REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY

to the

API MEDICAL ADVISORY COMMITTEE

On Tuesday, October 25th, the Subcommittee on Carcinogenicity met in Dr. Eckardt's room in the Terrace Plaza Hotel in Cincinnati. The meeting got under way about 9:00 with the following members in attendance: Dr. M. N. Newquist, Dr. E. K. Linder, Dr. R. C. Mithoff, Dr. E. W. Adams, Dr. M. M. Marisic, and Dr. R. E. Eckardt. The reports by Dr. Horton and Dr. Phair were discussed. At about 10:30 the group moved to the Kettering Laboratory and conducted their meeting in the presence of Dr. Kehoe, Dr. Horton, Dr. Phair, and Dr. Heyroth of the Kettering Laboratory. In addition, Dr. B. E. Bennison of the Medical Research Division of Esso Research and Engineering Company sat in as a guest.

Distributed to all members of the Medical Advisory Committee prior to the San Francisco meeting are reports by Dr. Horton and Dr. Phair dated October 1955 and summarizing all the work which has been done on this project to date. In addition data tables of Dr. Horton's work will have been distributed to the members of the Medical Advisory Committee by the time of the San Francisco meeting.

In Table 1 of these summary tables, which is seventeen pages long, the data on various fractions from the refining of petroleum have been collected. Included in the Table besides the relative carcinogenic potency is a column listing the benzpyrene content of the oil sample as determined by the method Dr. Horton had published in the scientific literature. In general it can be said that particularly for severely cracked materials the relative carcinogenic potency at least roughly follows the benzpyrene content of the oil. There are however certain samples, in particular lubricants and uncracked stocks, which show a much greater carcinogenic potency for the mouse than would be anticipated from the benzpyrene content. It was this observation which led the Kettering Laboratory to the theory that certain materials serve as accelerators to the carcinogenic action of polycyclic aromatic hydrocarbons. As a result of this theory the laboratory is now tentatively expressing its concept of carcinogenic potency in the following formula:

$$P_{MC} = M_a (C_1 + C_2 + C_3)$$

In this summary the various terms are defined as below:

P_{MC} is equal to the carcinogenic potency for mice exhibited by an oil, expressed in terms of the concentration of methylcholanthrene in benzene that produces tumors in the skin of mice at the same rate and under comparable experimental conditions as that produced by the oil.

M_a equals the contribution to potency due to accelerators.

C_1 equals the benzpyrere type polycyclic carcinogens expressed in methylcholanthrene equivalents.

C_2 equals the carcinogenic substances extractable by maleic anhydride (probably derivatives of benzanthracene) expressed in methylcholanthrene equivalents.

C_3 equals carcinogenic substances insoluble in concentrated sulfuric acid expressed in methylcholanthrene equivalents.

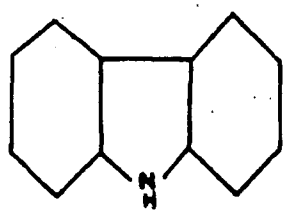
Chromatography will presumably separate a given oil into two components, the first of which will represent the M_a in the above equation and the remainder of which will represent the $(C_1 + C_2 + C_3)$. Thus by chromatographing a series of oils in which the P_{MC} is known (as shown in Table 1, last column) it should be possible to solve the above equation for M_a since the $(C_1 + C_2 + C_3)$ portion of the equation will be retained on the chromatograph column and can be elutriated as a group free of the M_a component. This work naturally will be principally devoted to a study of the differences between uncracked stocks since it is in these uncracked stocks that the M_a appears to have the greatest significance. In fact, the laboratory has developed some evidence, as indicated in Table 6 of their most recent tabulation summary, that the M_a factor may vary from one to six or possibly even more.

The laboratory has begun to use benzpyrene as a reference carcinogen since it has been the feeling of the Subcommittee and the laboratory that benzpyrene might be a more representative carcinogen for petroleum products than methylcholanthrene. The data collected by the laboratory and summarized in Table 4 suggest that benzpyrene at a given concentration has only about 50% of the activity that the same concentration of methylcholanthrene has. This fact should be kept in mind in attempting to interpret any experimental work which the laboratory is doing in which the benzpyrene is used as a carcinogen.

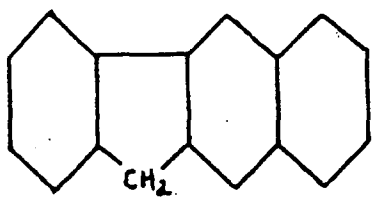
The laboratory has undertaken some work on the possible inhibiting effect of one carcinogen upon another and believes that all published data claiming to show inhibition of one carcinogen by another are subject to the error of poor health of the animals due to high concentrations of mixtures of the two carcinogens. The experimental data in support of this concept are presented in Table 5.

