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AMERICAN PETROLEUM INSTITUTE
MEDICAL ADVISORY COMMITTEE

NINETEENTH MEETING

April 25, 1955
Statler Hotel
Buffalo, N. Y.

Registration

MEMBERS PRESENT OR REPRESENTED

George M. Saunders, M. D. - Chairman
F. D. Gassaway, M. D. - Secretary

W. O. Armstrong, M. D.
Lamson Blaney, M. D.
F. F. Boys, M. D.
Marshall Clinton, M. D.
J. W. Crookshank, M. D.
L. E. Curtis, M. D.
R. E. Eckardt, M. D.
K. R. Fourcher, M. D.
T. M. Frank, M. D.
C. H. Hine, M. D.
T. J. Kelly, M. D.
E. P. Luongo, M. D.
C. R. Miller, M. D.
M. N. Newquist, M. D.
J. W. Osborn, M. D.
R. J. Potts, M. D.
B. B. Reeve, M. D.
J. C. Ruddock, M. D.
Leo J. Wade, M. D.
(Rep. by J. J. Thorpe, M. D.)
E. R. Ware, M. D.

TECHNICAL ADVISORS PRESENT

E. W. Adams
C. T. Brown
E. K. Daniels,
A. E. Dooley
P. D. Halley
C. A. Neilson
A. C. Pabst

OTHERS REGISTERED

Philip Drinker	-	Harvard University
Robert R. Dugan, M. D.	-	Continental Oil Company
A. E. Hoag, M. D.		
E. O. Mattocks	-	American Petroleum Institute
William L. Oviett	-	Standard-Vacuum Oil Co.
F. H. Pretsch, M. D.	-	Humble Oil & Refining Co.
Lucian E. Reaes	-	Phillips Petroleum Co.
H. O. Sappington, M. D.	-	Humble Oil & Refining Co.
W. E. Scovill	-	The Standard Oil Co. (Ohio)
Jack Spence	-	Standard Oil Co. of California
D. V. Stroop	-	American Petroleum Institute

MEMBERS NOT REGISTERED OR REPRESENTED

V. C. Baird, M. D.
Kieffer Davis, M. D.
W. F. Kahle, M. D.
E. K. Linder, M. D.
R. C. Page, M. D.

I

MINUTES OF EIGHTEENTH MEETING

ACTION: The committee voted to approve the minutes of the Eighteenth Meeting as circularized with letter dated September 16, 1954.

II

SUBCOMMITTEE REPORTS

A. Subcommittee on C_9 - C_{12} Aromatics - C. H. Hine, M. D., Chairman

Dr. Hine reported recommendations for the subcommittee as follows:

1) A contract be negotiated between the Medical Advisory Committee of the API and the University of Texas Medical Branch for the purpose of conducting studies on the toxicity of C_9 - C_{12} aromatics derived from petroleum.

2) The principal investigator in these studies should be Dr. Carl A. Nau, Professor and Chairman of the Department of Preventive Medicine and Public Health of the Texas Medical Branch.

3) The C_9 - C_{12} Subcommittee act as a steering committee for this study.

4) Funds in the amount of $20,000 be made available by 1 July 1955 to be used in support of this study.

5) The experimental design be agreed upon by both parties and fundamentally should involve chronic inhalation exposures of suitable species of test animals to vapors of a representative sample of C_9 - C_{12} aromatics and adequate controls (n-decane and benzene).

6) The sample should be prepared under the auspices of the subcommittee from a composite mixture of aromatic fractions obtained from interested participating member companies of the API.

7) The project be terminated provided there is no evidence of significant toxicity upon completion of the presently planned study.

8) The project be continued for an additional year providing the data collected at the completion of the proposed study indicates that further study is warranted and that $20,000 be tentatively budgeted for 1 July 1956 for that purpose.

ACTION: The report was adopted by the Medical Advisory Committee for recommendation to the Medical and Health Committee.

B. Subcommittee on Carcinogenicity - R. E. Eckardt, M. D., Chairman

Dr. Eckardt presented the subcommittee's report which is attached to these minutes as Exhibit A.

ACTION: The Medical Advisory Committee voted to adopt the subcommittee recommendation for continuation of Research Project MC-1 at Kettering Laboratory with a budget of $58,500 for the fiscal year ending June 30, 1957 with the understanding that of this amount $15,000 to $20,000 would be used for epidemiological work.

C. Subcommittee on Atmospheric Pollutants - E. P. Luongo, M. D., Chairman

Dr. Luongo presented the report which is attached as Exhibit B.

ACTION: The report was accepted.

D. Subcommittee on Dermatology - Leo J. Wade, M. D., Chairman

In the absence of Dr. Wade, Dr. Thorpe presented an interim report on the status of the dermatitis survey of the Division of Marketing which is attached as Exhibit C.

E. Subcommittee on Economic Poisons - C. H. Hine, M. D. Chairman

Dr. Hine presented a brief status report which is attached as Exhibit D.

F. Subcommittee on Physical Agents - J. W. Osborn, M. D. Chairman

Dr. Osborn submitted the subcommittee report which is attached as Exhibit E.

