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

DATE: 1953 Jan-May

DOC#: API030

DOCUMENT DESCRIPTION: Letters, Memos, Reports, Financial Reports & Other Relevant Documents from Jan-May, 1953

ITEM 1

RP(MC-1)

The minutes of the Fourth Meeting of the ~~Medical~~ Advisory Committee were approved. Subsequently the meeting followed the agenda which had been prepared by Dr. Newquist prior to the meeting with slight modification in that the progress report and the research activities for the year beginning 7/1/53 were combined in both Dr. Horton's and Dr. Phair's reports.

ITEMS 2 AND 4 - DR. HORTON'S REPORT

As the basis for his discussions, Dr. Horton used the attached "Memorandum from the Kettering Laboratory-Fifth Meeting of the Advisory Committee API Research Project MC-1" dated January 16, 1953. Considerable discussion was given to the opening two paragraphs which justified the use of mice in appraising the hazards of skin cancer in workmen. In response to a specific question from Dr. Adams, Dr. Horton stated that washing is more effective in reducing carcinogenic potency than a reduction in the dosage of carcinogen applied. As evidence he presented the experimental evidence which was obtained with washing experiments with API-8 and API-113. It was then suggested that consideration be given to a washing experiment with API-113 and API-57 in which these oils would be painted on at a level of 100 mg. two times a week and washed off after 9 hours in contact with the skin.

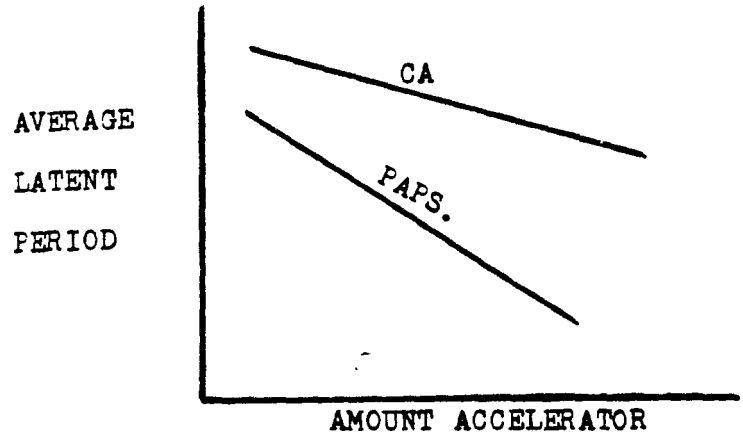
Perhaps the greatest interests in Dr. Horton's report are his observations or theories that the potency of a particular material is dependent less on the amount of carcinogen than on its concentration; whereas, the effect of accelerators is dependent less on the concentration than on the total amount applied at each application. Although this is an interesting thought, it appears somewhat

difficult to understand how this could be the situation and how the proper definitive experiments could be conducted in order to conclusively establish these observations. The concept that accelerators may act because of their similarity in structural configuration with the carcinogenic agents is an interesting one insofar as it applies to benzo(c)phenanthrene and highly branched dodecylbenzene. It is difficult, however, to see how this concept could apply to compounds like 3,4-benzpyrene or to dodecylbenzene in which the side chain is not highly branched.

The formula presented by Dr. Horton on page 9 of his report is an extremely interesting formula from a theoretical standpoint, but whether it will ever have any practical application seems highly problematical since the determination of the effective concentration of accelerator in an oil may be extremely difficult, particularly if there is more than one accelerator present in such an oil. Similarly, such a formula allows for the presence of only two carcinogens, namely, benzpyrene and one C4 aromatic. It seems highly unlikely that there would be only two carcinogens present in as complex a mixture as slurry oil, and this is partially borne out by the observations reported by the Standard Oil Development Company in which 6-isopropyl benzanthracene was determined in a relative state of purity from one of these oils. It therefore seems likely that this formula will be exceedingly complicated by a great number of accelerators and inhibitors, such that the effective concentration of accelerator will have to be determined for each individual oil, and also by the presence of a large number of carcinogenic compounds, which will highly complicate the usefulness of any such equation.

Another interesting observation made by Dr. Horton during

his discussion was that the average latent period decreases more rapidly for papillomas, depending upon the amount of accelerator, than the average latent period for carcinomas. This may be graphically expressed somewhat as follows:



ITEMS 2 AND 4 - DR. PHAIR'S REPORT

Dr. Phair used as a basis of his report the attached memorandum, which is essentially a tabular summary of the number of cases which he has thus far collected from the various companies. It appears that an increasing number of companies are participating in reporting cases to Dr. Phair but that there is a heavy imponderance of cases being reported from companies along the eastern seaboard as compared with companies in southwestern United States. It was agreed that Dr. Phair would outline briefly and send to the Chairman of the Subcommittee on Carcinogenicity his latest thoughts on pertinent data which he wishes to have included in the current reporting of cancer cases among employes in the petroleum industry, and that the Chairman of the Subcommittee on Carcinogenicity would then reattempt to stimulate all medical directors to report current cases to Dr. Phair.

ITEM 4 - DR. KEHOE'S REPORT

Dr. Kehoe discussed the budgetary allocations of funds and indicated that it would be possible for the Kettering Laboratory to live within the presently assigned budget of $79,000, but that it must be remembered that this will result in approximately one-quarter less work being done during the year July 1, 1953-June 30, 1954. Dr. Kehoe wished to reserve the right to allocate funds under any of the headings given, depending upon the Kettering Laboratory's estimation of how the funds should be allocated. Thus, for instance, if full cooperation with Dr. Phair is not obtained, it may well be that the $17,500 allocated for epidemiological work may be re-allocated into other phases of the Research Project. There seems to be a general agreement among the members of the committee that Dr. Kehoe should have freedom in allocating the total funds to any of the four phases of the project that he feels the funds should be allocated to. Dr. Kehoe also made a plea that if there is a determined effort to have a gradual reduction in the budget of this project during the coming years, he would like to be informed of this as far in advance as possible so that he might make his plans accordingly. Thus, if the budget is to be cut one-half in the year July 1, 1954-June 30, 1955, and to a quarter of its present figure in the succeeding years, Dr. Kehoe would like to know of this as soon as possible.

ITEM 5

Dr. Horton discussed the report from the British on the carcinogenicity of the mineral oils. He felt that their tests had been performed with applications of oil which were so small that they are not getting tumors in the mice, yet they were observing tumors in

the rabbits due to the effects of accelerators. He seemed to feel that the fractionation of their oils left much to be desired, and that same fractionation of oils in his laboratories, which were then applied on his own animals by his own techniques, had resulted in the appearance of a considerable number of tumors, particularly in the K-4, L-4 and O-4 fractions. He felt that this was probably the result principally of accelerators, and that the carcinogens would be found in the highest concentrations in the K-5, L-5 and O-5 residues. It was suggested at the meeting that the workers at the Kettering Laboratory feel free to communicate on a professional basis with the workers in England in discussing their mutual work, and furthermore, it was felt that if the Kettering Laboratory felt they would like to keep this communication in the established channels, this could be done by having Dr. Horton prepare a critique of the British work and then having Dr. Newquist forward this to the British workers through Colonel Auld. It is evident that it is too early to draw conclusions with respect to the British work which has been reported thus far.

ITEM 6

Dr. Kehoe indicated that he has written a supplemental letter to Dr. Kotin suggesting that Dr. Kotin more definitely outline what information he would like to receive in order that the Kettering Laboratory might be able to provide it to him. Dr. Kehoe did not feel that any of the Kettering Laboratory reports should be sent to Dr. Kotin or anyone else since they are at the present time so tentative. It was also suggested that a possible means of handling this situation would be to have Dr. Kotin come in to the Kettering Laboratory and discuss their mutual problems verbally, and that such a discussion could get to Dr. Kotin all the information

which he might need and yet not jeopardize the position of the Kettering Laboratory.

ITEM 7

Dr. Eckardt reported to the committee that 5 additional cases of skin cancer resulting from cutting oils have recently come to his attention. One of these cases was a scrotal cancer and none of the cases had previously been reported to the group. This simply served to emphasize the growing importance of cutting oils as a possible carcinogenic agent in industry.

ITEM 8

Some discussion was given to the possibility of holding the next meeting of the Advisory Committee at the Hotel Shamrock on the 29th of September, 1953, and that at this time it would be a joint meeting with the Subcommittee on Carcinogenicity. Decision on this matter was left to the Chairman of the Subcommittee, with the recommendation that if the meeting is to be held on that date, members should be notified and hotel reservations should be made well in advance.

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

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

MEMORANDUM FROM THE KETTERING LABORATORY

FIFTH MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

January 16, 1953

A. The use of mice in the experimental appraisal of the relative hazards of cancer of the skin of workmen from exposure to various petroleum products.

1. Materials which in industrial experience have caused cancer of the skin of workmen have been shown to be carcinogenic to mice.

2. The correlation of the responses of men and mice is particularly close in the case of straight run wax distillates, cancers having resulted in both species from intermittent, severe exposure (100 mg. doses applied three times per week on the skin of the mice), when the carcinogenic material was not removed by washing. Data reported by the New York University group indicate that mice develop very few tumors when low dosages (15 mg. per application) of wax distillates are applied. The mouse, like man, seems to be affected adversely by these oils only when exposure is severe. A confirmatory test at low dosage will be carried out on C3H mice with the Midcontinent paraffin distillate, API-56 (P_{MC} 0.1 at the 100 mg. level of dosage).

B. Relationships between potency of oils and the level of dosage applied upon the skin per application.

1. Variation of the relative potency, P_{MC}, with the level of dosage (over certain ranges of dosage) is just what one

would expect on the basis of human experience with such alleged carcinogens as coal tar, shale oil or the distillates which have been handled in wax presses in the petroleum industry, i.e., the higher the level of exposure, the greater the chance of skin cancer. The results of the tests on mice at different levels of dosage which have been reported for the catalytically cracked residua, API-8 and 71, are therefore neither surprising nor distressing when considered from the overall aspect of the program. Really unexpected results are coming from the tests on standard solutions and refinery streams containing either very low or very high levels of concentration of accelerating constituents.

2. Certain materials demonstrate a constant potency over a broad range of dosage:

   (1) Solutions of methylcholanthrene or benzpyrene in benzene

   (2) Some blended industrial fuel oils, e.g., API-113

   (3) Some thermal tars from virgin feeds, e.g., API-108

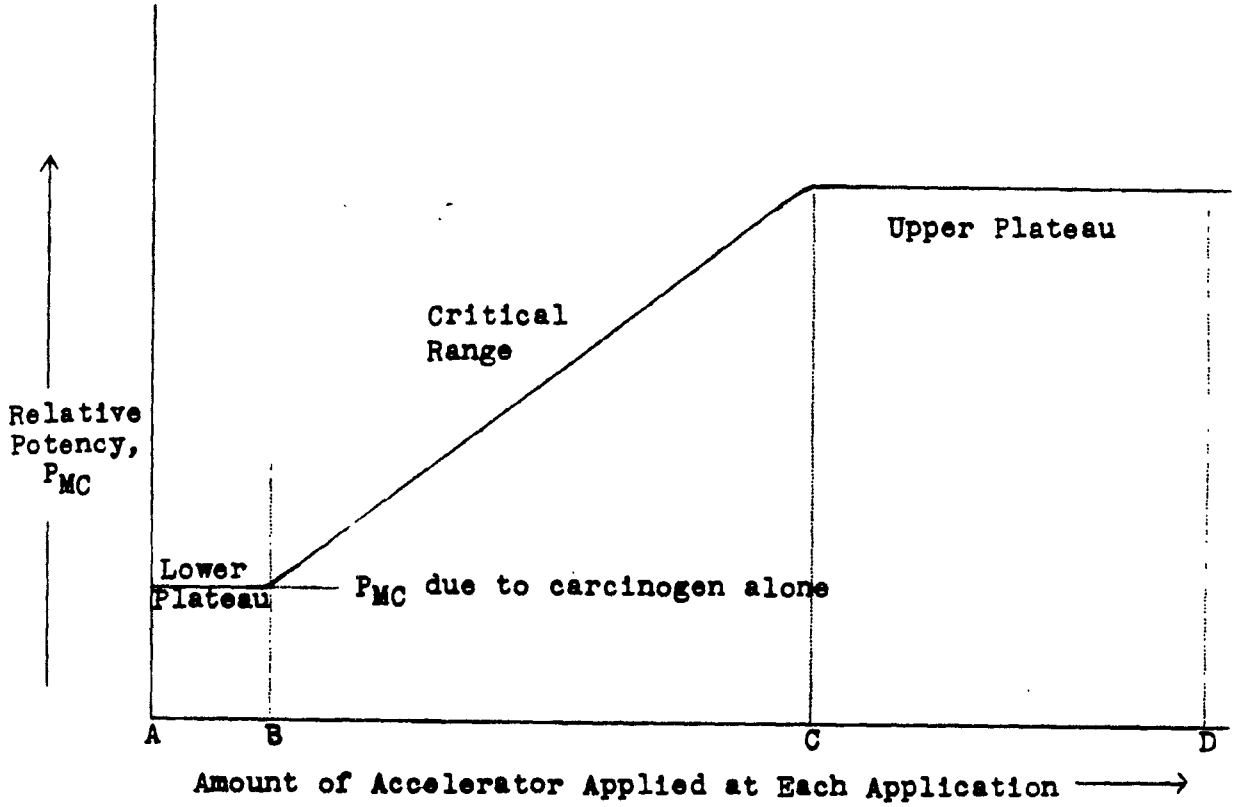
   (4) Solutions of methylcholanthrene or benzpyrene in dodecylbenzene

   (5) Some catalytically cracked gas oils, e.g., API-102.

   Types (1), (2), and (3) probably contain, at the most, very low concentrations of accelerating constituents,

types (4) and (5) relatively high concentrations. The types of oils discussed in section B.1, apparently have a critical level of concentration of such components. The situation may best be pictured graphically (see Figure 1):

Figure 1



Thus, if no accelerators are present in an oil (A), it will exhibit only the potency due to its carcinogen content. Similarly, oils containing accelerators will show only their base level of potency if the dosage per application is kept sufficiently low so that the amount of the

accelerator applied to the skin of the mouse each time does not exceed B. What dosage this will be for any given oil obviously depends on the concentration of accelerators in the oil.

If the dosage per application of such oils is increased until the amount of the accelerating constituent actually being applied each time reaches the critical range between B and C, the relative potency, P_{MC}, as measured by a shortened latent period for tumor induction, will rise. This effect will then increase as higher levels of dosage are tested until the maximum response for a given concentration of carcinogen is obtained (upper plateau in Figure 1).

Proceeding in the reverse direction (from D towards C) it will be apparent that the higher the level of the concentration of accelerators in an oil, the more the dosage per application may be reduced before a significant reduction in potency will be observed. This category probably includes a large number of the current distillate gas oils with End Boiling Points >700°F. from fractionators of catalytic cracking units.

Because of the obvious importance of these relationships between the amount of accelerator applied and the rate at which an oil containing carcinogens will induce cancer in exposed animals, steps are being taken to establish:

(1) the exact magnitude of levels B and C (with blends of synthetic hydrocarbons),

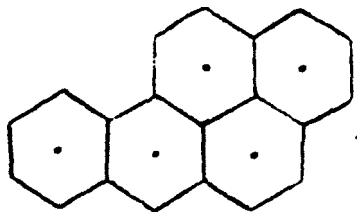
(2) the classes and boiling ranges of the hydrocarbons in catalytically cracked gas oils and residua responsible for the acceleration observed, and

(3) the levels of concentration of such hydrocarbons in various refinery streams.

C. The nature of the compounds contributing to the carcinogenic potencies of refinery streams.

1. Polycyclic carcinogenic compounds.

a.



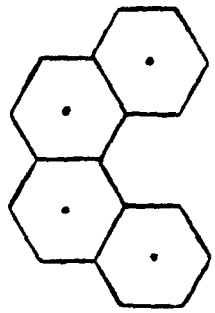
3,4-Benzpyrene

A direct method of analysis for the 5-ringed carcinogen, 3,4-benzpyrene, has been developed. Its reliability has been tested and confirmed with four of the major types of refinery streams under consideration, including cycle gas oils and bottoms products from catalytic cracking, tars from thermal cracking of catalytic feeds, and straight run distillates.

By application of this method, it has been shown that about 70% of the base potency exhibited by the FCC decanted oil, API-8, at 5-20 mg. levels of dosage is

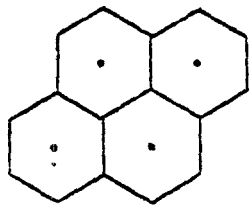
contributed by benzpyrene. Approximately 40% of the constant P_{MC} value of the No. 4 fuel oil blend, API-113, is due to benzpyrene.

b.

