oxide
carbon black
chromate salts
copper napthenate
di alkyl sulfates
ethylene dichloride
hydrocyanic acid
naphthalene
a-naphthol
nickel carbonyl
potassium bromide
potassium chloride
potassium chromate
potassium hydroxide
potassium iodine
potassium nitrate
potassium permanganate
pyridine
sulfur trioxide
tributyl phosphite
trichlorethylene
tricresyl phosphate
triphenyl phosphate

4. Animal Studies - mineral oil in kerosine poisoning.

5. Animal Studies - Silica-alumina Catalyst.

II. Program for Future Work at Harvard

1. Continuation of toxicological surveys.

2. Continuation of silica-alumina catalyst studies.

3. Report on present status of treatment of burns - with a recommendation for a preferred procedure for treatment.

4. Review available information on toxicity of $C_4$ to $C_{12}$ aldehydes with recommendations for further investigation if needed.

5. That Professor Drinker and associates at Harvard University be authorized to add an industrial hygiene engineer to their staff to work full time for one year with Dr. Seeler on the environmental aspects of toxic hazards relating to the petroleum industry.

III. Report on Assignment of Experimental Study of $C_9$ - $C_{12}$ aromatics to Baylor University, College of Medicine

Increase appropriation from $10,000 to $15,000 - additional appropriations will be necessary to carry out chronic toxicity studies upon the completion of this work:

BAYLOR UNIVERSITY
College of Medicine
Houston 1, Texas
P.O. Box 156

October 12, 1948

Dr. V. C. Baird
Humble Oil and Refining Company
Houston, Texas

Dear Dr. Baird:

We are enclosing herewith a revised initial program for the toxicity studies on the aromatic hydrocarbons. This has been revised in the light of the information sent to us by Dr. Holt and from the point of view that it would furnish necessary data, not now available, to initiate the more important chronic inhalation and absorption studies. Arbitrary selection of dose levels in inhalation studies as suggested by Dr. Seeler, while furnishing a working hypothesis, could be extremely time-consuming and expensive without establishing, with any degree of certainty, maximum limits of exposure or truly significant functional changes from chronic exposure.

We would appreciate any further suggestions that either you or Dr. Holt may have on this program. As near as we could estimate, it will probably cost about $15,000 to carry through the work we have indicated on the eight different compounds. As soon as we hear from you, sufficient copies will be furnished to Dr. Baird to be supplied to the members of the committee for reading before their meeting.

Trusting that this program meets with your approval, we are

Cordially yours,

/s/ Carroll A. Handley

CARROLL A HANDLEY, Chairman
Department of Pharmacology

/s/ Joseph H. Gast

JOSEPH H. GAST, Chairman
Department of Biochemistry

JHG:bb
cc: Dr. J. P. Holt

## SUGGESTED INITIAL PROGRAM FOR TOXICITY STUDIES ON CERTAIN AROMATIC HYDROCARBONS

While the information most urgently desired on these compounds is the chronic toxic effect following inhalation and absorption through the skin, in order to do chronic inhalation and absorption studies it is necessary to obtain preliminary information on toxicity of varying dosage levels. Moreover, some information should be at hand on the earliest pathognomonic signs observable. To attain these ends expeditiously so that the chronic inhalation studies can be initiated, it is suggested that the following program be inaugurated:

A. Compounds to be studied (these to be supplied to us):

1. Typical C-9
2. Typical C-10
3. Typical C-11
4. Typical C-12
5. Fraction of typical commercial product containing principally C-9 aromatics
6. Fraction of typical commercial product containing principally C-10 aromatics
7. Fraction of typical commercial product containing principally C-11 aromatics
8. Fraction of typical commercial product containing principally C-12 aromatics
9. Benzene for positive control

B. Studies to be carried out:

1. Acute oral toxicity

Determination of dose mortality curve and calculation of LD-50. It would be desirable to determine the LD-50 in more than one species, and to contrast pathological changes with those found in acute inhalation.

2. Acute inhalation toxicity

Exposure to saturated vapors of compounds under consideration for varying times to obtain the necessary preliminary information on concentration levels and the most prominent functional and pathological changes to use later in chronic studies.

3. Skin absorption

The daily application to the clipped skin of rabbits (or the continuous application under a rubber sleeve as suggested by Draize, Woodard and Calvary) could be used to approximate the acute skin absorption. Blood studies and tissue pathology should be performed on these animals, so that data can be used to plan chronic studies.

4. Skin sensitization

Landsteiner and Jacobs showed that while male guinea pigs are suitable for evaluating the sensitization potential of compounds applied to the skin. This method has been used to distinguish between agents that will affect only a few individuals in a large population from those that have a relatively great sensitization potential. *

C. Animals to be used

In the acute oral and acute inhalation studies, rats, guinea pigs, and rabbits or dogs could be used. When sufficient information of skin absorption and sensitization is available, patch tests can be carried out on humans. The selection of species for chronic studies depends to some extent on the species variation observed in these studies.

D. Facilities available

1. Six to twelve air-conditioned animal rooms
2. Histopathological laboratory for studies of tissue sections
3. Completely equipped biochemical and pharmacological laboratory facilities
4. Supervisory personnel on the permanent faculty in the departments of Pharmacology, Biochemistry and Pathology

E. Purposes for which funds supplied would be used

1. Animals, feed and expendable supplies
2. Additional animal cages and equipment for inhalation studies
3. Personnel for histological, physiological studies, care and observation of animals
4. Overhead and maintenance

While we are aware of the need for the information to be obtained from chronic studies, we believe it would be wasteful of time and money to attempt such studies until the preliminary data outlined above on the acute toxicity via three paths of entrance to the body and their pathology were available as well as adequate equipment for sufficient groups of inhalation and skin absorption studies so that the biological variable inherent in all animal work could be adequately controlled.

All data obtained, not trade secrets, to be published in reputable scientific journals.

IV. Proposed collection of data on silica-catalyst problem. This data will be summarized by Dr. Seeler and presented to our committee at the Spring meeting - this data to be collected by circularization of industry.

V. Health hazards in the vicinity of Fluid Catalyst Cracking Units - to be presented by T. M. Frank, M.D.

* Clarification of this paragraph is desirable - Editor.

VI. Budget for next 12 months

1. Continuation of work at Harvard University - Estimated at $10,000 per year.

2. Requested but unassigned - $15,000.

3. Studies for $C_9$ - $C_{12}$ aromatics ($10,000 already appropriated) - $5,000.

AS AMENDED NOVEMBER 12, 1948