In Table 7 data are presented by the laboratory on solutions of benzpyrene in various solvents which suggest that many of the solvents have a significant accelerating action of benzpyrene much as they did upon methylcholanthrene. For instance, this accelerating effect seems to have made itself evident in paraffins, olefins, cycloparaffins, alkyl benzenes, and alkyl naphthalenes, particularly when these materials exceeded a certain chain length. Other experiments which have been conducted by the laboratory are summarized in Tables 8, 9, 10, and 11 and the washing experiments are summarized in Table 12, which contains three pages.

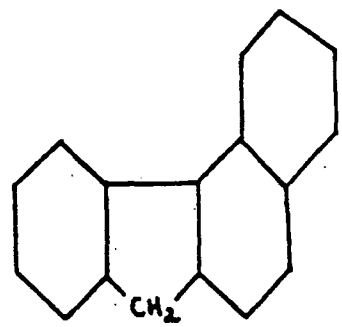
The laboratory is now collecting evidence which suggests that the aromatics of oils of the nature of API-8 contain about 15-20% of non-hydrocarbons. These non-hydrocarbons seem to be of the carbazole type. For instance, the laboratory has isolated from API-8 (Table 1 page 13) and other higher fractions of this series the components carbazole which has the formula below.



In addition to this type compound the laboratory has isolated compounds of the 1,2-benzfluorine class and of the 2,3-benzfluorine class.



2,3-benzfluorine



1,2-benzfluorine

It is important to emphasize that though structurally these two classes of compounds appear quite similar, nonetheless chemically they are quite different.

In addition to this chemical work the laboratory is pursuing its attempt to isolate what it calls a low boiling carcinogen which presumably boils in the range of 720-750°F. It does not believe that carbazole or the benzfluorines are this carcinogen but it does believe that evidence has accumulated to suggest that there must be such a carcinogen so that isolating it may be of help in solving some of the problems now facing the laboratory in its solution of the problems of the carcinogenicity of this type oil.

It is the belief of the laboratory that when they have obtained an ultimate solution to the equation

$$P_{MC} = M_a (C_1 + C_2 + C_3)$$

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that it will then be possible to present to the petroleum industry an analytical tool which will permit the evaluation of the potential relative carcinogenicity of any petroleum material. It should be recognized however that this method will probably be long and tedious and require the determination of at least four components and therefore may not be particularly

practical for use in refinery operations. However, this bridge presumably can only be crossed when we come to it. At the present time the laboratory estimates that it will take six generations of mice at a minimum to obtain the necessary answers to the above equation. With a minimum life of nine months for each generation and assuming that each step proceeds without any hitch, this represents a minimum of fifty-four months of additional work by the laboratory in the solution of this problem.

The report by Dr. Phair shows encouraging results in attempts at making statistical evaluations of cancer in the various participating companies. It is, however, discouraging to realize that only sixteen of twenty-five companies have participated in this effort and that in the last few years the number of participants may have diminished even more than this. For instance, in 1954 only twelve companies participated in the epidemiological studies. It should be quite apparent to the medical members of the Medical Advisory Committee that if there is any hope of accomplishing anything with these epidemiological studies this hope resides in the full cooperation of all of the participating companies. This would then provide a large enough sample so that significant statistical analysis could be made and leads shown which might permit more detailed studies by individual companies or by the group as a whole. Nonetheless it must be recognized that if participation does not continue in this project it is doomed to failure through no fault of Dr. Phair, but strictly due to the failure of cooperation on the part of the participating companies and their medical directors on the Medical Advisory Committee. Since the Subcommittee has been emphasizing the epidemiological aspects on this problem so long and intends to push the epidemiological studies, even at the expense of the experimental studies, it therefore seems apparent that if we are unable to obtain cooperation the epidemiological studies might just as well be terminated. The Subcommittee is in no position to do anything but make suggestions to the individual medical directors who sit in on the Medical Advisory Committee, but it is the suggestion of this Subcommittee that the experimental work in and of itself has no real value since it has no direct tie in with the human experience. The whole meat of all of the work which has been sponsored by the Subcommittee on Carcinogenicity lies in an attempt to develop an understanding of things that may be of importance to man and if the studies on man, namely the epidemiological studies, are not successful then all of the work of the Subcommittee will have been in vain. The Subcommittee simply wishes to re-emphasize that for the past five or six years it has been stressing and encouraging all medical directors to participate in the epidemiological studies.

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October 31, 1955