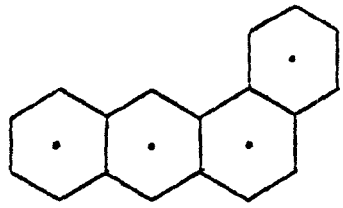


Benzo(c)phenanthrene

As might be expected, in view of the reported boiling point of 3,4-benzpyrene (860°F.), it has been found that the distillate refinery streams analyzed thus far, with true end boiling points less than 860°, contain relatively small amounts of this 5-ringed carcinogen. The available data from biological tests on fractions prepared from catalytically cracked oils suggest strongly that the important carcinogen in such cycle gas oils is a 4-ringed derivative of phenanthrene. Since the results further indicate that simple alkyl derivatives of pyrene and 1,2-benzanthracene



Pyrene



1,2-Benzanthracene

are not contributing significantly to the carcinogenicity of these oils, attention is being centered upon benzo(c)-phenanthrene. This is the hydrocarbon of lowest molecular weight which has been shown to be carcinogenic without the benefit of methylation.

Pure samples of benzphenanthrene and of each of its six monomethyl derivatives have been obtained. Their chemical and physical properties are being examined in the development of a direct method of analysis applicable to refinery streams.

2. Accelerating constituents - 475 to 700 boiling range.

It is of considerable interest that the number of carbon atoms (18) in the accelerator, dodecylbenzene, is the same as the number in the carcinogen, benzo(c)-phenanthrene. The known carcinogenic hydrocarbons have Carbon Numbers from 16 to 25. The approximate boiling range of branched-chain alkylbenzenes with 16-25 carbon atoms is 475-700°F., which is the very range that has been suspected of having accelerating activity from the results of biological tests on refinery streams and fractions thereof. It seems likely that we have here something more than just coincidence.

The problem of the identification of the important accelerators in refinery streams is being approached in two ways:

(1) Biological testing of certain synthetic liquid hydrocarbons as solvents for benzpyrene, to determine

which types have accelerating properties. The results obtained in the prosecution of this phase of the program will furnish a definite outline of the range of molecular weights and of the structural types of possible importance.

(2) Biological testing of fractions of certain catalytically cracked oils which have demonstrated (in tests at the 100 mg. level of dosage) potencies three to ten times as high as were expected on the basis of their content of four to six ringed aromatic hydrocarbons. These efforts are being concentrated on the components boiling below 700°F. which contain not more than two fused aromatic rings.

The foregoing phase (2) of this program has already led to the concentration of a colorless, liquid fraction from the TCC bottoms product, API-71, which possesses the specific irritant properties of dodecylbenzene. This fraction is being redistilled through an 80-plate column to prepare a number of well-defined cuts to be tested as possible accelerators of the carcinogenic action of benzpyrene.

In general, it is a much simpler matter to separate saturated hydrocarbons and monocyclic aromatics from oils and from each other than it is to fractionate any single class of polycyclic compounds from an oil. Furthermore, in the separation of compounds boiling in the range 500-650° at 760 mm.,

highly efficient distillations may be carried out at reduced pressure without fear of cracking. Hence there is little reason to doubt that systematic application of available techniques will lead to an adequate knowledge of the structural types of the accelerating constituents of refinery streams in a reasonable period of time. The step from that knowledge to a direct method of analysis for their effective concentration in any given stream should present no great difficulties.

3. Physicochemical methods for predicting the relative potencies of refinery streams.

During the last six months, the completion of the picture (Figure 1) of the interrelations between concentration of carcinogen, concentration of accelerator, dosage per application, and relative potency, P_{MC}, has brought with it a firm confidence that a reliable analytical tool will result from the further extension of this fundamental approach to the problem. The equation for which parameters are being determined is of the following type:

$$P_{MC} = f(c_a d)\left[K_5 C_5 + K_4 C_4\right] ,$$

where $f(c_a \cdot d)$ is a function of the amount of the accelerator component applied in each application of the whole oil, c_a being the effective concentration of accelerator in the oil, and d the total dosage of oil per application;

C_5 and C_4 are the concentrations of the 5-ringed benzpyrene and of the 4-ringed carcinogen respectively, while K_5 and K_4 are the respective potencies of benzpyrene and the 4-ringed compound based on methylcholanthrene.

Since the values for half of the factors in the equation for calculating P_{MC} are already known (d, K_5 and C_5), the remaining job is the determination of c_a, K_4C_4 and the breakpoints at B and C in the curve of Figure 1. These phases have been discussed in Sections B.2., C.1.b. and C.2.

ESTIMATED BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS

OF THE PETROLEUM INDUSTRY

ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS

IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

Salaries		
Direct Salaries	$ 30,000.00	
Indirect Salaries		
Histopathological Preparation	$ 2,000.00	
Other Services	$ 22,000.00	
		$ 54,000.00
Miscellaneous Expense		
Purchase of Animals	$ 1,500.00	
Special Laboratory Supplies	$ 5,500,00	
Travel	$ 4,000.00	
Overhead (Proportion of heat, gas, electricity, steam, telephone, general laboratory supplies, postage, annuities, pensions, maintenance, etc.)	$ 14,000.00	
		$ 25,000.00
Total		$ 79,000.00

ESTIMATED BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS

OF THE PETROLEUM INDUSTRY

ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS

IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

I. Further development of semi-quantitative biological testing methods for measuring the relative carcinogenic potencies of petroleum products and fractions thereof	$ 12,000.00
II. Determination of the relationships between the rapidity of induction of benign and malignant tumors in experimental animals and various exposure factors such as frequency of application, dosage per application, area of exposure, number of applications, special irritant or toxic properties of the oil applied, etc.	$ 14,500.00
III. Development of rapid analytical methods for estimating the relative carcinogenic potency of any given refinery intermediate or product	
A. Isolation and identification of compounds responsible for observed potency of various types of oils and determination of pertinent physical and chemical properties of these compounds	$ 30,500.00
B. Development of semi-empirical methods of estimation of carcinogenic potencies of oils based on the chemical or physical properties of known or suspected carcinogens and accelerators	$ 4,500.00
IV. Epidemiological Program Collection and correlation of data on cases of cancer among employees of the petroleum industry including any special investigations in particular plants of the industry	$ 17,500.00
Total	$ 79,000.00

FIGURE 1 - 1007* CASE REPORTS FROM 13 COMPANIES RECEIVED BY THE CENTRAL REGISTRY ACCORDING TO SEX, RACE AND MALIGNANCY

SEX	RACE	MALIGNANT	BENIGN	TOTAL
MALE	White	745	23	768
	Colored	26	-	26
	Not Given	114	38	152
	TOTAL	885	61	946
FEMALE	White	33	1	34
	Not Given	9	5	14
	TOTAL	42	6	48
NOT GIVEN		4	-	4
TOTAL BOTH SEXES		931	67	998

* Nine reports could not be used. Six were not tumors; one of these was Boeck's Sarcoid. Three gave only the occupational history.

FIGURE 2 - MALIGNANT TUMORS IN MALES AS REPORTED ACCORDING TO TYPE OF TUMOR AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90--	Total
Buccal Cavity 00-09	11	64		1				1			77
Digest. Sys. and Perit. 10-19	247	24		4				7		3	285
Respiratory System 20-29	28	91						1	2	3	125
Breast 30-39	1	1									2
Genital Organs 40-49	42	16							11		69
Urinary System 50-59	21	21						1	1		44
Skin and Soft Tissue 60-69		170			2			4	2	3	181
Bones 70-75	6	3		1				2	1		13
Brain 76-79		2			3	1				13	19
Lymph. and Hem. System 80-89			12	17							29
Other Sites 90---	8	27		1				1		4	41
Total	364	419	12	24	5	1		17	17	26	885

FIGURE 3 - MALIGNANT TUMORS IN FEMALES AS REPORTED ACCORDING TO TYPE OF TUMOR AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90---	Total
Buccal Cavity 00-09		1									1
Digest. Sys. and Perit. 10-19	8										8
Respiratory System 20-29	1	1									2
Breast 30-39	14	1									15
Genital Organs 40-49	2	3									5
Urinary System 50-59		1									1
Skin and Soft Tissue 60-69	1	6									7
Bones 70-75								1			1
Brain 76-79											
Lymph. and Hem. System 80-89											
Other Sites 90---		1	1								2
Total	26	14	1					1			42

FIGURE 4 - MALIGNANT TUMORS AS REPORTED BY SEX AND PRIMARY SITE COMPARED WITH U.S.A. MORBIDITY AND MORTALITY ESTIMATES

SEX	MALES				FEMALES				BOTH SEXES		
Site	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.** Per Cent Cancer Deaths
Buccal Cavity	77	8.7	10.0	4.7	1	2.4	2.0	1.2	78	8.4	2.9
Digestive System and Peritoneum	285	32.2	36.0	47.7	8	19.0	23.0	38.7	293	31.6	43.2
Respiratory System	125	14.1	8.0	15.4	2	4.8	2.0	3.9	127	13.7	9.6
Breast	2	0.2		0.2	15	35.7		19.1	17	1.8	9.7
Genital Organs	69	7.8	12.0	13.0	5	11.9	51.0	23.5	74	8.0	18.3
Urinary System	44	5.0	7.0	6.6	1	2.4	3.0	3.4	45	4.9	5.0
Skin and Soft Tissue	181	20.5	17.0	2.2	7	16.7	11.0	1.5	188	20.3	1.8
Bones	13	1.5		1.3	1	2.4		1.1	14	1.5	0.1
Brain	19	2.1		2.4				1.5	19	2.0	2.0
Lymph. and Hematopoietic System	29	3.3							29	3.1	
Other Sites	41	4.6	10.0	6.5	2	4.8	8.0	6.2	43	4.6	7.4
TOTAL	885	100.0	100.0	100.0	42	100.0	100.0	100.0	927	100.0	100.0

* Primary site of development of cancer among white males and females according to Dorn, Harold F.: Illness from cancer in the United States. Reprint No. 2537, Public Health Reports. (Based upon morbidity records collected from ten large cities in the United States between 1937 and 1939.)

** Cancer deaths by site in the United States for 1948 as prepared by the Statistical Research Section, American Cancer Society, utilizing statistics from the National Office of Vital Statistics.

Copy from D. V. Stroop for Information of Members and Associates of the Medical Advisory Committee

1-19-53

ESSO LABORATORIES
Standard Oil Development Company

Medical Research Division

P. O. Box 51
Linden, N. J.

January 15, 1953

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am attaching a reprint of an article recently written by Dr. Hueper. I think that this article should be brought to the attention of all of the members and associates of the Medical Advisory Committee of the API.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Encl. - Environmental Cancers:
A Review by Dr. W. C. Hueper
Reprinted from CANCER RESEARCH
Vol. 12, No. 10, pp. 691-97, October 1952.

Reprinted for private circulation from
CANCER RESEARCH
Vol. 12, No. 10, pp. 691–97, October 1952

Environmental Cancers: *A Review*

W. C. HUEPER

(*National Cancer Institute, United States Public Health Service, Federal Security Agency, Bethesda, Md.*)

Although the knowledge of an environmental causation of human cancer is much older than that of the exogenous origin of infectious diseases, there exists a striking, if not alarming, contrast between the extent to which this information has been put to scientific and practical use in the study and control of these two important groups of diseases. In the attack on the infectious diseases the main efforts were expended on the discovery of the specific causative agents and on their subsequent elimination from the external and internal human environment by appropriate preventive, prophylactic, and therapeutic measures. Interest in the endogenous properties of the host, as represented by heredity, constitution, aging processes, race, and sex, in determining the development and course of infectious diseases did not, as a rule, assume a dominating character. These factors were recognized as having mainly a modifying, but not a causal role, by exerting a certain influence on individual susceptibility to the pathogenic microorganisms and on the course of the disease. The investigation of the anatomic and biologic properties on the various reaction products, particularly those of chronic granulomatous nature, remained usually a less important side issue in devising effective control measures.

The investigations directed against human cancer, on the other hand, paid relatively little attention to the factual evidence of its established environmental causation, but concentrated first on the various morphological aspects of cancer and cancer cells and, more recently, on the biochemical and biophysical properties of cancer tissue. Cancer was, and still is, considered by many investigators a distinct disease entity and is not regarded as an atomic reaction product to a large number of diverse chemical and physical agents. It has been for the same reason that the rather diffuse etiologic concepts of physiologic aging and heredity have enjoyed a much greater and much more lasting appeal than the much more definite and reliable observations on the diverse exogenous causes of a considerable variety of human cancers.

Received for publication June 23, 1952.

HEREDITY

Since, in a recent discussion of the age aspects of environmental and occupational cancers (15) the fundamental fallacy of this concept as to the majority of human cancers was discussed in detail, it remains to point out that a similar situation seems to prevail as to the validity of the heredity theory. Conclusions drawn from selectively inbred strains of mice, a notorious biologic artifact without parallel in nature, have been instrumental in giving to hereditary factors an exaggerated and distorted significance as immediate causes of human cancer. While it may be conceded that there exist a few rare cancers which display hereditary tendencies, at least one of them (cancer of the skin in xeroderma pigmentosum) depends in its causation on the primary action of an exogenous agent. Although xeroderma pigmentosum is due to an inherited hypersensitivity to solar radiation prevalent among some inbred family groups, this fact would scarcely justify the conclusion that the ordinary type of solar cancer of the skin is primarily an inherited manifestation of the host organism which is activated by an exposure to solar rays. Such an inversion or perversion of normal reasoning would have to disregard the fundamental fact that without solar radiation there is no cancer, irrespective of the constitution of the individual.

The allegation that hereditary factors based on

prolonged inbreeding play an important causal role in the production of the lung cancers among miners of radioactive ore in Schneeberg and Joachimsthal (Vesin [39]; Macklin [27]; Lorenz [26]) represents another example of the rather loose speculations which have been advanced to bolster the cause of the heredity theory. Apart from the fact that none of the various proponents has offered any concrete evidence in support of such a claim, any significant degree of inbreeding in a community of about 10,000 inhabitants (Schneeberg) having a railroad station for many years would indeed represent a most remarkable biologic and sociologic feat. This speculation advanced by investigators remote from these operations has no basis in fact according to German investigators.[1]

The occasional occurrence of lung cancers in several members of the same family working in these mines certainly cannot be regarded as proof of a hereditary liability. Similar observations of a familial appearance of skin (scrotal) cancers were reported from England during the past century in families of chimney sweeps. Such familial cancers were obviously caused by an occupational or environmental exposure to soot by several members of such families without necessitating the assumption of a common hereditary susceptibility.

The high rates of attack of several environmental cancers rather clearly indicate that heredity evidently plays a relatively insignificant role in their production (cancer of the lung in 75 per cent of miners employed in radioactive mines—Baader [3]; Hueper [16]; cancer of the bladder in almost 100 per cent of dye workers following highly excessive and prolonged exposure to certain aromatic amines—Goldblatt [11]; Mueller [32]; Gross [12]; Hueper [17]; cancer of the skin in 100 per cent of workers with contact with pitch for more than 40 years—Sladden [35]).

It is likely, however, that such an almost complete obliteration of individual inherited or acquired constitutional differences in susceptibility to exogenous carcinogens occurs only in the presence of an overwhelming, high intensity exposure. Whenever groups of individuals become exposed to carcinogens of low potency or sustain exposures of low intensity and duration, there appears evidence indicating variations in the speed and character of the individual responses to the environmental carcinogen. A constitutional influence evidently controls the susceptibility of different races t solar cancer of the skin, to which light-pigmente individuals are much more liable than dark pigmented individuals. The effect of this racia difference in reactivity to the carcinogenic actio of the ultraviolet radiation from solar sources i reflected not only in a lower incidence of ski cancer in Negroes than in whites, but also in different topographical distribution of the ski cancers observe in the two racial groups. Whil skin cancers in whites are mainly located in th skin of the exposed parts of the head, neck, an upper extremities, those observed in Negroes ar predominantly situated in the usually covere parts of the body and the lower extremities (31).

Since arsenical cancers not infrequently involv the unexposed parts of the skin, it is reasonable t conclude from the above evidence that the varia tions in the topographical distribution of ski cancers in whites and Negroes are, in part, due t differences in causal agents active in the produc tion of these cancers.

It is unwise, however, to generalize or overem phasize the role of racial factors in the causation o environmental cancers. Although primary hepati cancer incidence is high among West Africa Negroes, their American descendants do not di play any such tendency (Berman [5]), indicatin thereby that not racial or hereditary factors bu environmental factors are underlying the Africa experience. Likewise, it can be considered a established that the absence of penile canc among Jews and the high liability of Chinese t this type of malignant tumor do not depend upo race-conditioned constitutional differences, but ar mainly the result of differences in personal hy giene, especially the circumcision practiced at a early age by the Jews. There thus exist not onl "environmental familial cancers," but also "en vironmental racial cancers," which have no rel tion to heredity.

Sex

Differences in the sex distribution of cancers a fecting several organs (lip, mouth, larynx, bronchi skin, and bladder) have given rise to the concep of a sex-conditioned susceptibility to certai cancers. Observations on environmental cancer lend no substantial support to such a theory Cancer of the lung of unknown origin has a mal female sex ratio of from 4:1 to 24:1, according t various investigators (18). Asbestosis cancer of th lung, on the other hand, displays a male-female se ratio of 2.4:1, indicating that with an equalizatio of exposure to a carcinogenic agent there occur also an equalization of the incidence rates of lun

[1] None of the numerous German workers mentioned in their papers the occurrence of inbreeding in the mining population of the Erzgebirge and Linzbach in answer to a recent inquiry stated that nothing is known among German scientists in this respect.

cancer for the two sexes (Merewether [30]). Likewise, it is most improbable that the male-female sex ratio of 1:1 for Mexican men and women (Steiner, Butt, and Edmondson [37]) living in Los Angeles reflects sex-related factors. It is noteworthy in this respect that the entrance of female mulespinners in the English textile plants was followed after a suitable latent period by the appearance of cancers of the vulva in some of these operators, which fact thereby demonstrates that female mulespinners acquire the anatomic equivalent of the scrotal cancer of their male counterparts (13). While oral cancer is rare in white women, this tumor is rather frequent in Indian women chewing betel quids (Bashford [4]). This buyo cancer of the oral cavity represents 12 per cent of all cancers among Filipino women. For this reason, the sex ratio of oral cancer among Filipinos is inverse to that found among white people inhabiting the temperate zones, where the male-female sex ratio is 3:1 (Maxwell [29]; Vedder [38]).