III

PUBLIC GROUP SESSION AT SAN FRANCISCO

In the absence of Dr. V. C. Baird, Chairman, Dr. Eckardt reported that members of the Program Committee had discussed and were recommending a group session program as follows:

Monday, November 14, 1955
Group Session
10:00 A.M.

Medical Advisory Committee
Open Session (Fairmont Hotel)
Presiding: M. J. Rathbone, Standard Oil Co. (N.J.)

Outline of History, Membership, Scope and Activities of the Medical Advisory Committee. Dr. Saunders

The Ailing, Aging Truck Driver. (Wade or Newquist)

Industrial Hygiene in Our day to Day Operations. (Industrial Hygienists)

Are There Noise Problems in Our Industry? (Industrial Hygienist)

Toxicological Evaluation of Chemicals and Products of the Petroleum Industry. C. H. Hine

ACTION: The committee approved the program as outlined.

IV

BUDGET ESTIMATES FOR 1956-1957

The committee reviewed the budget for 1955-1956 and the preliminary recommendations of the several subcommittees and voted to recommend to the Medical and Health Committee of the Board that the budget estimates for 1956-1957 should include the following:

1) University of Cincinnati	
a) Carcinogenicity -$58,500	
b) Physiology of Skin - 5,000	$63,500
2) Professor Philip Drinker	3,000
3) Toxicity of C_9 - C_{12} Aromatics	20,000
4) Miscellaneous	1,000
	$87,500

V

NEW BUSINESS

A. Precautionary Labeling

Mr. Stroop read the report made by M. J. Rathbone to the Board of Directors. See copy attached as Exhibit F.

B. Round Table Session

The committee requested the reservation of a conference room at the Fairmont Hotel, San Francisco on Tuesday, November 15, 1955 for the holding of an informal round table discussion on subjects of common interest to members. (Note: Arrangements have been made to reserve such a room for this unscheduled meeting.)

VI

ADJOURNMENT

There being no further business to come before the committee the meeting was adjourned.

F. D. Gassaway, M. D.
Secretary

Approved by:
George M. Saunders, M. D.
4/29/55 Chairman

EXHIBIT A

TO MINUTES OF MEETING OF MEDICAL ADVISORY COMMITTEE
April 25, 1955

REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY
Robert E. Eckardt, M. D., Chairman

I. Status of Publications

The manuscript on the method of determining benzpyrene is published. A slight modification of the method, which is attached as Appendix A, will be attached to reprints of this publication.

The manuscript on Carcinogenesis of the Skin was returned to Kettering Laboratory with suggestions for condensation of portions of the paper, and expansion of the introduction so it will have more meaning to cancer research workers. This expansion of the introduction and other modifications is attached as Appendix B.

II. Status of the Biological and Chemical Work

The interim report of the Laboratory is attached as Appendix C.

The original concept that petroleum products in the boiling range of 450-650°F or 700°F all contained significant quantities of accelerators now appears untenable. Rather it appears that in this range, there are variations in accelerator content which the laboratory is now in the process of working out. It is felt by the laboratory that this is important because a comparison of mouse data with available human data, suggests to the laboratory that accelerators may have significance in human skin carcinogenesis. This may be even more important in the petroleum industry than the coal tar industry.

Work to date suggests that petroleum cuts boiling in the range 625-650°F may be low in their accelerator content. On the other hand, above 650°F there appears to be another surge of accelerators.

Present work also suggests that alkyl naphthalenes are very potent accelerators, far more so than straight chain paraffins. Furthermore, they may not be as easily reduced in their activity by dilution as the straight chain paraffins.

Washing experiments suggest there is no advantage, and possibly a distinct disadvantage to using a petroleum material as a rinse prior to washing.

III. Future Chemical and Biological Work

About 55% of the effort of the laboratory in this direction will be in chasing down the nature of the carcinogens in the 700-725-750° F boiling range. To date 3 classes of carcinogens have been identified: (1) Benzpyrene types, (2) Types which form an adduct with maleic anhydride, presumably benzanthracenes, and (3) the as yet unidentified types in the 700-725-750° F range.

About 35% of the effort of the laboratory in this direction will be devoted to separating and characterizing the properties of accelerators. For this, boiling range, gravity, refractive index and aniline point have been

found to be useful tools. Liquid thermal diffusion as another useful tool will be investigated.

To date four types of accelerators are known: (1) straight chain paraffins, (2) Alkyl benzenes, (3) Alkyl naphthenes and (4) Alkyl naphthalenes. It appears that there is a chain length in each type which gives optimum accelerating properties. Further work on the definition of optimum chain length is planned.

From what has been said, it is evident that accelerators are major components of petroleum. In contrast, carcinogens constitute only minor components.

IV. Epidemiology

A progress report by Dr. Phair is attached as Appendix D.

500 new cases have been reported, bringing the total to 1800. The data on all 1800 of these are now being transferred from the previous manual sort cards to electronic sort cards. It is anticipated that this transfer, and initial correlations will be available by the next meeting of the Medical Advisory Committee. It is possible that preliminary incidence figures will also be available at that time.

