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~~SECRET~~ CONFIDENTIAL

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

January 31, 1949
New York, N.Y.

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

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

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

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

Review of Discussion

1. Purpose of Meeting

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

2. Objectives

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

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

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

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

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

5. Selection of Samples for Testing

(a) Crudes

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

(b) Processes

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

<u>Thermal</u>	-	Gas Oil
		Resids
		Reforming
		Coking
		Gas Reversion
		Steam Cracking

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

4. Samples Tested by the Kettering Laboratory

Dr. Horton reviewed the results of the studies by the Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, on eight samples which had been selected some time ago by the Subcommittee on Carcinogenicity. The results were reported in detail under date of November 5, 1948, by Dr. F. F. Heyroth. Only one sample, Oil No. W-3632 (a clarified oil from catalytic cracking) disclosed a high order of carcinogenic activity. Another oil, W-3631, (a residual from thermal cracking) produced only one tumor of a low grade of malignancy. A third oil, No. 11930, (a low-boiling distillate from catalytic cracking) produced changes in the skin of two animals which gave a moderate evidence of malignancy. In this connection, Dr. Horton stressed the need for subjecting as many animals as possible to a pathological examination in order to avoid errors that frequently arise from gross observation. He cited an example where lesions that had been reported as tumors by visual inspection (Oil No. 3631) were found to be not malignant when areas of the skin were examined microscopically. In another case (Oil W-3632-3) a tumor was found that was not detected by visual examination.

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

The question was raised whether information was available on the feed stocks to the processes from which the eight W-3631 samples were produced, and also yield data and operating conditions. Mr. Warrick, who had been instrumental in obtaining these samples, stated that such information had not been requested, as it was doubted that it would have been furnished; however, he agreed to acquaint Dr. Horton with his contacts in procuring these samples and Dr. Horton will attempt to obtain whatever information the respective companies may be in a position to disclose to him.

5. Products from Other Industries

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

6. Funds Available

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

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

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

The meeting adjourned at 12:45 P.M.

Roxy Dowling
Acting Secretary

2/8/49

(C O P Y)

STANDARD OIL DEVELOPMENT COMPANY

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

January 7, 1949

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

Dear Mr. Stroop:

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

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

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

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

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

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

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

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

Please advise.

Very truly yours,

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

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

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Recd. 3/21/49

CONFIDENTIAL

MINUTES

SUBCOMMITTEE ON CARCINOGENICITY

March 11, 1949

Dr. Horton

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

MEMBERS PRESENT:

A.E. Hoag
J.P. Holt
W.R. Levis
M.N. Newquist
McIver Woody

R.S. Bonsib
A.E. Dooley
H.G.M. Fischer
H.P. Lankelma
K.G. MacKenzie

GUESTS:

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

TOTAL IN ATTENDANCE - 13

MEMBERS ABSENT:

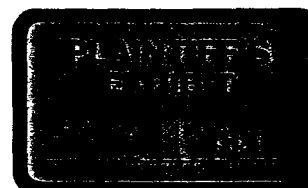
L.E. Curtis
T.M. Frank
T.J. Kelly
C.A. Swan

L.C. Beard
~~A.J. Koewing, Jr.~~
H.H. Zuidema

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

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

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



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

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

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

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

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

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

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

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

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

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

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

Dr. Holt divided the problem into four aspects:

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

2. Where does it exist; in what operations, oils, fractions, materials, etc. is there a hazard that requires protective measures?
3. Can these operations be changed to control the problem?
4. Development of a technique to eliminate animal testing.

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

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

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

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

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

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

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

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

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

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

and the foot-note was omitted.

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

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

A.E. Dooley
Secretary

McIver Woody
Chairman

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AMERICAN PETROLEUM INSTITUTE
SUBCOMMITTEE ON CARCINOGENICITY

SPRING MEETING

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

MEMBERS PRESENT

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

ASSOCIATES PRESENT

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

VISITORS

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

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

GUESTS

S.J.M. Auld
R.D. Bent
J.W. Hammond
R.A. Kehoe
W.L. Simpson
J.B. Stucker
H.G.S. vanRaalte
H.R. Warrick

Institute of Petroleum, London
Atlantic Refining Company, Philadelphia
Humble Oil Company, Houston
University of Cincinnati
Detroit Institute of Cancer Research
Pure Oil Company, Chicago
Shell Oil Company, Curacao, Neth. Antill.
The Texas Company, New York

ADVISOR

D.V. Stroop - API

TOTAL IN ATTENDANCE - 36

MEMBERS ABSENT

○ W.R. Levis
○ C.A. Swan



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New members of the Subcommittee and guests were introduced.

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

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

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

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

- a. Supervising application of the samples to the mice.
- b. Establishing standard criteria for:
 1. Determining existence of tumors.
 2. Differentiating between tumors and dermatitis.
 3. Establishing whether tumors are benign or malignant.

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

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

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

Dr. Newquist thought experiments on primates should be started at an early date because of the time required to get results. Dr. Kehoe replied that investigators of carcinogenicity of petroleum and its products had two objectives: first, to find a tool for determining potencies; and second, to determine whether results of animal tests are applicable to man. The first phase required a group of stable, non-variable animals, such as the highly inbred C₃H mouse strain. This stability and lack of variability between the individual animals was not found in primates. As to the second phase, there was no definite evidence as yet that the results obtained in mice were applicable to man. It might be necessary to use other animals to establish the relationship. In that case, the laboratory had other animals available and, while it was not anticipated that monkeys would be used at first, this might be done later. Human experiments could not be set up until a good deal more information and knowledge was available, and even then only carried out under his personal responsibility.

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

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

Venezuelan crude - naphthenic type

Middle East crude - Kuwait

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

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

fractions on plants some index of carcinogenicity might be developed.

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

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

- 1 - Information on carcinogenicity be exchanged with the Institute of Petroleum.
- 2 - The budget for the year beginning July 1st, 1949 for the program at Kettering Laboratory be increased to \$100,000.00

McIver Woody
Chairman

A.E. Dooley
Secretary