These and other similar observations indicate that the differences in the sex ratio of certain cancers of unknown origin are apparently not due, in the main, to hormonal factors but rather reflect variations in the types and intensity of exposure to environmental carcinogens affecting members of the two sexes to a different degree for reasons of occupations, habits, customs, clothing, hobbies, and general living conditions.

Epidemiologic Pattern

The type of the epidemiologic pattern of environmental cancers depends less on certain constitutional factors of the population studied (heredity, race, sex, age) than on the composition, as well as the type, intensity, and duration of action of the agents constituting the environmental carcinogenic spectrum to which they have been exposed. The physical and chemical carcinogens exert their disease-producing effect, just like the pathogenic micro-organism, whenever and wherever they operate under proper conditions of exposure and irrespective of the special type of contact (occupational, medicinal, dietary, habitual, environmental, etc.) present.

The general soundness of this concept is attested by the following observations. The appearance of occupational cancers in the various industrialized countries has closely followed the spread of certain industries. This sequence of events is well illustrated by the chronologic and geographic appearance of bladder cancer among dye workers in different countries following the establishment of aniline dye industries (Table 1).

Additional support for the concept proposed is derived from the demonstration of a centrifugal spread and scatter pattern of occupational cancer hazards from the focus of original production of carcinogens in basic industries through processing and consumer industries to the ultimate handler and general consumer of the finished products. This pattern becomes apparent in the occurrence of skin and lung cancer among the producers of tar and pitch in gas plants and coke ovens, the appearance of similar cancers among tar refinery workers, roofers, road construction workers, cork brick manufacturers, and other members of secondary industries and trades handling and using tar and pitch. An identical chain of environmental cancers among successively exposed population groups exists in regard to arsenicals, which have

TABLE 1

CHRONOLOGIC AND GEOGRAPHIC APPEARANCE OF BLADDER CANCER AMONG DYE WORKERS IN DIFFERENT COUNTRIES (17)

Country	First year reported	Author	Total no. recorded up to 1951
Germany	1895	Rehn	Approximately 350
Switzerland	1905	Schedler	190
Great Britain	1918	Ross	300
Russia	1926	Rosenbaum and Gottlieb	71
Austria	1932	Schueller	(2)
United States	1934	Ferguson *et al.*	250
Italy	1936	di Maio	90
Japan	1940	Nagayo and Kinosita	(7)
France	1946	Billiard-Duchesne	41

elicited cancers among miners of arsenic-containing ores, smelter workers, manufacturers of arsenical insecticides, users and consumers of foodstuffs and drinking water contaminated with such arsenicals, as well as individuals receiving arsenicals for medicinal reasons (Hueper [16]; Neubauer [33]; Arhelger and Kremen [2]; Butzengeiger [8]; Hill and Faning [14]; Arguello, Tello, Macola, and Manzano [1]).

Occupational cancer hazards also display a cancer distribution pattern which shows the highest attack rates among the population groups employed within the immediate vicinity of the carcinogenic industrial foci and gradually decreasing attack rates among population groups increasingly remote from it and thus less intensely and frequently in contact with carcinogenic agents. A good illustration of this concentric distribution pattern of occupational cancers is offered by the aromatic amine bladder cancers. The bladder cancer incidence rate, according to past experience, was highest among intermittently but intensely exposed maintenance and repair men who were followed in decreasing order by operators regularly

employed in the manufacture of beta-naphthylamine and benzidine, these by truck drivers, yard men, chemists, engineers, and supervisors who have irregular and mitigated exposures. Whether or not "neighborhood cases" of aromatic amine cancers actually occurred among the population residing or working within the fume and waste disposal zone of aromatic amine operations is still doubtful and controversial (Mueller [32], Hueper [17], and Gross [12]). Since, according to Gehrmann, Foulger, and Fleming (10), workers employed in a building formerly used for the production of beta-naphthylamine have an occupational bladder cancer hazard from contact with the minute amounts of the chemical volatilized from impregnated building material, neighborhood cases of this occupational cancer may conceivably occur among persons living near aniline dye plants with defective loading, shipping, and waste disposal arrangements for beta-naphthylamine and benzidine.

Another major factor determining the character of the epidemiologic pattern of occupational cancers is represented by their latent period, which in turn depends upon the relative potency of a particular carcinogen, its physicochemical properties (solubility, dispersion, chemical reactivity and affinity, etc.), the physicochemical and cocarcinogenic or anticarcinogenic properties of its vehicle or its associated agents, the route of contact, the intensity of the individual exposures, their rhythm, and the total duration of exposure. These factors, which have a distinct influence upon the incidence rate of cancers among exposed population groups, also exert a definite influence upon the length of the latent period. With decreasing intensity of exposure there occurs a reduction in the incidence of cancers and a lengthening of their latent period. Apart from individual differences in susceptibility, these irregularities in the intensity of exposure to environmental carcinogens mainly account for the wide range of latent periods recorded for environmental cancers (Table 2).

TABLE 2

LATENT PERIODS OF ENVIRONMENTAL AND OCCUPATIONAL CANCERS

Organ	Agent	Av. latent period (years)	Range of latent period (years)
Skin	Arsenic: medicinal	18	3–40
	occupational	25	4–46
	Tar	20–24	1–50
	Creosote oil	25	15–40
	Mineral oil	50–54	4–75
	Crude paraffin oil	15–18	3–35
	Solar radiation	20–30	15–40
	X-radiation	7	1–12
Lung	Asbestos	18	15–21
	Chromates	15	5–47
	Nickel	22	6–30
	Tar fumes	16	9–23
	Ionising radiation	15–35	7–50
Bladder	Aromatic amines	11–15	2–40

The target organ of environmental carcinogen depends on various factors. Special tissue affinity of benzene to the fat tissue contained in hematopoietic organs thus seems to account for its exclusive leukemogenic action. The intensity of ex-

TABLE 3

SITE OF CANCER AND ROUTE OF EXPOSURE

Type of contact	Carcinogenic agent	Site of cancer
Cutaneous	Arsenic	Skin
	Coal tar, pitch, soot, asphalt	
	Creosote oil, anthracene oil	
	Petroleum asphalt, coke, tar	
	Petroleum oils (high boiling)	
	Shale oil, crude paraffin oil	
	Lignite oil and paraffin oil	
	Ultraviolet radiation	
	X-radiation, radioactive chemicals	
	Benzene	Hematopoietic tissues
Respiratory	Arsenic dust	Lung
	Chromium compound dust and fumes	Lung
	Nickel dust and vapors	Lung, nasal cavity and sinuses
	Asbestos dust	Lung
	Beta-naphthylamine, benzidine dust and vapors	Bladder
	Coal tar fumes	Lung
	Petroleum oil mist	Lung
	Isopropyl oil vapors*	Nasal sinuses, larynx, and lung
	Radioactive dust and gases	Lung
Ingestion	Arsenic	Skin
	Radium, mesothorium	Bone

* Isopropyl oil is the crude liquor from which isopropanol is obtained by distillation (40).

posure to some environmental carcinogens also seems to determine the distributory mechanism of the resulting cancers. The relatively high frequency of heterotopic multiple primary cancers observed among dye workers with cancers of the urogenous tract as well as other organs (lung, stomach, intestine, prostate—Mueller [32]; Hueper [16]) seems to be due to an unusual hematogenous spread of the carcinogenic hydrocarbons ordinarily mainly excreted through the urine (Bonser [7]). The principal reason for the appearance of cancers in various organs, however, is represented by the route of exposure (Table 3).

Epidemiologic and demographic studies carried out during the past two decades have demonstrated the existence of marked and significant variations in the total incidence of cancer as well as in the organ, sex, age, and race distribution of cancers in different countries, regions and popula-

tion groups. While a part of such variations is due to differences in the age distribution of the various population groups surveyed as well as in the quality of medical care and of medical recording of diseases, there remains for many of these discrepancies in rates of regional cancer incidence no other plausible explanation than the differences in exposure to environmental carcinogenic factors (Table 4).

The striking differences in the lung cancer morbidity rates in metropolitan centers located in the same part of the country militate against the concept that such local discrepancies can justly be attributed to variations in medical care and recording, or to differences in the biologic composition and hereditary properties of the populations concerned, or to the predominant action of a single etiologic environmental factor, especially cigarette smoking (Wynder and Graham [41]). The local variations as well as the consistent increase of lung cancer morbidity rates must be ascribed to a combination of exogenous factors affecting, to differing degrees, the various population groups as well as the two sexes surveyed. Since the known environmental lung cancers have a latent period ranging usually from 10 to 25 years, it may be concluded that the rising trend of lung cancers is attributable to changes in the environmental carcinogenic spectrum which started around the turn of the century and the effects of which are becoming increasingly evident (Hueper [18]). Supporting this concept is the fact that the majority of environmental and occupational cancers discovered during the last 25 years involve cancers of the respiratory tract (cancers produced by chromium compounds, nickel, arsenicals, asbestos, coal tar, petroleum oils, isopropyl oil, radioactive substances) (21, 28).

In the conduct of epidemiologic studies on environmental cancers certain important precautions have to be observed, if misleading, incorrect, or inconclusive results are to be avoided (Hueper [17]; Downing [9]). It is essential to survey as far as practicable the total effectively exposed population, and to exclude from membership in the actually exposed population group all those individuals who have merely an "administrative" adherence to it. In a survey of environmental cancers among oil refinery workers, for instance, it is scientifically not permissible to include office personnel, sales people, and other white-collar workers, unless they sustain real contact within the refinery area to suspected or recognized carcinogenic agents for occupational reasons. Similarly, whenever, within an industrial population to be surveyed, only a restricted group is shown to have a carcinogenic hazard, figures on incidence must be calculated for this group only, and not for the total plant population, since the latter procedure results in an undue dilution of positive evidence and thereby in distorted epidemiologic information. The limited occurrence of bladder cancer to relatively small and restricted groups of dye workers (10), the excessive liability to scrotal cancer limited to workers employed in paraffin pressing operations in oil refineries (34), and the increased liability to lung cancer among persons with asbestosis—and not among all persons employed in asbestos operations—provide pertinent illustrations of this point.

TABLE 4

LUNG CANCER MORBIDITY RATE, 1937 AND 1947, FOR RESIDENTS OF EIGHT METROPOLITAN CENTERS PER 100,000 POPULATION*

	Males		Females		Total	
City	1937	1947	1937	1947	1937	1947
Atlanta	5.0	13.4	1.0	5.0	2.9	8.9
New Orleans	13.1	39.1	2.8	4.2	7.6	20.8
Dallas	5.9	29.0	0.5	6.4	3.1	17.2
Birmingham	4.5	18.9	2.1	3.9	3.3	11.0
Denver	9.1	21.9	4.2	8.1	6.6	14.8
San Francisco	15.6	34.3	3.9	8.1	9.8	20.8
Chicago	13.3	29.5	4.3	7.0	8.8	18.0
Pittsburgh	9.7	26.1	4.9	5.5	7.3	15.6

* Supplied by Biometrics Section, National Cancer Institute.

An analysis of the population "at risk" should include not only workers presently employed for a sufficiently long period, so as to cover the minimal latent period of the average occupational cancer (5 years), but also all formerly employed workers dead or alive who left the industry, plant, operation, or trade group fulfilling this condition. The inclusion of large groups of short-term employees with insufficient exposure and latent period into the surveyed group also introduces a serious dilution factor which causes misleading or inconclusive results (23, 36).

Since the occurrence of environmental cancers rarely has the character of an epidemic, but as a rule appears as an endemic, it is necessary to conduct epidemiologic studies as long-term investigations, which means the analysis of data covering periods of at least 5 years. Negative results obtained from short-term investigations comprising periods of 1 or 2 years give, at best, inconclusive results if not incorrect ones (6).

In view of the long latent period of environmental cancers it is necessary to restrict occupational cancer surveys to plants which have been in operation for at least 10 years, unless a large portion of the workers in their employ has previously been employed in similar operations elsewhere.

The absence of published reports on the occur-

rence of occupational cancers in an industry having known or suspected cancer hazards is no assurance that a serious occupational cancer problem in these establishments is nonexistent. Perhaps the most notorious example that can be cited as an illustration of such occurrences is represented by the long delayed discovery of the lung cancers among uranium miners of Joachimsthal. Although the existence of a high lung cancer incidence among the Schneeberg miners was established in 1876, despite repeated inquiries made by German investigators with the various governmental authorities under whose jurisdiction the uranium mines in Joachimsthal located nearby on the southern slope of the Erzgebirge were operated, it was not until some 50 years later that the high frequency of lung cancers among this group of similarly exposed workers was recognized. Until that time (1926), the century-old practice of mistaking lung cancers of the Joachimsthal miners for pulmonary silicosis or tuberculosis was continued. Likewise, associated pathologic conditions sometimes may operate in obscuring the co-existence of an occupational cancer. This danger exists, for instance, for absestosis cancer of the lung, unless a thorough necropsy study is made.

Carcinogenesis

An analysis of the action mechanism of the various recognized, suspected, or potential human carcinogens supports the viewpoint that the majority of cancers develop at sites where, for some reason, the most intense or most prolonged exposure to the carcinogen takes place. The following types of mechanisms determining the distribution of environmental cancers may be distinguished.

a) Cancers developing at sites of primary contact.—To this group belong the cancers of the skin resulting from cutaneous exposures to substances such as coal tar, petroleum oils, creosote oil, soot, and similar combustion and high temperature distillation products of carbonaceous matter, as well as to ultraviolet and ionizing radiations; moreover, the cancers of the nasal cavity, nasal sinuses, larynx, and lung elicited by the inhalation of arsenicals, chromium, and nickel compounds, (beryllium?), asbestos, isopropyl oil, tarry matter, and radioactive gases and dusts. The cancers of the connective, bony, and hematopoietic tissues following exposure to penetrating ionizing radiation may be included in this group of primary contact cancers.

b) Cancers developing at sites of selective deposition.—Arsenical cancers of the skin, osteogenic sarcomas following ingestion of radium and/or mesothorium, leukemia following contact with benzene, (thyroid carcinoma following radioactive iodine medication, leukemia subsequent to radioactive phosphorus medication, osteogenic sarcoma following inhalation of beryllium compounds?) may be included in this group.

c) Cancers developing in organs with special functional or toxic affinity for carcinogens.—Representatives of this group are almost exclusively caused by carcinogens of potential importance as far as humans are concerned and thus have been observed mainly in experimental animals. Cancers of this type are the tumors of the liver developing following exposure to various azo dyes, aminofluorene compounds, chlorinated hydrocarbons and selenium, the cancers of the breast and uterus subsequent to an excessive exposure to estrogens, and cancers of the thyroid following the prolonged administration of thiouracil derivatives.

d) Cancers developing in organs of excretion of carcinogens.—Cancers of the bladder, ureter, and kidney observed in individuals and experimental animals having cutaneous, ingestive, and respiratory contact with certain aromatic amines and azo compounds due to the presence of carcinogenic material in the urine belong to this group.

e) Cancers developing on the basis of functional abnormalities due to certain dietary deficiencies and representing a type of indirect or secondary environmental carcinogenesis.—Cancers of the hypopharynx and of the liver noted among population groups subjected to a diet deficient in vitamin B complex and protein as well as cancer of the liver in rats kept on a choline-deficient diet are members of this group.

f) Cancers of the young resulting from a transplacental penetration of carcinogens.—There exists so far only experimental evidence in support of such an exposure route in the demonstration of the development of pulmonary tumors in the offspring of pregnant mice given urethan near term (Larsen [25]; Klein [24]). Whether or not a similar mechanism may be active in the production of congenital cancers or cancers developing during infancy and early childhood appears to be a worthwhile subject of investigation in view of these findings.

While it is not likely that exogenous agents are the only factors responsible for human cancers, the increasing number and widening variety of environmental carcinogenic agents suggest that they seem to be operative in a much larger proportion of cancers than is recognized or realized at present. It appears from the evidence available that the study of environmental cancer hazards and cancers offers not only the most

promising approach to the determination of the causation of human cancers, but is also the principal route through which the primary prevention of cancer may be achieved.

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bc: DVS

January 23, 1953

Dr. A. Wesley Horton
University of Cincinnati
The Kettering Laboratory
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Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Horton:

We received today the stencils of a memorandum from Kettering Laboratory.

In accordance with your wishes, the stencils will be duplicated and distributed to members and associates of the API Medical Advisory Committee.

