

For Information Only - Not For Publication

REPORT ON THIRD MEETING

Research Project MC-1 Advisory Committee
July 10, 1952
Kettering Laboratory
Cincinnati, Ohio

.....

MEMBERS PRESENT OR REPRESENTED

M. N. Newquist, M.D. - Chairman
R. E. Eckardt, M.D. - Acting Sec'y.
L. C. Beard, Jr.
Kieffer Davis, M.D.
C. M. Doane (For E. W. Adams)
T. M. Frank, M.D.
R. M. Landon
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

MEMBERS ABSENT AND NOT REPRESENTED

C. M. Hine, M.D.
E. K. Linder, M.D.

OTHERS PRESENT

F. F. Heyroth, M.D. - University of Cincinnati
A. W. Horton - University of Cincinnati
Arthur Pabst (Socony-Vacuum Oil Co., Inc.)
J. J. Phair, M.D. University of Cincinnati

EB 005127

API 05383

SC-API-2295

The attached agenda of the meeting, which had been distributed by Dr. Newquist prior to the meeting, was used as the program.

ITEMS 1 AND 3

Dr. Horton presented to each of the members the attached "Memorandum from the Kettering Laboratory, Third Meeting of the Advisory Committee, API Research Project MC-1". Dr. Horton followed the outline presented in this memorandum with additional comments, as follows:

- a. The year 1951 in terms of the health of the experimental animals did not satisfy the laboratory as well as the year 1950 and, therefore, the laboratory has considerable reservations concerning the accuracy of mouse test data determined in 1951. This has led to the adoption of correction factors for the determination of the P_{MC} values of the various materials tested. One source of this difficulty was discovered in infestation of the animals with mites. These mites presumably caused an eye disease in the mice, which was thought to be due to the scratching by the animals in an attempt to rid themselves of the mites. The mites have now been controlled by using a dusting powder consisting of a low concentration of Chlordane plus pyrenones.
- b. Criteria used by the laboratory for determination of what is considered a good animal test include 85% survival of the animals for at least 6 months, or until 50% of the animals have tumors.
- c. Experiments are designed so that the average latent period will be not less than 100 days or more than 280 days. If the average latent period is less than 100 days or more than 280 days, it is believed that the accuracies of the P_{MC} determination will be considerably reduced.
- d. The desirability of weighing the animals once a week is now recognized and attempts to weigh them at this frequency will be made in order that no breaks in the weight curves will be present in the data sheets presented to the group.

EB 005128

ITEM 2

In the discussion that followed on Dr. Horton's comments it was brought out by Dr. Beard that he had heard of some data from England which indicated that in straight run distillates maximum carcinogenicity is observed in the 300-400°C. cut. Dr. Horton then emphasized that the nature of the distillation must be fully understood before the significance of this observation could be accepted, since in distillations in which poor fractionation occurs a material presumably cut between 300 and 400°C. could contain considerable amounts of material boiling below 300°C. and boiling above 400°C.

Later, Dr. Beard placed on the board the following 9 variables which may affect the quantitative nature of mouse tests and their extrapolation to human significance:

1. The amount of carcinogen per unit of area. EB 005129
2. The dilution of the carcinogen.
3. The frequency of application.
4. The effect of the physical state, i.e., viscosity and surface tension.
5. The health of the animals.
6. The psychic state of the animals as concerns eating.
7. The effect of area of application.
8. The persistence of carcinogenesis if applications are stopped.
9. The variability of susceptibility of human skin, i.e., black versus whites.

Mr. Shepardson then brought up the possibility that the work which Dr. Horton has done indicates that there may be several types of response to carcinogenic agents. Thus, with fuel oils and methycholanthrene it would appear that the activity of a given oil does not increase with the increase in dosage. This conclusion was reached as a result of the experiments using 20 and 100 mg. of

material per application with solutions of methycholanthrene and with API No. 8. In the latter case activity seemed to increase with dosage. Dr. Eckhardt then commented that this variation in activity might be both a function of the dosage per application and the dosage per week (frequency).