Very truly yours,

Joan Bierschenk
Department of Technical Services

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
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January 19, 1953

Mr. David V. Stroop
Director, Technical Service
American Petroleum Institute
50 W. 50th Street
New York 20, New York

Dear Mr. Stroop:

We are forwarding under separate cover by Railway Express the stencils of a memorandum for duplication and distribution to members and associates of the API Medical Advisory Committee. All members, except Dr. T. M. Frank, of the Research Project Advisory Committee received copies at our meeting January 16.

Very truly yours,

A. W. Horton

A. Wesley Horton

AWH:mjg

AMERICAN PETROLEUM INSTITUTE
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February 2, 1953

Mr. T. J. Sullivan
Chairman, Study Committee
API Division of Refining
c/o Gulf Oil Corporation
Gulf Building
Pittsburgh 30, Pennsylvania

Dear Sir:

As requested in your letter of November 19, the views of the Medical Advisory Committee membership on the report and recommendations of the Working Group are transmitted for your consideration, as follows:

1. That portion of the report, as well as the first recommendation, dealing with the epidemiological phase of the Kettering project constitutes encouraging support to recommendations which have been considered and advocated repeatedly by the committee. The members need and welcome the assistance of refining executives in the compilation of adequate standardized records for the petroleum industry.

2. The balance of the report and the recommendation for an investigation of the epidemiology of cancer in other industries lack definition necessary for a critical review; however, in principle, the members deem it unwise for the American Petroleum Institute to initiate such a project. It seems unnecessary to recite the many difficult problems incidental to such an undertaking.

For your information, the members of the Subcommittee on Carcinogenicity of the Medical Advisory Committee, by letter ballot in September 1952, expressed considerable doubt as to the wisdom of extending to employees of customers the epidemiological studies of cancer by the Kettering Laboratory under the sponsorship of the American Petroleum Institute.

On behalf of members of the Medical Advisory Committee, I express my sincere appreciation for the interest shown by members of the Study Committee and its Working Group in this subject.

Very truly yours,

E. Kern Linder

E. Kern Linder, M. D.
Chairman, Medical
Advisory Committee

mc: To Members
Medical Advisory Committee

From DVS for signature [illegible]

5-17-53

UNIVERSITY OF CINCINNATI

DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

File

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

February 17, 1953

CABLE ADDRESS KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am sending you herewith a statement of expenditures made on behalf of American Petroleum Institute for the fourth quarter of 1952. I believe that the statement will be self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

ef

Enc.

API 05565

UNIVERSITY OF CINCINNATI

KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR 4th Quarter 1952

SALARIES (Based on Proportion of Time Actually Spent on Project)

Direct Salaries	9688.64	
Indirect Salaries		
Histopathological Preparation	990.00	
Other Services	9073.20	19,751.84

MISCELLANEOUS EXPENSE

Purchase of Animals	448.80	
Special Laboratory Supplies	396.46	
Travel	1628.34	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	5732.91	8,206.51
TOTAL		27,958.35

Balance Available for Further Work at End of 3rd Quarter 1952	34,342.49
Balance Due Kettering Laboratory at End of	
Receipts December 1952	46,372.98
Total Sum Available	80,715.47
Expenditures 4th Quarter	27,958.35
Balance Available for Further Work at End of 4th Quarter 1952	52,757.12
Balance Due Kettering Laboratory at End of	

FORM 1230I KET LAB 500 7-52

API 05566

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20. N Y.

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

March 13, 1953

To Members and Associates
Subcommittee on Carcenogenicity

Kieffer Davis M.D. (Chairman)	R. C. Cole
Marshall Clinton M.D.	L. C. Beard, Jr.
L. E. Curtis M.D.	R. C. Mithoff
Robert E. Eckardt M.D.	R. M. Shepardson
F. D. Gassoway M.D.	R. M. Landon
C. H. Hine M.D.	L. C. Burroughs
E. K. Linder M.D.	R. D. Bent
M. N. Newquist M.D.	Allan E. Dooley
James W. Osborn M.D.	F. J. Sanders
B. B. Reeve, M.D.	E. W. Adams

L. M. Henderson

Gentlemen:

At the request of Doctor Newquist, we enclose agenda and minutes of Fifth Meeting - RP (MC-1) Advisory Committee held January 16, 1953.

Very truly yours,

W Stroop

DVS: jb
mc: Members and Associates
Medical Advisory Committee
Drs. A. Wesley Horton
Robert A. Kehoe
John J. Phair

FOR INFORMATION ONLY

NOT FOR PUBLICATION

AGENDA AND MINUTES OF THE FIFTH MEETING RP(MC-1) ADVISORY COMMITTEE KETTERING LABORATORY, UNIVERSITY OF CINCINNATI January 16, 1953 9:30 A.M. E.S.T.

AGENDA

1. Approval of minutes of Fourth Meeting held 9/24/52
2. Progress report - Dr. A. W. Horton
3. Progress report on Epidemiological Survey - Dr. J. J. Phair
4. Research activities for the year beginning 7/1/53
   - Chemical and biological - Dr. A. W. Horton
   - Epidemiological - Dr. J. J. Phair
   - Budgetary allocations - Dr. R. A. Kehoe
5. Report of the Committee on the Carcinogenic action of Mineral Oils to the Medical Research Council (Great Britain) on their "First Three Years' Work"
6. Communications with Dr. Paul Kotin, University of Southern California
7. Other
8. Time and place of next meeting (MAC meets Hotel Shamrock - Houston 9/30/53)

MINUTES

The Fifth Meeting of the RP(MC-1) Advisory Committee was convened in Dr. Kehoe's office at the Kettering Laboratory of the University of Cincinnati at 9:30 A.M., January 16, 1953. In attendance were the following:

M. N. Newquist, M.D.
R. E. Eckhardt, M.D.
E. K. Linder, M.D.
Kieffer Davis, M.D.
C. H. Hine, M.D.
R. A. Kehoe, M.D.
F. F. Heyroth, M.D.
J. J. Phair, M.D.
A. W. Horton
L. C. Beard, Jr.
K. G. Mackenzie
R. M. Landon
R. C. Mithoff
E. W. Adams
R. M. Shepardson

ITEM 1

The minutes of the Fourth Meeting of the RP(MC-1) Advisory Committee were approved. Subsequently the meeting followed the agenda which had been prepared by Dr. Newquist prior to the meeting with slight modification in that the progress report and the research activities for the year beginning 7/1/53 were combined in both Dr. Horton's and Dr. Phair's reports.

ITEMS 2 AND 4 - DR. HORTON'S REPORT

As the basis for his discussions, Dr. Horton used the attached "Memorandum from the Kettering Laboratory-Fifth Meeting of the Advisory Committee API Research Project MC-1" dated January 16, 1953. Considerable discussion was given to the opening two paragraphs which justified the use of mice in appraising the hazards of skin cancer in workmen. In response to a specific question from Dr. Adams, Dr. Horton stated that washing is more effective in reducing carcinogenic potency than a reduction in the dosage of carcinogen applied. As evidence he presented the experimental evidence which was obtained with washing experiments with API-8 and API-113. It was then suggested that consideration be given to a washing experiment with API-113 and API-57 in which these oils would be painted on at a level of 100 mg. two times a week and washed off after 9 hours in contact with the skin.

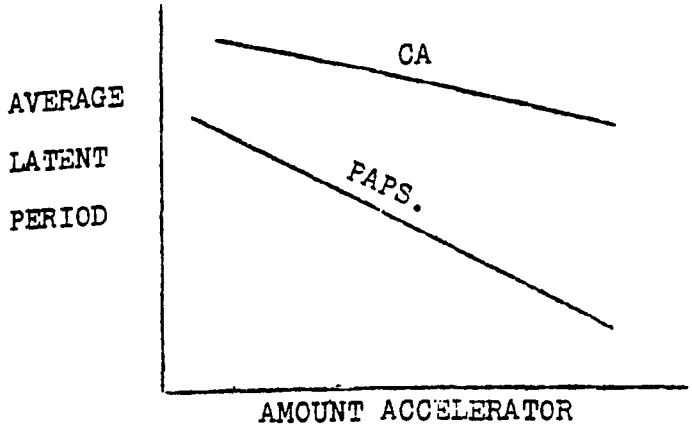
Perhaps the greatest interests in Dr. Horton's report are his observations or theories that the potency of a particular material is dependent less on the amount of carcinogen than on its concentration; whereas, the effect of accelerators is dependent less on the concentration than on the total amount applied at each application. Although this is an interesting thought, it appears somewhat

difficult to understand how this could be the situation and how the proper definitive experiments could be conducted in order to conclusively establish these observations. The concept that accelerators may act because of their similarity in structural configuration with the carcinogenic agents is an interesting one insofar as it applies to benzo(c)phenanthrene and highly branched dodecylbenzene. It is difficult, however, to see how this concept could apply to compounds like 3,4-benzpyrene or to dodecylbenzene in which the side chain is not highly branched.

The formula presented by Dr. Horton on page 9 of his report is an extremely interesting formula from a theoretical standpoint, but whether it will ever have any practical application seems highly problemmatical since the determination of the effective concentration of accelerator in an oil may be extremely difficult, particularly if there is more than one accelerator present in such an oil. Similarly, such a formula allows for the presence of only two carcinogens, namely, benzpyrene and one C4 aromatic. It seems highly unlikely that there would be only two carcinogens present in as complex a mixture as slurry oil, and this is partially borne out by the observations reported by the Standard Oil Development Company in which 6-isopropyl benzanthracene was determined in a relative state of purity from one of these oils. It therefore seems likely that this formula will be exceedingly complicated by a great number of accelerators and inhibitors, such that the effective concentration of accelerator will have to be determined for each individual oil, and also by the presence of a large number of carcinogenic compounds, which will highly complicate the usefulness of any such equation.

Another interesting observation made by Dr. Horton during

his discussion was that the average latent period decreases more rapidly for papillomas, depending upon the amount of accelerator, than the average latent period for carcinomas. This may be graphically expressed somewhat as follows:



ITEMS 2 AND 4 - DR. PHAIR'S REPORT

Dr. Phair used as a basis of his report the attached memorandum, which is essentially a tabular summary of the number of cases which he has thus far collected from the various companies. It appears that an increasing number of companies are participating in reporting cases to Dr. Phair but that there is a heavy imponderance of cases being reported from companies along the eastern seaboard as compared with companies in southwestern United States. It was agreed that Dr. Phair would outline briefly and send to the Chairman of the Subcommittee on Carcinogenicity his latest thoughts on pertinent data which he wishes to have included in the current reporting of cancer cases among employes in the petroleum industry, and that the Chairman of the Subcommittee on Carcinogenicity would then reattempt to stimulate all medical directors to report current cases to Dr. Phair.

ITEM 4 - DR. KEHOE'S REPORT

Dr. Kehoe discussed the budgetary allocations of funds and indicated that it would be possible for the Kettering Laboratory to live within the presently assigned budget of $79,000, but that it must be remembered that this will result in approximately one-quarter less work being done during the year July 1, 1953-June 30, 1954. Dr. Kehoe wished to reserve the right to allocate funds under any of the headings given, depending upon the Kettering Laboratory's estimation of how the funds should be allocated. Thus, for instance, if full cooperation with Dr. Phair is not obtained, it may well be that the $17,500 allocated for epidemiological work may be re-allocated into other phases of the Research Project. There seems to be a general agreement among the members of the committee that Dr. Kehoe should have freedom in allocating the total funds to any of the four phases of the project that he feels the funds should be allocated to. Dr. Kehoe also made a plea that if there is a determined effort to have a gradual reduction in the budget of this project during the coming years, he would like to be informed of this as far in advance as possible so that he might make his plans accordingly. Thus, if the budget is to be cut one-half in the Year July 1, 1954-June 30, 1955, and to a quarter of its present figure in the succeeding years, Dr. Kehoe would like to know of this as soon as possible.

ITEM 5

Dr. Horton discussed the report from the British on the carcinogenicity of the mineral oils. He felt that their tests had been performed with applications of oil which were so small that they are not getting tumors in the mice, yet they were observing

tumors in the rabbits due to the effects of accelerators. He seemed to feel that the fractionation of their oils left much to be desired, and that same fractionation of oils in his laboratories, which were then applied on his own animals by his own techniques, had resulted in the appearance of a considerable number of tumors, particularly in the K-4, L-4 and O-4 fractions. He felt that this was probably the result principally of accelerators, and that the carcinogens would be found in the highest concentrations in the K-5, L-5 and O-5 residues. It was suggested at the meeting that the workers at the Kettering Laboratory feel free to communicate on a professional basis with the workers in England in discussing their mutual work, and furthermore, it was felt that if the Kettering Laboratory felt they would like to keep this communication in the established channels, this could be done by having Dr. Horton prepare a critique of the British work and then having Dr. Newquist forward this to the British workers through Colonel Auld. It is evident that it is too early to draw conclusions with respect to the British work which has been reported thus far.

ITEM 6

Dr. Kehoe indicated that he has written a supplemental letter to Dr. Kotin suggesting that Dr. Kotin more definitely outline what information he would like to receive in order that the Kettering Laboratory might be able to provide it to him. Dr. Kehoe did not feel that any of the Kettering Laboratory reports should be sent to Dr. Kotin or anyone else since they are at the present time so tentative. It was also suggested that a possible means of handling this situation would be to have Dr. Kotin come in to the Kettering Laboratory and discuss their mutual problems verbally,

and that such a discussion could get to Dr. Kotin all the information which he might need and yet not jeopardize the position of the Kettering Laboratory.

ITEM 7

Dr. Eckardt reported to the committee that 5 additional cases of skin cancer resulting from cutting oils have recently come to his attention. One of these cases was a scrotal cancer and none of the cases had previously been reported to the group. This simply served to emphasize the growing importance of cutting oils as a possible carcinogenic agent in industry.

ITEM 8

Some discussion was given to the possibility of holding the next meeting of the Advisory Committee at the Hotel Shamrock on the 29th of September, 1953, and that at this time it would be a joint meeting with the Subcommittee on Carcinogenicity. Decision on this matter was left to the Chairman of the Subcommittee, with the recommendation that if the meeting is to be held on that date, members should be notified and hotel reservations should be made well in advance.

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

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

MEMORANDUM FROM THE KETTERING LABORATORY

FIFTH MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

January 16, 1953

A. The use of mice in the experimental appraisal of the relative hazards of cancer of the skin of workmen from exposure to various petroleum products.

1. Materials which in industrial experience have caused cancer of the skin of workmen have been shown to be carcinogenic to mice.

2. The correlation of the responses of men and mice is particularly close in the case of straight run wax distillates, cancers having resulted in both species from intermittent, severe exposure (100 mg. doses applied three times per week on the skin of the mice), when the carcinogenic material was not removed by washing. Data reported by the New York University group indicate that mice develop very few tumors when low dosages (15 mg. per application) of wax distillates are applied. The mouse, like man, seems to be affected adversely by these oils only when exposure is severe. A confirmatory test at low dosage will be carried out on C3H mice with the Midcontinent paraffin distillate, API-56 (P_{MC} 0.1 at the 100 mg. level of dosage).

B. Relationships between potency of oils and the level of dosage applied upon the skin per application.

1. Variation of the relative potency, P_{MC}, with the level of dosage (over certain ranges of dosage) is just what one

would expect on the basis of human experience with such alleged carcinogens as coal tar, shale oil or the distillates which have been handled in wax presses in the petroleum industry, i.e., the higher the level of exposure, the greater the chance of skin cancer. The results of the tests on mice at different levels of dosage which have been reported for the catalytically cracked residua, API-8 and 71, are therefore neither surprising nor distressing when considered from the overall aspect of the program. Really unexpected results are coming from the tests on standard solutions and refinery streams containing either very low or very high levels of concentration of accelerating constituents.

2. Certain materials demonstrate a constant potency over a broad range of dosage:

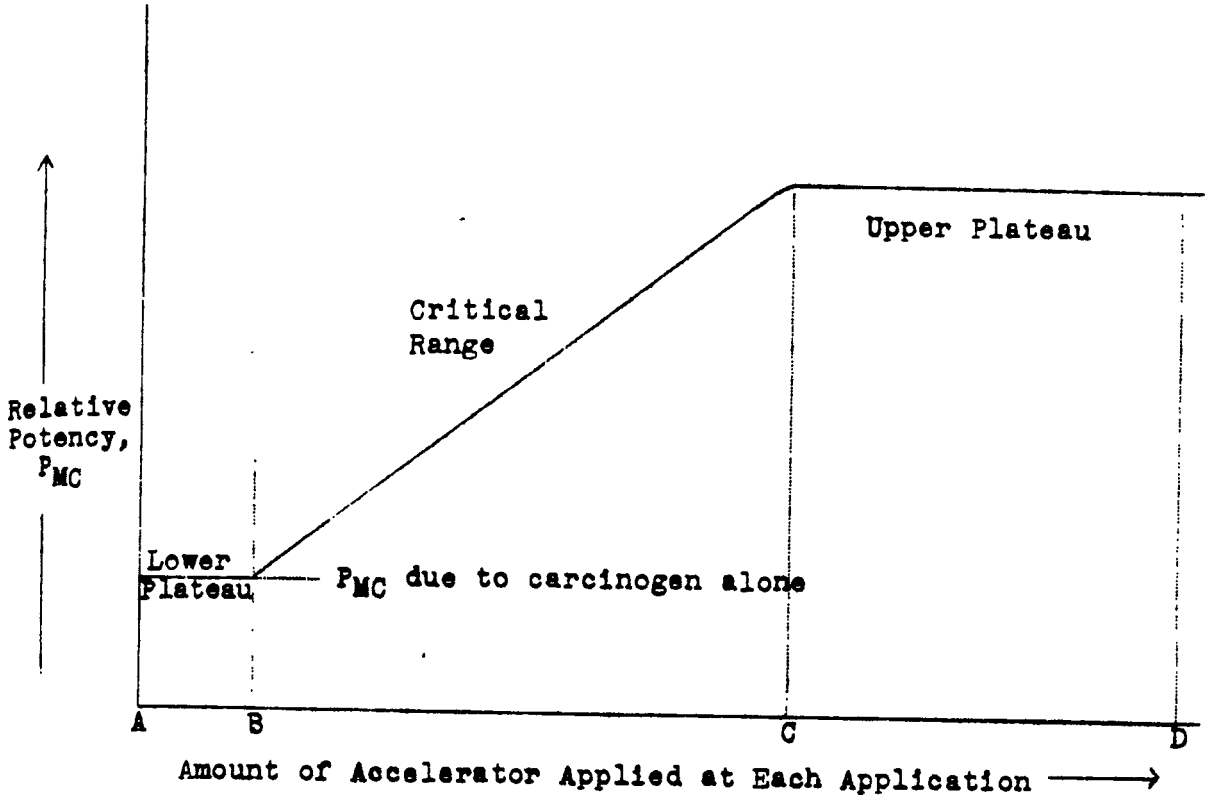
   (1) Solutions of methylcholanthrene or benzpyrene in benzene
   (2) Some blended industrial fuel oils, e.g., API-113
   (3) Some thermal tars from virgin feeds, e.g., API-108

   (4) Solutions of methylcholanthrene or benzpyrene in dodecylbenzene
   (5) Some catalytically cracked gas oils, e.g., API-102.

   Types (1), (2), and (3) probably contain, at the most, very low concentrations of accelerating constituents,

types (4) and (5) relatively high concentrations. The types of oils discussed in section B.1. apparently have a critical level of concentration of such components. The situation may best be pictured graphically (see Figure 1):

Figure 1



Thus, if no accelerators are present in an oil (A), it will exhibit only the potency due to its carcinogen content. Similarly, oils containing accelerators will show only their base level of potency if the dosage per application is kept sufficiently low so that the amount of the

accelerator applied to the skin of the mouse each time does not exceed B. What dosage this will be for any given oil obviously depends on the concentration of accelerators in the oil.

If the dosage per application of such oils is increased until the amount of the accelerating constituent actually being applied each time reaches the critical range between B and C, the relative potency, P_{MC}, as measured by a shortened latent period for tumor induction, will rise. This effect will then increase as higher levels of dosage are tested until the maximum response for a given concentration of carcinogen is obtained (upper plateau in Figure 1).

Proceeding in the reverse direction (from D towards C) it will be apparent that the higher the level of the concentration of accelerators in an oil, the more the dosage per application may be reduced before a significant reduction in potency will be observed. This category probably includes a large number of the current distillate gas oils with End Boiling Points >700°F. from fractionators of catalytic cracking units.

Because of the obvious importance of these relationships between the amount of accelerator applied and the rate at which an oil containing carcinogens will induce cancer in exposed animals, steps are being taken to establish:

(1) the exact magnitude of levels B and C (with blends of synthetic hydrocarbons),

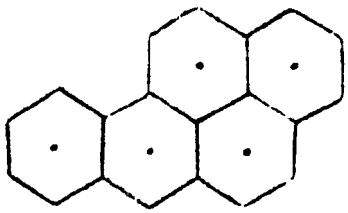
(2) the classes and boiling ranges of the hydrocarbons in catalytically cracked gas oils and residua responsible for the acceleration observed, and

(3) the levels of concentration of such hydrocarbons in various refinery streams.

C. The nature of the compounds contributing to the carcinogenic potencies of refinery streams.

1. Polycyclic carcinogenic compounds.

a.



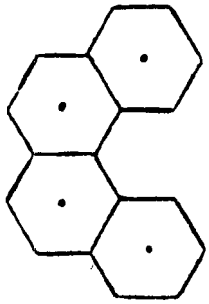
3,4-Benzpyrene

A direct method of analysis for the 5-ringed carcinogen, 3,4-benzpyrene, has been developed. Its reliability has been tested and confirmed with four of the major types of refinery streams under consideration, including cycle gas oils and bottoms products from catalytic cracking, tars from thermal cracking of catalytic feeds, and straight run distillates.

By application of this method, it has been shown that about 70% of the base potency exhibited by the FCC decanted oil, API-8, at 5-20 mg. levels of dosage is

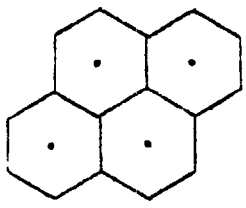
contributed by benzpyrene. Approximately 40% of the constant P_{MC} value of the No. 4 fuel oil blend, API-113, is due to benzpyrene.

b.

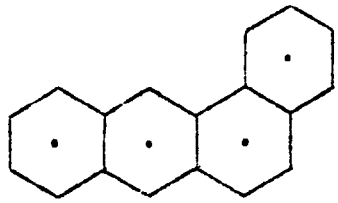


Benzo(c)phenanthrene

As might be expected, in view of the reported boiling point of 3,4-benzpyrene (860°F.), it has been found that the distillate refinery streams analyzed thus far, with true end boiling points less than 860°, contain relatively small amounts of this 5-ringed carcinogen. The available data from biological tests on fractions prepared from catalytically cracked oils suggest strongly that the important carcinogen in such cycle gas oils is a 4-ringed derivative of phenanthrene. Since the results further indicate that simple alkyl derivatives of pyrene and 1,2-benzanthracene



Pyrene



1,2-Benzanthracene

are not contributing significantly to the carcinogenicity of these oils, attention is being centered upon benzo(c)-phenanthrene. This is the hydrocarbon of lowest molecular weight which has been shown to be carcinogenic without the benefit of methylation.

Pure samples of benzphenanthrene and of each of its six monomethyl derivatives have been obtained. Their chemical and physical properties are being examined in the development of a direct method of analysis applicable to refinery streams.

2. Accelerating constituents - 475 to 700 boiling range.

It is of considerable interest that the number of carbon atoms (18) in the accelerator, dodecylbenzene, is the same as the number in the carcinogen, benzo(c)-phenanthrene. The known carcinogenic hydrocarbons have Carbon Numbers from 16 to 25. The approximate boiling range of branched-chain alkylbenzenes with 16-25 carbon atoms is 475-700°F., which is the very range that has been suspected of having accelerating activity from the results of biological tests on refinery streams and fractions thereof. It seems likely that we have here something more than just coincidence.

The problem of the identification of the important accelerators in refinery streams is being approached in two ways:

(1) Biological testing of certain synthetic liquid hydrocarbons as solvents for benzpyrene, to determine

which types have accelerating properties. The results obtained in the prosecution of this phase of the program will furnish a definite outline of the range of molecular weights and of the structural types of possible importance.

(2) Biological testing of fractions of certain catalytically cracked oils which have demonstrated (in tests at the 100 mg. level of dosage) potencies three to ten times as high as were expected on the basis of their content of four to six ringed aromatic hydrocarbons. These efforts are being concentrated on the components boiling below 700°F. which contain not more than two fused aromatic rings.

The foregoing phase (2) of this program has already led to the concentration of a colorless, liquid fraction from the TCC bottoms product, API-71, which possesses the specific irritant properties of dodecylbenzene. This fraction is being redistilled through an 80-plate column to prepare a number of well-defined cuts to be tested as possible accelerators of the carcinogenic action of benzpyrene.

In general, it is a much simpler matter to separate saturated hydrocarbons and monocyclic aromatics from oils and from each other than it is to fractionate any single class of polycyclic compounds from an oil. Furthermore, in the separation of compounds boiling in the range 500-650° at 760 mm.,

highly efficient distillations may be carried out at reduced pressure without fear of cracking. Hence there is little reason to doubt that systematic application of available techniques will lead to an adequate knowledge of the structural types of the accelerating constituents of refinery streams in a reasonable period of time. The step from that knowledge to a direct method of analysis for their effective concentration in any given stream should present no great difficulties.

3. Physicochemical methods for predicting the relative potencies of refinery streams.

During the last six months, the completion of the picture (Figure 1) of the interrelations between concentration of carcinogen, concentration of accelerator, dosage per application, and relative potency, P_{MC}, has brought with it a firm confidence that a reliable analytical tool will result from the further extension of this fundamental approach to the problem. The equation for which parameters are being determined is of the following type:

$$P_{MC} = f(c_a d)\,[K_5 C_5 + K_4 C_4] ,$$

where $f(c_a \cdot d)$ is a function of the amount of the accelerator component applied in each application of the whole oil, c_a being the effective concentration of accelerator in the oil, and d the total dosage of oil per application;

C_5 and C_4 are the concentrations of the 5-ringed benzpyrene and of the 4-ringed carcinogen respectively, while K_5 and K_4 are the respective potencies of benzpyrene and the 4-ringed compound based on methylcholanthrene.

Since the values for half of the factors in the equation for calculating P_{MC} are already known (d, K_5 and C_5), the remaining job is the determination of c_a, K_4C_4 and the breakpoints at B and C in the curve of Figure 1. These phases have been discussed in Sections B.2., C.1.b. and C.2.

ESTIMATED BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS

OF THE PETROLEUM INDUSTRY

ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS

IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

Salaries		
Direct Salaries	$ 30,000.00	
Indirect Salaries		
Histopathological Preparation	$ 2,000.00	
Other Services	$ 22,000.00	
		$ 54,000.00
Miscellaneous Expense		
Purchase of Animals	$ 1,500.00	
Special Laboratory Supplies	$ 5,500.00	
Travel	$ 4,000.00	
Overhead (Proportion of heat, gas, electricity, steam, telephone, general laboratory supplies, postage, annuities, pensions, maintenance, etc.)	$ 14,000.00	
		$ 25,000.00
Total		$ 79,000.00

ESTIMATED BUDGET OF THE KETTERING LABORATORY

FOR THE INVESTIGATION OF POTENTIAL HEALTH PROBLEMS

OF THE PETROLEUM INDUSTRY

ASSOCIATED WITH THE PRESENCE OF CARCINOGENIC COMPOUNDS

IN CERTAIN MATERIALS AND PRODUCTS

API RESEARCH PROJECT MC-1

July 1, 1953 - June 30, 1954

I. Further development of semi-quantitative biological testing methods for measuring the relative carcinogenic potencies of petroleum products and fractions thereof	$ 12,000.00
II. Determination of the relationships between the rapidity of induction of benign and malignant tumors in experimental animals and various exposure factors such as frequency of application, dosage per application, area of exposure, number of applications, special irritant or toxic properties of the oil applied, etc.	$ 14,500.00
III. Development of rapid analytical methods for estimating the relative carcinogenic potency of any given refinery intermediate or product	
A. Isolation and identification of compounds responsible for observed potency of various types of oils and determination of pertinent physical and chemical properties of these compounds	$ 30,500.00
B. Development of semi-empirical methods of estimation of carcinogenic potencies of oils based on the chemical or physical properties of known or suspected carcinogens and accelerators	$ 4,500.00
IV. Epidemiological Program Collection and correlation of data on cases of cancer among employees of the petroleum industry including any special investigations in particular plants of the industry	$ 17,500.00
Total	$ 79,000.00

FIGURE 1 - 1007* CASE REPORTS FROM 13 COMPANIES RECEIVED BY THE CENTRAL REGISTRY ACCORDING TO SEX, RACE AND MALIGNANCY

SEX	RACE	MALIGNANT	BENIGN	TOTAL
MALE	White	745	23	768
	Colored	26	-	26
	Not Given	114	38	152
	TOTAL	885	61	946
FEMALE	White	33	1	34
	Not Given	9	5	14
	TOTAL	42	6	48
NOT GIVEN		4	-	4
TOTAL BOTH SEXES		931	67	998

* Nine reports could not be used. Six were not tumors; one of these was Boeck's Sarcoid. Three gave only the occupational history.

ACCORDING TO TYPE OF TUMOR
AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90--	Total
Buccal Cavity 00-09	11	64		1				1			77
Digest. Sys. and Perit. 10-19	247	24		4				7		3	285
Respiratory System 20-29	28	91						1	2	3	125
Breast 30-39	1	1									2
Genital Organs 40-49	42	16							11		69
Urinary System 50-59	21	21						1	1		44
Skin and Soft Tissue 60-69		170			2			4	2	3	181
Bones 70-75	6	3		1				2	1		13
Brain 76-79		2			3	1				13	19
Lymph. and Hem. System 80-89			12	17							29
Other Sites 90---	8	27		1				1		4	41
Total	364	419	12	24	5	1		17	17	26	885

API 05588

FIGURE 3 - MALIGNANT TUMORS IN FEMALES AS REPORTED ACCORDING TO TYPE OF TUMOR AND PRIMARY SITE

Type of Tumor / Site	Gland. Epith. 00-09	Non-Gland. Epith. 10-19	Leuke-mias 20-29	Lympho-mas 30-39	Nervous Tissues 40-49	Vascular Tissues 50-59	Muscle 60-69	Non-Epith. Tissues 70-79	Embry. - Mixed Tissues 80-89	Tumors Not Class. 90---	Total
Buccal Cavity 00-09		1									1
Digest. Sys. and Perit. 10-19	8										8
Respiratory System 20-29	1	1									2
Breast 30-39	14	1									15
Genital Organs 40-49	2	3									5
Urinary System 50-59		1									1
Skin and Soft Tissue 60-69	1	6									7
Bones 70-75								1			1
Brain 76-79											
Lymph. and Hem. System 80-89											
Other Sites 90---		1	1								2
Total	26	14	1					1			42

FIGURE 4 - MALIGNANT TUMORS AS REPORTED BY SEX AND PRIMARY SITE COMPARED WITH U.S.A. MORBIDITY AND MORTALITY ESTIMATES

SEX	MALES				FEMALES				BOTH SEXES		
Site	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.* Per Cent Cancer Cases	U.S.A.** Per Cent Cancer Deaths	Number Reported	Per Cent of Total	U.S.A.** Per Cent Cancer Deaths
Buccal Cavity	77	8.7	10.0	4.7	1	2.4	2.0	1.2	78	8.4	2.9
Digestive System and Peritoneum	285	32.2	36.0	47.7	8	19.0	23.0	38.7	293	31.6	43.2
Respiratory System	125	14.1	8.0	15.4	2	4.8	2.0	3.9	127	13.7	9.6
Breast	2	0.2		0.2	15	35.7		19.1	17	1.8	9.7
Genital Organs	69	7.8	12.0	13.0	5	11.9	51.0	23.5	74	8.0	18.3
Urinary System	44	5.0	7.0	6.6	1	2.4	3.0	3.4	45	4.9	5.0
Skin and Soft Tissue	181	20.5	17.0	2.2	7	16.7	11.0	1.5	188	20.3	1.8
Bones	13	1.5		1.3	1	2.4		1.1	14	1.5	0.1
Brain	19	2.1		2.4				1.5	19	2.0	2.0
Lymph. and Hematopoietic System	29	3.3							29	3.1	
Other Sites	41	4.6	10.0	6.5	2	4.8	8.0	6.2	43	4.6	7.4
TOTAL	885	100.0	100.0	100.0	42	100.0	100.0	100.0	927	100.0	100.0

* Primary site of development of cancer among white males and females according to Dorn, Harold F.: Illness from cancer in the United States. Reprint No. 2537, Public Health Reports. (Based upon morbidity records collected from ten large cities in the United States between 1937 and 1939.)

** Cancer deaths by site in the United States for 1948 as prepared by the Statistical Research Section, American Cancer Society, utilizing statistics from the National Office of Vital Statistics.

March 17, 1953

Dr. Kieffer Davis
Phillips Petroleum Company
Bartlesville, Oklahoma

Dear Dr. Davis:

For your information as Chairman of the Sub-committee on Carcinogenicity, we enclose a copy of the statement of expenditures made by Kettering Laboratory in connection with research project MC-1.

According to my records and this statement the total expenditures by Kettering 1945-1952 have amounted to $343,749.79, leaving a balance of $52,757.12 available on January 1, 1953 to meet expenses during the first two quarters of 1953 as budgeted.

Very truly yours,

DVS:jb
cc: Dr. T. M. Frank
Enclosure

Copy From Mr. D. V. Stroop for Information of Dr. Kieffer Davis and Dr. T. M. Frank
3-17-53

UNIVERSITY OF CINCINNATI
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

February 17, 1953

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am sending you herewith a statement of expenditures made on behalf of American Petroleum Institute for the fourth quarter of 1952. I believe that the statement will be self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

/s/ E. R. Fortlage, Secretary to
Dr. Kehoe

ef

Enc.