A considerable amount of discussion followed, the outgrowth of which seemed to be that a great deal more additional work will have to be done in order to develop all of the various variables which seem to influence the quantitative nature of the mouse test. There were many who expressed the opinion that to think that we could begin tapering off on the amount of effort in this program in 2 years' time is an extremely optimistic outlook. Rather, it was their feeling that this type of research will have to continue for a considerably longer period than 2 years at the present level of effort. Dr. Eckardt introduced the concept that perhaps we have the practical answers which we need at the present time to control this problem and that these various refinements of the technique, although of extreme interest, would not contribute appreciably to the development of any practical solutions. He compared to a degree the establishment of MAC values in which a considerable safety factor is always allowed, and where the MAC value is exceeded certain medical supervision is carried out. From the strictly medical standpoint, this is the type of approach which most medical departments and industrial hygiene departments will require. Whether this approach will provide the answers needed by the refiners is a question that can only be answered by the refiners.

ITEM 4

Dr. Beard brought with him a sample of alkylated polystyrene which had been shown to increase the viscosity of a catalytically cracked recycle oil from about 84 to about 1100 when 5% of the material was added to the oil. It was suggested as a possible agent to use in increasing the viscosity of carcinogenic oils without appreciably changing their chemical composition. Reference was made to a letter submitted by Mr. Shepardson which indicated that Vistanex and polypropylenes would apparently not satisfy the requirement of increasing the viscosity sufficiently with a sufficiently small addition of the agent.

ACTION

Dr. Horton will test on mice some petroleum fractions of known potencies but those viscosities have been altered by the addition of alkylated polystyrenes (using Dr. Beard's sample) in order to evaluate the effect of viscosity on potency.

EB 005131

ITEM 5a

Dr. Beard indicated that experience thus far has shown that most occupational cancers allegedly due to petroleum products had resulted from prolonged contact with uncracked distillates and residua. For this reason it is his belief that additional studies should be carried out on this type of material in order to help us develop the answers to the problems of this type of material.

ACTION

Dr. Horton feels that the samples he already has on hand including the fractions of the three crudes (Cklahoma, Kuwait, La Gunillas) presently being studied in Great Britain would suffice for the time being.

API 05387

ITEM 5b

Dr. Beard suggested that it probably would be helpful if Dr. Phair could or would review critically the literature on cancer as related to petroleum with particular emphasis on keeping the members of the committee informed of any new articles which are appearing in the literature on this subject by circulating to the members of the committee a critical abstract of each of these articles. Dr. Phair felt that this could well be done by himself and is presumably planning to undertake such a critical abstracting of current literature for the committee.

ACTION While Dr. Phair is favorable to such an undertaking he hesitated to commit Kettering Laboratory in the absence of Dr. Kehce. Therefore, this matter awaits official clearance from Kettering Laboratory.

EB 005132

ITEM 6

Dr. Beard told the group of the activities of the Sub-Panel on Lubricants and Process Products Hygiene of the API Lubrication Committee. A small subcommittee has been formed to discuss the advisability of labelling petroleum products in order to warn customers of potential hazards. Solvents prepared from petroleum should probably bear labels which are in conformity with those recommended by the Manufacturing Chemists' Association. Other materials, such as lube and cutting oils, should probably bear a simple label which indicates that the oil may cause skin irritation, that it should be kept off of the skin and that if it cannot be kept off of the skin, it should be washed off as soon after contact

API 05388

as practicable. Mr. Mackenzie emphasized the need of making such washings practicable so that workers would not be spending half of their day washing things off of their hands.

ACTION None taken

ITEM 7

Dr. Landon reported that a verbal summary of the report of the RPA Committee was given to the General Committee, Division of Refining, in May of 1952. As a result, the General Committee, Division of Refining, addressed a letter to the chairman of the Medical Advisory Committee asking that the Committee recommend minimum standards for medical care, qualifications of medical directors and minimum standards for adequate medical records. This letter will presumably be presented to the Medical Advisory Committee at its next meeting. It was the feeling of the RPA Committee that the General Committee, Division of Refining, recognizes the importance of the carcinogenic problem to the petroleum industry and the general recommendations of Dr. Kehoe that the petroleum industry must develop the adequate medical and industrial hygiene measures to control this problem. However, the General Committee, Division of Refining, went further than the simple problem of carcinogenesis and included, presumably, all of the medical problems of the petroleum industry in their request.