UNIVERSITY OF CINCINNATI
KETTERING LABORATORY

ACCOUNT OF The American Petroleum Institute

FOR Fourth Quarter 1952

SALARIES (Based on Proportion of Time Actually Spent on Project)

Direct Salaries	9688.64	
Indirect Salaries		
Histopathological Preparation	990.00	
Other Services	9073.20	19,751.84

MISCELLANEOUS EXPENSE

Purchase of Animals	448.80	
Special Laboratory Supplies	396.46	
Travel	1628.34	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	5732.91	8,206.51
TOTAL		27,958.35

Balance Available for Further Work at end of 3rd Quarter 1952	34,342.49	
Balance Due Kettering Laboratory at end of		
Receipts December 1952	46,372.98	
Total Sum Available	80,715.47	
Expenditures 4th Quarter	27,958.35	
Balance Available for Further Work at end of 4th Quarter 1952	52,757.12	
Balance Due Kettering Laboratory at end of		

---oooOooo---

API 05593

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP, DIRECTOR

March 24, 1953

To Members and Associates
Medical Advisory Committee

Gentlemen:

Dr. Kieffer Davis, Chairman, Subcommittee on Carcinogenicity has appointed for 1953 the subcommittee's Research Project MC-1 Advisory Committee comprising:

Robert E. Eckardt, M.D., Chairman
C. H. Hine, M.D.
E. K. Linder, M.D.
M. N. Newquist, M.D.
E. W. Adams
L. C. Beard, Jr.
L. M. Henderson
R. C. Mithoff

It is our hope that each appointee can take an active part in the important work of this committee, if not, we shall expect him to notify Dr. Davis promptly.

Very truly yours,

W Stroop

DVS: jb

PHILLIPS PETROLEUM COMPANY

BARTLESVILLE, OKLAHOMA

March 18, 1953

MEDICAL DEPARTMENT
KIEFFER DAVIS M D
MEDICAL DIRECTOR
CAMP S HUNTINGTON, M D
ASST MEDICAL DIRECTOR

ALBERT M MERY M D
ASSOCIATE PHYSICIAN
LUCIAN E RENES
INDUSTRIAL HYGIENIST

Mr. D. V. Streop
American Petroleum Institute
50 West 50th
New York 20, New York

Dear Dave:

I wish to appoint the following as members of our RP-MC-1 Advisory Committee:

Robert E. Eckardt, M.D., Chairman
C. H. Hine, M.D.
E. K. Linder, M.D.
M. N. Newquist, M.D.
E. W. Adams
L. C. Beard, Jr.
L. M. Henderson
R. C. Mithoff

Please inform each of these men of their appointment and notify me in case anyone should decline.

Unless there is some reason to change our plans, the next meeting of our Subcommittee on Carcinogenicity will be at the Shamrock Hotel in Houston September 30, 1953.

With best personal regards, I remain

Sincerely yours,

Kieffer Davis, M.D.
Medical Director

KD:dt
cc: George M. Saunders, M.D.
Robert E. Eckardt, M.D.

API 05595

Copy From D. V. Stroop for Information of Members and Associates of Medical Advisory Committee — April 3, 1953

ESSO LABORATORIES
Standard Oil Development Company

P. O. Box 51, Linden, N. J.

March 18, 1953

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

The enclosed apparently represents a publication of the data which members of the Subcommittee on Carcinogenicity of the A.P.I. have had an opportunity to review in connection with the exchange of information between the British and our own Subcommittees on Carcinogenicity.

I thought you might wish to have this article reproduced and distributed to the members of the Medical Advisory Committee of the American Petroleum Institute.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M.D.

REE/hml

Encl.
(The Value of the Rabbit
For Carcinogenicity Tests
on Petroleum Fractions,
by Hiefer and Woodhouse
Repr. from THE BRITISH JNL.
OF CANCER, 1952, Vol. VI, Pg. 293.)

Reprinted from
The British Journal of Cancer,
1952, Vol. VI, p. 293.

THE VALUE OF THE RABBIT FOR CARCINOGENICITY TESTS ON PETROLEUM FRACTIONS.

I. HIEGER AND D. L. WOODHOUSE.

From the Chester Beatty Research Institute, The Royal Cancer Hospital, London, S.W. 3, and the Cancer Research Laboratories, Department of Pathology, The Medical School, Birmingham, 15.

Received for publication May 28, 1952.

THE experiments recorded in this article were carried out in the course of investigations on behalf of the Medical Research Council, a sub-committee having been set up in 1949 to inquire into the carcinogenic properties of mineral oils and allied products. The arrangements for co-ordinating the research have been briefly described by Auld (1950).

The entire series of tests have been made in duplicate at the Cancer Research Laboratories, Department of Pathology, University of Birmingham, and at the Chester Beatty Research Institute, The Royal Cancer Hospital, London. At each centre the activity of 3 selected crude oils, 4 fractions derived from each crude by methods of distillation specially designed to avoid high temperature cracking, and the final residues, have been tested on groups of 50 mice for each sample and also on a total of 105 rabbits. The results appear to be of particular interest, since it must be concluded from them that it is unsatisfactory to exclude carcinogenicity on the basis of tests on mice only.

The desirability of utilising in industry those types of oils which are least likely to cause dermatitis or cancer of the skin of workers has been recognised for over 20 years, and in 1934 the Committee on Cancer of Manchester Corporation proposed a standard for assessing the potency of mineral oils depending on physical properties (specific gravity and refractive index) which it was believed would ensure that the lubricants used in the textile industry would be substantially free from carcinogenic properties. This Manchester formula, which is not now regarded as a satisfactory criterion, was put forward following the investigations of Twort and his co-workers (Twort and Fulton, 1929; Twort and Twort, 1930, 1931, 1933; Twort and Lyth, 1939; Twort, 1941), who tested a wide range of crude mineral oils, distillates, solvent extracts, spindle and shale oils, using mice almost exclusively, however, for the biological assessment of their carcinogenicity. In the past, also, mice have for the most part been employed in skin tests with "oil" fractions derived from coal tars and with the pure chemical carcinogens either isolated or synthesised.

It is true that the classical experiments of Yamagiwa and Itchikawa (1918), in which the carcinogenicity of coal tar was first proved, utilised rabbits, and this species has also been employed in a number of early experiments on tar cancer, e.g., Bonne (1927), Leroux (1927), Babès (1929) and Twort and Twort (1930). Also a few early workers have used other species to a limited extent, e.g., rats and guinea-pigs (Watson, 1932). The majority, however, have favoured the mouse for large scale experiments, no doubt partly because of low maintenance costs and

availability, but probably influenced also by the experience of early workers that the skin of rats did not readily respond to coal tars, and that papillomata on rabbits so produced remained small and often regressed when applications ceased.

Thus the mouse has become accepted as the most sensitive test animal for such work; the possibility that other species might prove more suitable under certain circumstances does not appear to have been sufficiently appreciated. Schurch (1939), however, found that his experiments with rabbits indicated that carcinogenic ingredients in addition to the recognised carcinogen 3 : 4-benzpyrene were probably present in certain coal tars. This was pointed out by Berenblum (1947), who demonstrated that the relative carcinogenic activity of a number of fractions, obtained by chromatographic procedures, varied greatly according to whether standardised against the skin of the mouse or of the rabbit. He had already shown (Berenblum, 1945*a*) that tumours were readily elicited on the rabbit by 9 : 10-dimethyl-1 : 2-benzanthracene, which was found to be more potent to rabbits than to rats or guinea-pigs, in which positive results were, however, obtained (Berenblum, 1945*b*). He also subsequently observed (1947) that this hydrocarbon when injected subcutaneously did not induce rabbit tumours, though rats and guinea-pigs responded by this method. Much earlier, Oberling, Sannié, Guerin and Guerin (1937) had shown that a 1 per cent solution of 3 : 4-benzpyrene in benzene was active on rabbits' skins, and Berenblum (1945*a*) observed that 9 : 10-dimethyl-1 : 2-benzanthracene was much more active than benzpyrene at a similar (0·5 per cent) concentration.

Experiments using a high boiling fraction of mineral oil from an experimental catalytic cracking operation have recently been carried out by Smith, Sunderland and Sugiura (1951), testing the residue after removing the lower boiling naphtha and light gas oil cuts, upon mice, rats, guinea-pigs, rabbits and rhesus monkeys. The rats and guinea-pigs were found to be refractory to skin applications but papillomata were elicited in all of the 6 monkeys, 2 being proved cancerous by biopsy 4 years after the start of the experiment. Papillomata were produced on the inner surface of the ears of the 21 rabbits within 100 days. The number and size of such growths tended to increase during the 2 years in which painting was continued, and in 3 of the 6 surviving animals cancerous changes in the growths were observed. For tests on the type of material which they intended to study, namely, samples containing oils which had been subjected to a process of fluid catalysis up to 950° F. in the presence of alumina or silica, these workers concluded that white mice were the best animals.

Recently Cruikshank and Squire (1950) obtained numerous papillomata on the ear and body skin of albino rabbits after applications of a "cutting oil" obtained from a machine sump. Only 1 benign papilloma was produced by the oil in a group of 46 mice, of which 50 per cent survived 40 weeks' and 28 per cent 52 weeks' treatment, and they suggested that such materials should be tested against both species before being regarded as non-carcinogenic to man.

In the present investigation it was decided that it was of importance that the properties of the mineral oils in question should be tested on both rabbits and mice.

Crudes and oil fractions.

The 3 crudes were obtained from Kuwait, Lagunillas and Oklahoma respectively and had the following characteristics:

Kuwait (Kuwait Oil Co.): an extensively produced Middle East crude likely to be much used in the United Kingdom, of paraffinic-asphaltic base and containing lubricating oil fractions.

Lagunillas Venezuela (Shell Petroleum Co.): a typical naphthenic crude yielding well-known lubricating distillates.

Oklahoma City Mid-Continental (Socony Vacuum Oil Co.): yields Mid-Continental distillates, bright stock and residual lubricating oils.

The derived fractions were produced by a research group appointed by the Institute of Petroleum, which has been responsible for the choice of the crudes having regard to their type, distribution and industrial importance. The initial fractionation of the 3 crudes was carried out at delimited temperatures using vacuum and steam in an apparatus selected to preclude cracking. These operations were carried out at the Thornton Research centre, Shell Refining and Marketing Co. Ltd., for the Institute of Petroleum.

Full details regarding the physical characteristics of these samples are not pertinent to the purpose of this communication, but will be presented in due course in connection with the wider aspects of the investigations.

Experimental arrangement and procedure.

Mouse tests.

For each fraction 50 animals 10 to 12 weeks of age were housed in metal boxes 11 × 8½ × 4½ inches, 5 in each box. At Birmingham they were selected, 25 of each sex, from an outbred laboratory albino strain previously employed in grading a series of oil fractions (Woodhouse and Irwin, 1950). In London the mice used were from laboratory stocks randomised so that each group of 50 contained some of each colour and genetic constitution. They were fed on Thomson's cube diet with addition of oats and a little green food. Water from bottles was always available.

The oils were applied twice weekly for 52 weeks to the inter-scapular region using approximately 0·2 ml. on each occasion. All applications were made by the same person throughout for each centre. Records of deaths, appearance of papillomata, etc., were kept, and the skin from the treated area of all mice which survived 12 weeks' treatment were prepared for histological examination. Animals surviving were killed after 52 weeks.

Rabbit tests.

It was not possible to obtain the requisite number (105) of animals of one inbred strain, and at Birmingham medium-sized males of Dutch breed with erect ears and predominantly brown or grey in colour were randomised. In London the rabbits were males of mixed commercial stock, with agouti, Flemish giant, black and albino well represented. They were housed in fairly small cages of usual type and fed on greens alternated with crushed oats and a little bran. Applications of the oils to patches of skin about 3 cm. square from which the hair had been removed by electric clippers, were made twice weekly. Six areas on each of 30 animals were used for testing the 3 crudes, and 75 animals were used for the 15 derived fractions employing 7 areas on each animal. The 6 areas comprised the 2 ears, left and right thoracic, and the left and right lateral abdominal. The seventh area was the inter-scapular region. These sites are shown in Fig. 1.

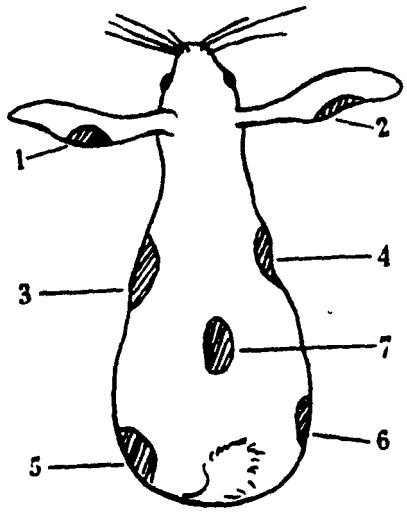


FIG. 1.—Painting sites on rabbits.
Owing to an error in the drawing of this figure, Area 7 has been placed too low and should be higher between the scapulae.

The scheme for allocating the fractions and crudes to the various areas was in accordance with the arrangement shown in Tables I and II, which were devised

TABLE I.—*Distribution of Crude Oils on Rabbit Sites* (*Fig.* 1).

Rabbits.	Sites.					
	1.	2.	3.	4.	5.	6.
1–5	L	L	K	K	O	O
6–10	K	K	O	O	L	L
11–15	O	O	L	L	K	K
16–20	L	L	O	O	K	K
21–25	K	K	L	L	O	O
26–30	O	O	K	K	L	L

L = Lagunillas crude, O = Oklahoma crude, K = Kuwait crude.

TABLE II.—*Distribution of Derived Fractions and Residues on Rabbit Skins* (*Fig.* 1).

Rabbits.	Sites.						
	1.	2.	3.	4.	5.	6.	7.
31–35	L3	K3	O4	LR	OR	L4	K4
36–40	O1	O3	L4	K2	O2	O4	OR
41–45	OR	K1	L2	KR	O4	L1	L4
46–50	O2	K2	K4	K1	L1	LR	O4
51–55	O4	LR	KR	O1	L2	K4	O3
56–60	K2	O4	L3	L2	KR	K3	O2
61–65	L1	O1	K3	O4	O3	L3	K1
66–70	K4	L2	O2	L1	L4	O3	L3
71–75	K1	L3	K2	L4	K4	O1	KR
76–80	KR	L4	O3	O2	K3	K1	LR
81–85	L4	L1	O1	K3	LR	K2	L2
86–90	L3	O2	K1	K4	O1	OR	K3
91–95	K3	K4	OR	O3	K2	KR	L1
96–100	LR	KR	L1	OR	L3	O2	O1
101–105	O3	OR	LR	L3	K1	L2	K2

R = Residue.

by Dr. J. O. Irwin (Medical Research Council's Statistical Research Unit, University of London), so that a statistical evaluation of the effects of site variation and differences in response by the individual animals might be possible. It will be apparent that each crude was applied to 60 sites and each of the other fractions to 35 sites.

Applications were made twice weekly using approximately 0·3 ml. for each. It was necessary to remove hair approximately every 10 days to ensure clear areas. This was done with special care to avoid scratching the skin. Much less trouble than had been anticipated was encountered from the animals spreading the oil to other areas of the body, though some difficulty resulted because some patches became caked with thick layers of dandruff. Records were made of the condition of the sites throughout the 52 weeks, and finally the appropriate skin areas were preserved for histology.

RESULTS.

The general results for all the mice and rabbit series are set out in Table III. In addition to the mouse tumours recorded in this Table, with several fractions a number were observed which regressed after a short period and had not recurred up to the time of death or at the fifty-second week, in spite of continued applications

TABLE III.—*Results Obtained from the* Birmingham *Laboratories* (= *B*) *compared with those from* London (= *L*).

Oil (Fractions arranged in order, light→heavy).			Rabbit test: Yield of tumours. B/L.	Mouse test: Yield of tumours. B/L.
Kuwait	Crude oil	K	0/0	2/0
	Light fraction	K1	1/0	2/0
	↓	K2	3/1	4/1
		K3	5/4	3/0
	Heavy fraction	K4	12/8	2/1
	Residue	K5	0/0	1/0
Lagunillas	Crude oil	L	0/0	0/0
	Light fraction	L1	1/0	2/0
	↓	L2	4/2	5/0
		L3	13/3	5/2
	Heavy fraction	L4	16/6	3/1
	Residue	L5	0/1	0/0
Oklahoma	Crude oil	O	0/2	0/0
	Light fraction	O1	0/1	0/0
	↓	O2	1/2	0/0
		O3	1/4	2/1
	Heavy fraction	O4	4/4	2/1
	Residue	O5	0/1	0/0

Although such spontaneous regressions are not uncommon, the frequency has been a particular feature of these tests at both centres.

It will be observed that the total number of mouse tumours in the Birmingham series was 33 900 and only 6 900 in the London series, although the survival rate was better in the latter. The greatest number observed with any fraction was 5. Thus the activity of all these materials was very slight in the mouse tests; the Birmingham results suggest that the Lagunillas derived fractions were somewhat more active than the Kuwait and that the Oklahoma set were essentially inert.

In contrast, there was a total of 61 tumour-bearing rabbit sites in the Birmingham series and 39 in the London series out of a possible 705 sites in each case, or, excluding the crudes and residues, which altogether yielded only 4 tumours (London series), the remaining 12 fractions produced 61 and 35 tumours in the Birmingham and London series respectively on a possible 420 sites. Thus the skin of the rabbit was distinctly more sensitive to these fractions than that of the mouse. This observation was confirmed by the type, rate of growth and other characteristics of the papillomata; for example several tumours appeared on one rabbit site, and this is also corroborated by full statistical analyses of the results with reference to survival rate of the mice, the effect of site distribution in the rabbits, etc., which have been undertaken by Dr. Irwin.

DISCUSSION.

Both in the rabbit and in the mouse tests a somewhat higher incidence of tumours was obtained at Birmingham than at London. This may possibly be due to a difference in the strain of animals, for Smith and Sunderland (1951) have observed differences in the response of different strains of mice. It is impossible to exclude the possibility of slight differences in technique. Considering that the strains of mice were different in the two laboratories, the agreement between the Birmingham and the London results is better than might have been expected. Although the absolute yield of tumours is different in the two cases, the relative activity of the different fractions shows an appreciable consistency (Table III).

To account for the greater activity on rabbit skin the possibility that these mineral oil fractions may contain types of carcinogen differing chemically from the polycyclic hydrocarbons hitherto encountered must be entertained. In this connection it is important to emphasize that the cracked oils used by Smith, Sunderland and Sugiura (1951) would probably constitute a series containing considerable quantities of different types of hydrocarbons from those present in the fractions utilised in the present investigation. From the oils employed by the American investigators, compounds such as isopropyl-1 : 2-benzanthracene and methyl chrysene were isolated, while the presence of pyrene and benzphenanthrene derivatives was also demonstrated by Fischer, Priestley, Eby, Wanless and Rehner (1951).

The extraordinary complexity of mineral oils and the minute proportion of carcinogenic components in the uncracked oils must present very considerable difficulties in any effort to isolate or characterise them. Twort (1951) reported preliminary attempts to do this but they were not continued. Further experiments using both species of animals to test fractions selected from these crude oils are being carried out which it is believed will provide further information and facilitate future attempts to identify the carcinogenic agents.

SUMMARY.

Tests have been carried out in two laboratories to determine the carcinogenic action to the skin of mice and rabbits of three typical mineral oil crudes and 15 fractions derived from them by processes avoiding cracking. The activity on mice of all the fractions was very slight : some, particularly those with a boiling range of 325 to 375° C., showed high activity on the rabbit ear and body skin.

Both series of experiments demonstrated, therefore, that the rabbit was more

sensitive to these types of oil than the mouse, and it is concluded that this species should be included in carcinogenic tests on this type of material.

The Chester Beatty Research Institute receives grants from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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YAMAGIWA, K., AND ITCHIKAWA, K.—(1918) *J. Cancer Res.*, **3**, 1.

Made and printed in Great Britain for
H. K. Lewis & Co. Ltd., by
Adlard & Son, Ltd., Bartholomew Press, Dorking.

ESSO LABORATORIES
STANDARD OIL DEVELOPMENT COMPANY

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH D., M.D
DIRECTOR
N V HENDRICKS, B. E., CH. E.
DIRECTOR, INDUSTRIAL HYGIENE SECTION
FRANKLIN W CHURCH, B S., (CH. E.)
INDUSTRIAL HYGIENIST

P. O. BOX 51, LINDEN, N. J.

March 18, 1953

Mr. D. V. Stroop
American Petroleum Institute
50 W. 50th St.
New York, 20, N.Y.

Dear Mr. Stroop:

The enclosed apparently represents a publication of the data which members of the Subcommittee on Carcinogenicity of the A.P.I. have had an opportunity to review in connection with the exchange of information between the British and our own Subcommittees on Carcinogenicity.

I thought you might wish to have this article reproduced and distributed to the members of the Medical Advisory Committee of the American Petroleum Institute.

Very truly yours,

R. E. Eckardt

REE/hml

R. E. ECKARDT, M.D.

Encl.
(The Value of the Rabbit
For Carcinogenicity Tests
on Petroleum Fractions.
by Hiefer & D.L.Woodhouse
Repr.from THE BRITISH JNL.
OF CANCER,1952,Vol.VI,Pg.293.)

Reprinted from
The British Journal of Cancer,
1952, Vol. VI, p. 293.

THE VALUE OF THE RABBIT FOR CARCINOGENICITY TESTS ON PETROLEUM FRACTIONS.

I. HIEGER AND D. L. WOODHOUSE.

From the Chester Beatty Research Institute, The Royal Cancer Hospital, London, S.W. 3, and the Cancer Research Laboratories, Department of Pathology, The Medical School, Birmingham, 15.

Received for publication May 28, 1952.

THE experiments recorded in this article were carried out in the course of investigations on behalf of the Medical Research Council, a sub-committee having been set up in 1949 to inquire into the carcinogenic properties of mineral oils and allied products. The arrangements for co-ordinating the research have been briefly described by Auld (1950).

The entire series of tests have been made in duplicate at the Cancer Research Laboratories, Department of Pathology, University of Birmingham, and at the Chester Beatty Research Institute, The Royal Cancer Hospital, London. At each centre the activity of 3 selected crude oils, 4 fractions derived from each crude by methods of distillation specially designed to avoid high temperature cracking, and the final residues, have been tested on groups of 50 mice for each sample and also on a total of 105 rabbits. The results appear to be of particular interest, since it must be concluded from them that it is unsatisfactory to exclude carcinogenicity on the basis of tests on mice only.

The desirability of utilising in industry those types of oils which are least likely to cause dermatitis or cancer of the skin of workers has been recognised for over 20 years, and in 1934 the Committee on Cancer of Manchester Corporation proposed a standard for assessing the potency of mineral oils depending on physical properties (specific gravity and refractive index) which it was believed would ensure that the lubricants used in the textile industry would be substantially free from carcinogenic properties. This Manchester formula, which is not now regarded as a satisfactory criterion, was put forward following the investigations of Twort and his co-workers (Twort and Fulton, 1929; Twort and Twort, 1930, 1931, 1933; Twort and Lyth, 1939; Twort, 1941), who tested a wide range of crude mineral oils, distillates, solvent extracts, spindle and shale oils, using mice almost exclusively, however, for the biological assessment of their carcinogenicity. In the past, also, mice have for the most part been employed in skin tests with "oil" fractions derived from coal tars and with the pure chemical carcinogens either isolated or synthesised.

It is true that the classical experiments of Yamagiwa and Itchikawa (1918), in which the carcinogenicity of coal tar was first proved, utilised rabbits, and this species has also been employed in a number of early experiments on tar cancer, e.g., Bonne (1927), Leroux (1927), Babès (1929) and Twort and Twort (1930). Also a few early workers have used other species to a limited extent, e.g., rats and guinea-pigs (Watson, 1932). The majority, however, have favoured the mouse for large scale experiments, no doubt partly because of low maintenance costs and

availability, but probably influenced also by the experience of early workers that the skin of rats did not readily respond to coal tars, and that papillomata on rabbits so produced remained small and often regressed when applications ceased.

Thus the mouse has become accepted as the most sensitive test animal for such work; the possibility that other species might prove more suitable under certain circumstances does not appear to have been sufficiently appreciated. Schurch (1939), however, found that his experiments with rabbits indicated that carcinogenic ingredients in addition to the recognised carcinogen 3 : 4-benzpyrene were probably present in certain coal tars. This was pointed out by Berenblum (1947), who demonstrated that the relative carcinogenic activity of a number of fractions, obtained by chromatographic procedures, varied greatly according to whether standardised against the skin of the mouse or of the rabbit. He had already shown (Berenblum, 1945*a*) that tumours were readily elicited on the rabbit by 9 : 10-dimethyl-1 : 2-benzanthracene, which was found to be more potent to rabbits than to rats or guinea-pigs, in which positive results were, however, obtained (Berenblum, 1945*b*). He also subsequently observed (1947) that this hydrocarbon when injected subcutaneously did not induce rabbit tumours, though rats and guinea-pigs responded by this method. Much earlier, Oberling, Sannié, Guerin and Guerin (1937) had shown that a 1 per cent solution of 3 : 4-benzpyrene in benzene was active on rabbits' skins, and Berenblum (1945*a*) observed that 9 : 10-dimethyl-1 : 2-benzanthracene was much more active than benzpyrene at a similar (0·5 per cent) concentration.

Experiments using a high boiling fraction of mineral oil from an experimental catalytic cracking operation have recently been carried out by Smith, Sunderland and Sugiura (1951), testing the residue after removing the lower boiling naphtha and light gas oil cuts, upon mice, rats, guinea-pigs, rabbits and rhesus monkeys. The rats and guinea-pigs were found to be refractory to skin applications but papillomata were elicited in all of the 6 monkeys, 2 being proved cancerous by biopsy 4 years after the start of the experiment. Papillomata were produced on the inner surface of the ears of the 21 rabbits within 100 days. The number and size of such growths tended to increase during the 2 years in which painting was continued, and in 3 of the 6 surviving animals cancerous changes in the growths were observed. For tests on the type of material which they intended to study, namely, samples containing oils which had been subjected to a process of fluid catalysis up to 950° F. in the presence of alumina or silica, these workers concluded that white mice were the best animals.

Recently Cruikshank and Squire (1950) obtained numerous papillomata on the ear and body skin of albino rabbits after applications of a "cutting oil" obtained from a machine sump. Only 1 benign papilloma was produced by this oil in a group of 46 mice, of which 50 per cent survived 40 weeks' and 28 per cent 52 weeks' treatment, and they suggested that such materials should be tested against both species before being regarded as non-carcinogenic to man.

In the present investigation it was decided that it was of importance that the properties of the mineral oils in question should be tested on both rabbits and mice.

Crudes and oil fractions.

The 3 crudes were obtained from Kuwait, Lagunillas and Oklahoma respectively and had the following characteristics:

Kuwait (Kuwait Oil Co.): an extensively produced Middle East crude likely to be much used in the United Kingdom, of paraffinic-asphaltic base and containing lubricating oil fractions.

Lagunillas Venezuela (Shell Petroleum Co.): a typical naphthenic crude yielding well-known lubricating distillates.

Oklahoma City Mid-Continental (Socony Vacuum Oil Co.): yields Mid-Continental distillates, bright stock and residual lubricating oils.

The derived fractions were produced by a research group appointed by the Institute of Petroleum, which has been responsible for the choice of the crudes having regard to their type, distribution and industrial importance. The initial fractionation of the 3 crudes was carried out at delimited temperatures using vacuum and steam in an apparatus selected to preclude cracking. These operations were carried out at the Thornton Research centre, Shell Refining and Marketing Co. Ltd., for the Institute of Petroleum.

Full details regarding the physical characteristics of these samples are not pertinent to the purpose of this communication, but will be presented in due course in connection with the wider aspects of the investigations.

Experimental arrangement and procedure.

Mouse tests.

For each fraction 50 animals 10 to 12 weeks of age were housed in metal boxes 11 × 8½ × 4½ inches, 5 in each box. At Birmingham they were selected, 25 of each sex, from an outbred laboratory albino strain previously employed in grading a series of oil fractions (Woodhouse and Irwin, 1950). In London the mice used were from laboratory stocks randomised so that each group of 50 contained some of each colour and genetic constitution. They were fed on Thomson's cube diet with addition of oats and a little green food. Water from bottles was always available.

The oils were applied twice weekly for 52 weeks to the inter-scapular region using approximately 0·2 ml. on each occasion. All applications were made by the same person throughout for each centre. Records of deaths, appearance of papillomata, etc., were kept, and the skin from the treated area of all mice which survived 12 weeks' treatment were prepared for histological examination. Animals surviving were killed after 52 weeks.

Rabbit tests.

It was not possible to obtain the requisite number (105) of animals of one inbred strain, and at Birmingham medium-sized males of Dutch breed with erect ears and predominantly brown or grey in colour were randomised. In London the rabbits were males of mixed commercial stock, with agouti, Flemish giant, black and albino well represented. They were housed in fairly small cages of usual type and fed on greens alternated with crushed oats and a little bran. Applications of the oils to patches of skin about 3 cm. square from which the hair had been removed by electric clippers, were made twice weekly. Six areas on each of 30 animals were used for testing the 3 crudes, and 75 animals were used for the 15 derived fractions employing 7 areas on each animal. The 6 areas comprised the 2 ears, left and right thoracic, and the left and right lateral abdominal. The seventh area was the inter-scapular region. These sites are shown in Fig. 1.

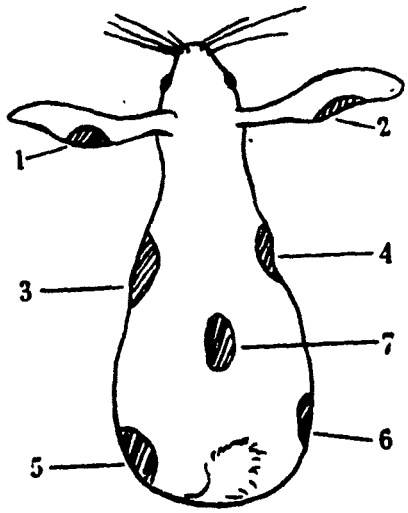

FIG. 1.—Painting sites on rabbits.
Owing to an error in the drawing of this figure, Area 7 has been placed too low and should be higher between the scapulae.

The scheme for allocating the fractions and crudes to the various areas was in accordance with the arrangement shown in Tables I and II, which were devised

TABLE I.—*Distribution of Crude Oils on Rabbit Sites* (*Fig.* 1).

Rabbits.	Sites.					
	1.	2.	3.	4.	5.	6.
1–5	L	L	K	K	O	O
6–10	K	K	O	O	L	L
11–15	O	O	L	L	K	K
16–20	L	L	O	O	K	K
21–25	K	K	L	L	O	O
26–30	O	O	K	K	L	L

L = Lagunillas crude, O = Oklahoma crude, K = Kuwait crude.

TABLE II.—*Distribution of Derived Fractions and Residues on Rabbit Skins* (*Fig.* 1).

Rabbits.	Sites.						
	1.	2.	3.	4.	5.	6.	7.
31–35	L3	K3	O4	LR	OR	L4	K4
36–40	O1	O2	L4	K2	O2	O4	OR
41–45	OR	K1	L2	KR	O4	L1	L4
46–50	O2	K2	K4	K1	L1	LR	O4
51–55	O4	LR	KR	O1	L2	K4	O3
56–60	K2	O4	L3	L2	KR	K3	O2
61–65	L1	O1	K3	O4	O3	L3	K1
66–70	K4	L2	O2	L1	L4	O3	L3
71–75	K1	L3	K2	L4	K4	O1	KR
76–80	KR	L4	O3	O2	K3	K1	LR
81–85	L4	L1	O1	K3	LR	K2	L2
86–90	L2	O2	K1	K4	O1	OR	K3
91–95	K3	K4	OR	O3	K2	KR	L1
96–100	LR	KR	L1	OR	L3	O2	O1
101–105	O3	OR	LR	L3	K1	L2	K2

R = Residue.

by Dr. J. O. Irwin (Medical Research Council's Statistical Research Unit, University of London), so that a statistical evaluation of the effects of site variation and differences in response by the individual animals might be possible. It will be apparent that each crude was applied to 60 sites and each of the other fractions to 35 sites.

Applications were made twice weekly using approximately 0·3 ml. for each. It was necessary to remove hair approximately every 10 days to ensure clear areas. This was done with special care to avoid scratching the skin. Much less trouble than had been anticipated was encountered from the animals spreading the oil to other areas of the body, though some difficulty resulted because some patches became caked with thick layers of dandruff. Records were made of the condition of the sites throughout the 52 weeks, and finally the appropriate skin areas were preserved for histology.

RESULTS.

The general results for all the mice and rabbit series are set out in Table III. In addition to the mouse tumours recorded in this Table, with several fractions a number were observed which regressed after a short period and had not recurred up to the time of death or at the fifty-second week, in spite of continued applications

TABLE III.—*Results Obtained from the* Birmingham *Laboratories* (= *B*) *compared with those from* London (= *L*).

	Oil (Fractions arranged in order, light→heavy).		Rabbit test: Yield of tumours. B/L.	Mouse test: Yield of tumours. B/L.
Kuwait	Crude oil	K	0/0	2/0
	Light fraction	K1	1/0	2/0
	↓	K2	3/1	4/1
		K3	5/4	3/0
	Heavy fraction	K4	12/8	2/1
	Residue	K5	0/0	1/0
Lagunillas	Crude oil	L	0/0	0/0
	Light fraction	L1	1/0	2/0
	↓	L2	4/2	5/0
		L3	13/3	5/2
	Heavy fraction	L4	16/6	3/1
	Residue	L5	0/1	0/0
Oklahoma	Crude oil	O	0/2	0/0
	Light fraction	O1	0/1	0/0
	↓	O2	1/2	0/0
		O3	1/4	2/1
	Heavy fraction	O4	4/4	2/1
	Residue	O5	0/1	0/0

Although such spontaneous regressions are not uncommon, the frequency has been a particular feature of these tests at both centres.

It will be observed that the total number of mouse tumours in the Birmingham series was 33 900 and only 6 900 in the London series, although the survival rate was better in the latter. The greatest number observed with any fraction was 5. Thus the activity of all these materials was very slight in the mouse tests; the Birmingham results suggest that the Lagunillas derived fractions were somewhat more active than the Kuwait and that the Oklahoma set were essentially inert.