ACTION None taken

EB 005133

ITEM 8a

Dr. Phair indicated that he has now received about 900 historical records. Apparently he is receiving very few current

API 05389

records and asked the cooperation of the Committee to stimulate the various medical directors to send in their current records of cancer cases. He indicated that since April, only 35 or 36 records have been sent to him. He stated that up until the present time there has been no real call on his services in a consultation capacity. Discussion by the Committee indicated that Dr. Newquist would provide the stimulus to the various medical directors to send in their current cancer cases, and that following the action of the Medical Advisory Committee, on the request of the General Committee, Division of Refining, much of the work of Dr. Phair may be implemented because some of the companies which do not now have adequate medical records may begin to develop them on the recommendation of the API as to what constitutes adequate medical service, adequate medical personnel and adequate medical records.

ACTION

The Chairman of the Subcommittee on Carcinogenicity will aid the epidemiological studies by stimulating the various medical directors in the petroleum companies to submit the data requested by Dr. Phair.

ITEM 3b

Dr. Newquist mentioned the need for epidemiological studies among the employees of customers of petroleum products since most of the cases are apparently occurring among users rather than among manufacturers. He indicated, however, that the collection of such data would require great tact. Dr. Phair felt that the University of Cincinnati could probably make such studies at the proper time and in a proper manner.

API 05390

ACTION

It was the consensus of the RPA

EB 005134

Committee that the University of Cincinnati should undertake epidemiological studies among customers at an appropriate time. This matter is subject to further action by the Subcommittee on Carcinogenicity.

ITEM 9

Under item 9 on the agenda Mr. Shepardson presented a table of data collected by the Standard Oil Development Company and New York University which indicated that there are at present 4 methods which will predict tumor potency within what it is believed to be a useful range of accuracy. These 4 methods involve: (1) ultraviolet absorption at 360 μ of a 650-1000 $^{\circ}$ F. cut of the oil, (2) polarographic determinations which depend upon the diffusion current at two voltages, (3) the caffeine number which depends upon the ultraviolet absorption at two wave lengths of caffeine extract of the oil, and (4) the high aromatics characterization which is a more complicated method and was not discussed in detail. He indicated that the Development Company is in the process of checking these four methods in three different laboratories in order to determine their reproducibility from laboratory to laboratory. He urged that the University of Cincinnati give serious consideration to checking these methods also since they have been found to be so useful by the Development Company. He indicated willingness to provide to the University of Cincinnati the details of each of the methods as soon as it had been determined that they were reproducible from laboratory to laboratory.

EB 005135

ACTION Dr. Horton has already been in communication with Mr. Shepardson on the above subject and he will give it further study in connection with Kettering's effort to develop an analytical tool.

API 05391

ITEM 10

The Committee adjourned at 4:30 p.m., after agreeing that the next RPA Committee meeting should be held September 24th, at the Conrad Hilton Hotel in Chicago, one day prior to the meeting of the Medical Advisory Committee which is to be on September 25th. It was felt by most members of the RPA Committee that a meeting of the Subcommittee on Carcinogenicity prior to the date of the September Medical Advisory Committee meeting would not be necessary if the Subcommittee could handle its interim work by mail. Considerable duplication of presentation and discussion can be eliminated by having the Subcommittee make its report, including Dr. Horton's report, to the Medical Advisory Committee as a whole on September 25th.

NOTE: During the meeting Dr. Horton distributed a sheaf of data sheets (copies mailed to MAC Members 7-16-53) on various mouse experiments which are to be included in the available data thus far submitted. Dr. Horton indicated that he would present a series of data tables for the consideration of the full Committee at its meeting in Chicago.

R. E. Eckardt, M.D.
Acting Secretary

EB 005136

M. N. Newquist, M.D.,
Chairman

API 05392

MEMORANDUM FROM THE KETTERING LABORATORY

THIRD MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

July 10, 1952

A. Tests to determine applicability of standard reference curves based on methylcholanthrene to determination of relative carcinogenic potency of refinery samples.

1. Preliminary data on catalytically cracked residuum, API-63:

<u>No. of 100 mg. Applications Per Week to C3H Mice</u>	<u>Average Latent Period for Tumor Induction</u>	<u>Relative Potency, P_{MC}</u>
1	34 weeks	~ 0.13
2	22 weeks	~ 0.14
3	15.4 weeks	0.14

2. Further tests under way on Fuel Oil 30 (API-113), previously examined in skin painting and washing experiments.

B. Further rechecks on reference standards to clarify influence of following variables:

EB 005137

1. Dosage per application.
2. Change from Jax to Heston sub-line of C3H strain of mice by suppliers (Roscoe Jackson Memorial Laboratory)
3. Purity of methylcholanthrene (all commercially available grades found to contain traces of a powerful skin irritant, removable to a large extent by chromatography).

API 05393

- C. Results on API-83-2 indicate that mild air oxidation of catalytically cracked residua not useful for reduction of concentration of carcinogens.
- D. Effects on rate of tumor induction of decreasing severity of tests by decreasing dosage per application.
1. For solutions of methylcholanthrene, same rate of tumor induction by 20 mg. and 100 mg. applications (results to be rechecked on Heston sub-line with purified methylcholanthrene).
 2. For fuel oil blends (probably relatively low concentration of accelerating constituents), preliminary data indicates rate of tumor induction same for 5 mg., 20 mg., or 100 mg. applications.
 3. For API-8 (catalytically cracked residuum of high potency) rate for 20 mg. applications significantly slower than for 100 mg. applications, possibly indicating a critical dosage level for action of accelerating constituents.
- EB 005138
- E. Correlation of potencies of finished lubricants with their ultraviolet absorption spectra.
1. API-99, spectrum type C (0.5), weakly acid treated naphthenic stock containing 0.2 percent anti-oxidant, PMC 0.07.
 2. API-100, spectrum type B (0.3), blended, solvent extracted lube containing no additives, yield of papillomas zero after 41 weeks of painting (3 applications per week, C3H mice).
- API 05394

- F. Tumor yield from white oils, API-80 and 95, zero after one year of painting.
- G. Fractionation studies to determine classes of 3- and 4-ring compounds responsible for carcinogenicity.
1. Exhaustive Diels-Alder reaction (maleic anhydride) on API-8 yielding anthracenes, benzanthracenes, dibenzanthracenes (?), naphthacenes, naphthopyrenes (?), and nitrogen bases (?). These classes separated by solubility properties of their succinic acid adducts and adsorption properties (on alumina) of the recovered parent compounds to prepare samples for biological testing.
 2. Indications from results of biological and analytical tests on API-8-19 and 8-20 that pyrenes and anthracenes not contributing to potency of distillate fractions, boiling 700-800°F. (vacuum corrected), from API-8.
EB 005139
 3. Fraction boiling lower than chrysene of aromatic compounds from API-12, F.C.C. residuum, being treated to remove pyrenes and anthracenes; fraction thus prepared for mouse testing to contain alkylphenanthrenes, alkylbenzfluorenes, benzphenanthrene (?), etc.
 4. Further chromatographic fractionation of distillate fractions of API-8 corresponding to 8-10, 8-11, and 8-12 to separate 4-ring compounds into classes for biological tests.

API 05395

H. Accelerating constituents of cracked oils.

1. Further evidence that colorless fraction from chromatography of API-8 has accelerating effect on rate of tumor induction. Potency of API-8-21 not significantly different from that of API-8, whereas comparable 50:50 blends with sec-amylbenzene (see 8-16) or with white oil and reduced crude (see 8-4) demonstrated marked reduction in potency.
2. Resin removed from API-71, T.C.C. residuum, not responsible for high potency of this relatively low boiling catalytically cracked product. Testing and further fractionation of colorless chromatographic fraction of API-71 to be carried out.
3. Low dosage tests on cracked sidestreams for further evidence on possible contribution of accelerating constituents to their moderately high potency when tested in 100 mg. applications.

EB 005140

API 05396