In contrast, there was a total of 61 tumour-bearing rabbit sites in the Birmingham series and 39 in the London series out of a possible 705 sites in each case, or, excluding the crudes and residues, which altogether yielded only 4 tumours (London series), the remaining 12 fractions produced 61 and 35 tumours in the Birmingham and London series respectively on a possible 420 sites. Thus the skin of the rabbit was distinctly more sensitive to these fractions than that of the mouse. This observation was confirmed by the type, rate of growth and other characteristics of the papillomata; for example several tumours appeared on one rabbit site, and this is also corroborated by full statistical analyses of the results with reference to survival rate of the mice, the effect of site distribution in the rabbits, etc., which have been undertaken by Dr. Irwin.

DISCUSSION.

Both in the rabbit and in the mouse tests a somewhat higher incidence of tumours was obtained at Birmingham than at London. This may possibly be due to a difference in the strain of animals, for Smith and Sunderland (1951) have observed differences in the response of different strains of mice. It is impossible to exclude the possibility of slight differences in technique. Considering that the strains of mice were different in the two laboratories, the agreement between the Birmingham and the London results is better than might have been expected. Although the absolute yield of tumours is different in the two cases, the relative activity of the different fractions shows an appreciable consistency (Table III).

To account for the greater activity on rabbit skin the possibility that these mineral oil fractions may contain types of carcinogen differing chemically from the polycyclic hydrocarbons hitherto encountered must be entertained. In this connection it is important to emphasize that the cracked oils used by Smith, Sunderland and Sugiura (1951) would probably constitute a series containing considerable quantities of different types of hydrocarbons from those present in the fractions utilised in the present investigation. From the oils employed by the American investigators, compounds such as isopropyl-1 : 2-benzanthracene and methyl chrysene were isolated, while the presence of pyrene and benzphenanthrene derivatives was also demonstrated by Fischer, Priestley, Eby, Wanless and Rehner (1951).

The extraordinary complexity of mineral oils and the minute proportion of carcinogenic components in the uncracked oils must present very considerable difficulties in any effort to isolate or characterise them. Twort (1951) reported preliminary attempts to do this but they were not continued. Further experiments using both species of animals to test fractions selected from these crude oils are being carried out which it is believed will provide further information and facilitate future attempts to identify the carcinogenic agents.

SUMMARY.

Tests have been carried out in two laboratories to determine the carcinogenic action to the skin of mice and rabbits of three typical mineral oil crudes and 15 fractions derived from them by processes avoiding cracking. The activity on mice of all the fractions was very slight : some, particularly those with a boiling range of 325 to 375° C., showed high activity on the rabbit ear and body skin.

Both series of experiments demonstrated, therefore, that the rabbit was more

sensitive to these types of oil than the mouse, and it is concluded that this species should be included in carcinogenic tests on this type of material.

The Chester Beatty Research Institute receives grants from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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Made and printed in Great Britain for
H. K. Lewis & Co. Ltd., by
Adlard & Son, Ltd., Bartholomew Press, Dorking.

Dear Mr. Stroop:

I am sending you herewith, for your information, a statement of expenditures made on behalf of American Petroleum Institute during the first quarter of 1953. I believe that the statement will be self-explanatory, but if you have any questions or comments, Dr. Mehoe would appreciate your bringing them to his attention.

Very truly yours,

/s/ E. V. Partlage

E. V. Partlage, Secretary to
Dr. Mehoe

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Enc.

API 05612

Copy From D. V. Stroop for Information of Doctors Frank, Saunders, Davis, and Reinhardt. 5-23-53

UNIVERSITY OF CINCINNATI

Department of Preventive Medicine and Industrial Health

The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

May 19, 1953

Mr. D. V. Stroop, Director
American Petroleum Institute
Department of Technical Services
50 West 50th Street
New York City 20

Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	6,454.46	8,454.91
	TOTAL	25,713.02

Balance Available for Further Work at End of 4th Quarter 1932	52,757.12
Balance Due Kettering Laboratory at End of	
Receipts	
Expenditures 1st Quarter 1933	25,713.02
Balance Available for Further Work at End of 1st Quarter 1933	27,044.10
Balance Due Kettering Laboratory at End of	

UNIVERSITY OF CINCINNATI

Kettering Laboratory

ACCOUNT OF The American Petroleum Institute

FOR 1st Quarter 1953

SALARIES (Based on Proportion of Time Actually Spent on Project)

Direct Salaries	10,063.86	
Indirect Salaries		
Histopathological Preparation	161.50	
Other Services	7,880.75	17,906.11

MISCELLANEOUS EXPENSE

Purchase of Animals	961.40	
Special Laboratory Supplies	1,078.41	
Travel	[illegible]	

from DVS for information of Doctors Frank, Davis, and Elizabeth - 5/19/53

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

May 19, 1953

Mr. D. V. Stroop, Director
American Petroleum Institute
Department of Technical Services
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am sending you herewith, for your information, a statement of expenditures made on behalf of American Petroleum Institute during the first quarter of 1953. I believe that the statement will be self-explanatory, but if you have any questions or comments, Dr. Kehoe would appreciate your bringing them to his attention.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

ef

Enc.

API 05614

UNIVERSITY OF CINCINNATI

KETTERING LABORATORY

ACCOUNT OF THE AMERICAN PETROLEUM INSTITUTE

FOR 1st Quarter 1953

SALARIES (Based on Proportion of Time Actually Spent on Project)

Direct Salaries	10,063.86	
Indirect Salaries		
Histopathological Preparation	163.50	
Other Services	7,280.75	17,508.11

MISCELLANEOUS EXPENSE

Purchase of Animals	343.40	
Special Laboratory Supplies	1,072.41	
Travel	294.64	
Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	6494.46	8,204.91
TOTAL		25,713.02

Balance Available for Further Work at End of 4th Quarter 1952	52,757.12
Balance Due Kettering Laboratory at End of	
Receipts	
Expenditures 1st Quarter 1953	25,713.02
Balance Available for Further Work at End of 1st Quarter 1953	27,044.10
Balance Due Kettering Laboratory at End of	

API 05615

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discernible but it was not anticipated that any such trends would be discernible prior to at least 5 years experience. It is hoped that the support which the General Committee, Division of Refining has given to the epidemiological study will stimulate renewed reporting of the cases with sufficient medical and occupational histories to permit some early correlations to be made about 1956.

Summary

1. The RP (MC-1) Advisory Committee believes that the Kettering Laboratory is performing important work in the field of carcinogenesis of refinery streams and materials. They believe that although a great many practical answers have already been obtained, the work should be pursued because the work of the laboratory promises to provide many fundamental answers to questions which now exist concerning industrial and occupational carcinogenesis.

2. It is believed that the work with non-accelerating solvents which relates the carcinogenic responses of a solution of pure carcinogen to the dose applied per unit area per week to the skin is of extreme fundamental importance. The Committee urges that additional work be conducted to establish firmly the curve which expresses this relationship.

3. It is also believed that the work with accelerating solvents is also of extreme fundamental importance and that this should be pursued vigorously in an attempt to develop a complete understanding of the relative role of carcinogens and accelerators in refinery streams and materials.

4. Since much of the correlation of chemical analyses with biological potency is dependent upon the accuracy of P_{MC} values, the Committee laments the fact that many of the P_{MC} values thus far reported are based on data which the laboratory recognizes as not having been obtained from the best biological experiment possible. The Committee suggests, therefore, that the laboratory devote considerable effort to repeating those experiments in an effort to develop P_{MC} values that are based on the soundest possible biological experiment.

5. The Committee believes that the work with washing techniques and protective creams may provide intensely practical guides to refinery hygiene practice and suggests that this work be pursued as new approaches appear to the laboratory.

6. The Committee recognizes that the epidemiological studies cannot be expected to produce significant results until at least 1956, and, therefore, urges that renewed efforts at adequate case and occupational history reporting be made during the next several years. It believes that adequate medical staffs can do most to insure the success of this program, and in this connection it acknowledges the stimulus that the General Committee, Division of Refining has given to the attainment of this objective.

7. The laboratory has already determined that a number of refinery streams and materials have a relatively high degree of carcinogenicity. Although data obtained with mice cannot be directly transposed to humans, there is sufficient data in occupational cancer experience to indicate that the

petroleum industry cannot take lightly the observations of the laboratory on the carcinogenicity of these refinery streams and materials.

8. The Committee recognizes that the laboratory at best can determine from its biological and chemical work only the relative carcinogenicity of various refinery streams and materials. The determination of the hazard is dependent upon factors of extent, frequency, duration, and length of exposure. As recognized by the laboratory in Dr. Kehoe's talk to the members of the General Committee, Division of Refining the determination of the hazard is at present a function of the individual petroleum companies. Adequate medical and industrial hygiene staffs are essential in these individual companies if they are adequately to appraise the hazard. The Committee supports Dr. Kehoe's plea that petroleum company managements recognize this truism and make plans for the development of such adequate medical and industrial hygiene staffs.

9. It is apparent that the laboratory has accumulated sufficient data that publication of results will be deemed desirable in the near future. The Committee recognizes the right of the laboratory to publish, and urges that the mechanism be established so that these publications can be reviewed in a finite period of time. As a suggestion, it is proposed that this mechanism be so established that review by API management and suggestions and criticisms for the laboratory from API management be made available within sixty (60) days. If no criticisms or suggestions are obtained by the laboratory at the expiration of this time, the laboratory can assume that none are forthcoming and proceed with publication. It should be recognized that this review is for the purpose of helpful criticisms and suggestions, and not for the determination of whether or not there will be publication, since the contract with the laboratory clearly states that the laboratory determines if and when publication occurs.

---ooOoo---

October 7, 1953

Copy from D. V. Stroop for information of Dr. George M. Saunders and Dr. R. E. Eckardt December 22, 1953

UNIVERSITY OF CINCINNATI

Department of Preventive Medicine and Industrial Health

Lettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

December 19, 1953

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am sending you herewith for your information, a statement of expenditures made on behalf of the American Petroleum Institute for the third quarter of 1953. I believe that this statement will be self-explanatory, but if you have any questions or comments, Doctor Kehoe would appreciate your bringing them to his attention.

Very truly yours,

/s/ E. R. Portlage

E. R. Portlage, Secretary to
Dr. Kehoe

of

Enc.

API 05730

UNIVERSITY OF CINCINNATI

KETTERING LABORATORY

ACCOUNT OF AMERICAN PETROLEUM INSTITUTE
FOR 3rd Quarter 1953

SALARIES	(Based on Proportion of Time Actually Spent on Project)		
	Direct Salaries	7,981.26	
	Indirect Salaries		
	Histopathological Preparation	602.58	
	Other Services	8,539.94	17,123.78
MISCELLANEOUS EXPENSE			
	Purchase of Animals	438.60	
	Special Laboratory Supplies	793.29	
	Travel	1,111.57	
	Overhead (Proportion of Heat, Gas, Electricity, Steam, Telephone, General Laboratory Supplies, Postage, Annuities, Pensions, Maintenance, etc.	4,868.57	7,212.03
	TOTAL		24,335.81
	Balance Available for Further Work at End of _____		
	Balance Due Kettering Laboratory at End of Second Quarter 1953	3,450.62	
	Receipts 3rd Quarter 1953	40,000.00	
	Balance Available	36,549.38	
	Expenditures 3rd Quarter 1953	24,335.81	
	Balance Available for Further Work at End of 3rd Quarter 1953	12,213.57	
	Balance Due Kettering Laboratory at End of _____		

API 05731

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

DEPARTMENT OF TECHNICAL SERVICES
DAVID V. STROOP DIRECTOR

December 23, 1953

Dr. Robert A. Kehoe
University of Cincinnati
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Pursuant to the extension of agreement dated June 30, 1953, we enclose the Institute's check in the amount of $[illegible] which represents the balance due and payable as of January 1, 1954.

The final payment of this account is made in our understanding that there was no unexpended balance in the fund at Kettering Laboratory on June 30, 1953.

Very truly yours,

DVS:jp
cc: Dr. Robert E. Schmidt
Mr. E. C. Barnes
Dr. George M. Saunders
Mr. Lacey Walker
Enclosure

File: Med. Adv. Comm. Expenditures

December 23, 1953

Dr. Robert A. Kehoe
University of Cincinnati
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Pursuant to the extension of agreement dated June 30, 1953, we enclose the Institute's check in the amount of $38,883 which represents the balance due and payable as of January 1, 1954.

The full payment of this amount is made in our understanding that there was no unexpended balance in the fund at Kettering Laboratory on June 30, 1953.

Very truly yours,

DVS:ja
cc: Dr. Robert E. Schmidt
Mr. E. O. Matteoda
Dr. George M. Saunders
Mr. Lenny Walker
Enclosure

API 05733

July 7, 1953

Dr. Robert A. Kehoe
University of Cincinnati
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

This will acknowledge receipt of two copies of the executed extension of agreement between the American Petroleum Institute and the University of Cincinnati, for the year ending June 30, 1954 which was enclosed with your letter dated July 1, 1953.

Pursuant to terms of the extension agreement, there is enclosed the Institute's check in the amount of $40,000.

Very truly yours,

WFMcJr
Enclosure
cc: Mr. Lenny Walker
Mr. L. G. Matheson
Dr. T. E. Frank
Dr. Kieffer Davis

API 05734

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

July 3, 1953

CABLE ADDRESS KETLAB, CINCINNATI
TELEPHONE, CAPITOL 1414

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I am returning to you herewith two copies of the executed extension of agreement between American Petroleum Institute and the University of Cincinnati, for the period June 30, 1953 to June 30, 1954.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

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Enc.

AMERICAN PETROLEUM INSTITUTE
50 WEST 50TH STREET
NEW YORK 20, N. Y.

June 30, 1953

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1954, according to the terms of the agreement dated January 8, 1946, and on the basis of a maximum budget for operating expenses of $78,283.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $40,000. The balance of $38,283, less the unexpended balance in the fund on June 30, 1953, will be paid on January 1, 1954.

It is understood that any balance in the fund on June 30, 1954 will be returned to the American Petroleum Institute, and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By Frank M. Porter
President

By
Secretary

Accepted and Approved:

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By Renton K. Brodie
Renton K. Brodie, Chairman
Board of Directors

By Ralph C. Bursiek
Ralph C. Bursiek, Clerk
Board of Directors

API 05737

June 24, 1953

Dr. Robert A. Kehoe
University of Cincinnati
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Doctor Kehoe:

Enclosed you will find four copies of the continuation agreement covering API Medical Research Project H-2 for the fiscal year ending June 30, 1954. These have been signed on behalf of the Institute.

Upon the return of two executed copies we shall send the initial payment of $40,000.

Very truly yours,

EWS:tm
Enclosures (4)

API 05738

June 30, 1953

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1954, according to the terms of the agreement dated January 8, 1946, and on the basis of a maximum budget for operating expenses of $78,283.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $40,000. The balance of $38,283, less the unexpended balance in the fund on June 30, 1953, will be paid on January 1, 1954.

It is understood that any balance in the fund on June 30, 1954 will be returned to the American Petroleum Institute, and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By_____
President

By_____
Secretary

Accepted and Approved:

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By_____

By_____

API 05739

June 30, 1952

Dr. Robert A. Kehoe
University of Cincinnati
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Doctor Kehoe:

Enclosed you will find four copies of the continuation agreement covering API Medical Research Project M-2 for the fiscal year ending June 30, 1953.

Inasmuch as President Porter is out of the city and will not return for two weeks we suggest that you have the contracts signed on behalf of the University of Cincinnati and return them to us so we may send you a check. We will send you two copies of the agreement for your files as soon as they have been signed by Mr. Porter.

Very truly yours,

DVS:c
Enclosures

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

June 30, 1952

Board of Directors
University of Cincinnati
Cincinnati 19, Ohio

Gentlemen:

This communication is authority to continue work on investigation of the toxicity and mode of action of certain petroleum products for the year ending June 30, 1953, according to the terms of the agreement dated January 6, 1946, and on the basis of a maximum budget for operating expenses of $104,760.

Upon receipt of your approval of the continuation of the project with this maximum budget we shall pay you the sum of $50,000. The balance of $54,760, less the unexpended balance in the fund on June 30, 1952, will be paid on January 1, 1953.

It is understood that any balance remaining in the fund on June 30, 1953 will be returned to the American Petroleum Institute, and that no excess over the amount of the budget is to be obligated or spent without written authorization.

Very truly yours,

AMERICAN PETROLEUM INSTITUTE

By Frank M. Porter
President

By
Secretary

Accepted and Approved:

UNIVERSITY OF CINCINNATI
Through its Board of Directors

By
Frank F. Dinsmore, Chairman

By Ralph C. Bursiek
Ralph C. Bursiek, Clerk

API 05741

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

December 28, 1953

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 1414

Mr. D. V. Stroop, Director
Department of Technical Services
American Petroleum Institute
50 West 50th Street
New York City 20

Dear Mr. Stroop:

I herewith acknowledge with thanks receipt of American Petroleum Institute's check in the amount of $38,283.00, covering expenditures to be made on their behalf.

Very truly yours,

E. R. Fortlage

E. R. Fortlage, Secretary to
Dr. Kehoe

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