The medical directors are again encouraged by the subcommittee to continue and extend whenever possible, their reporting of cases to Dr. Phair.

V. Budget

The budget for July 1, 1955 to June 30, 1956 is $65,000, to be expended as follows:

Biological Work	$20,000
Technical Work	32,250
Epidemiological Work	12,750

The subcommittee has requested of the Kettering Laboratory that a complete status report of the work be prepared in advance of the next Medical Advisory Committee Meeting. This status report should include significant conclusions of the work to date, with supporting data, grouped in accordance to important individual conclusions. In addition, a brief outline of future objectives should be included.

Recommendation:

The Subcommittee recommends that this work be continued with a budget of $58,500 for the period July 1, 1956 to June 30, 1957. Of this budget, from $15,000 to $20,000 shall be expended in the epidemiological work.

April 25, 1955

APPENDIX A

MODIFICATION OF METHOD DESCRIBED ON PAGE 252 OF THE REPRINT FROM ANALYTICAL CHEMISTRY, VOLUME 27, PAGE 248 TO 253, FEBRUARY 1955

Certain materials failed to give qualitatively satisfactory difference spectra by the routine method of analysis (see page 252). Amongst these are crude petroleum or shale oil and fractions of coal tar or cracked petroleum relatively rich in anthracenes. A substantial removal of the interfering substances from the sample may be accomplished by the action of concentrated sulfuric acid.

A 200 mg. sample is dissolved in 100 ml. of C.P. thiophene free benzene and shaken vigorously with 100 ml. of concentrated H_2SO_4 in a separatory funnel at 25-28°C. The contents of the funnel are then allowed to stand for ten minutes, during which time separation of layers should have occurred. The H_2SO_4 layer is allowed to run out over 500 g. of cracked ice. agitated by a glass stirring rod. The aqueous acid is then extracted by 100 ml. of benzene. The aqueous layer and any interfacial scums are then discarded (these scums will commonly constitute a volume of 5-10 ml. and contain approximately 5% of the benzopyrene). The benzene solution is now washed with 200 ml. of 5% NaOH in water, and again the aqueous layer and interfacial scums are discarded, with similar losses.

The benzene solution is now evaporated down to a volume of approximately 5 ml. and diluted with 5 ml. of isooctane. The resulting solution is then treated by the usual analytical process. The percent benzopyrene indicated may then appropriately be adjusted by the addition of 15% of the answer obtained.

Appendix B

CARCINOGENESIS OF THE SKIN. A reexamination of Basic Experimental Methods, and the Use of Reference Standards in Expressing the Relative Potencies of Complex Tars and Oils!

by A. Wesley Horton and Dorothy Templeton Denman

(Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio)

The investigation of cancer in this Laboratory has been directed toward the estimation of the potential hazards of various forms of this disease which sometimes arise in industrial operations. This paper deals with one essential phase of such appraisals, namely, the experimental determination of the relative carcinogenic potency of selected materials for the tissue in question, in this case the skin.

In certain situations, it may be sufficient to measure the order of magnitude of the activities of a pertinent series of samples. Such would perhaps be the situation if, in the industrial operation in question, a mixture is produced, the composition of which is relatively simple and can reasonably be expected to remain constant indefinitely. However, in the case of the materials with which we have been primarily concerned, complexity and change have been the rule rather than the exception. Our investigative program was, therefore, directed toward the development of a qualitative picture and a subsequent quantification of the basic relationships between the chemical composition and the relative carcinogenic potency of various complex tars and oils. Through this approach, it is hoped that the results will have continuing significance in a changing technology.

The chance that a logical program of chemical and biological investigation would successfully resolve this complex problem depended heavily upon the accuracy with which the potencies of the various samples could be determined. This need was particularly emphasized by the findings in the course of this work that, while in the case of many of the mixtures tested, potency was independent of the quantity used for each application, certain important materials exhibited as much as four times the potency when the dose of 100 mg. was applied each time than when that of 15 mg. was so applied.

Recent analyses of the variability of the latent periods to the appearance of papillomas led to an estimate by Blanding and coworkers (3) that the "tumor potency" of a given material to the skin could be measured within +31 percent or -24 percent (approximately +50 percent or -30 percent in terms of arithmetic dose) in tests involving 30 stock mice each. Shimkin and Andervont (23) had shown earlier that the rate of induction of sarcomas could be defined more accurately by using the inbred C3H strain rather than stock mice. However, they obtained discrepant results even with C3H mice in repeated tests of solutions of dibenzanthracene (24) which may have been partly responsible for the more conservative estimate by Bryan and Shimkin (7) of the possible error as +100 percent or -50 percent for assays involving 100 animals (see also, 22). Although one of the pertinent experiments in which this unexplained variation occurred was complicated by the occurrence of intercurrent infection among the animals (page 58 of reference 23), Shimkin and Andervont did not relate this phenomenon to the observed retardation of tumor induction.

In this Laboratory, in which the minute and sometimes insidious effects of prolonged exposure to potentially injurious agents have been under investigation, the rate of growth of experimental animals has been measured with

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regularity. The availability of such data in a large number of experiments involving application of a variety of potentially carcinogenic materials has enabled us to explain certain discrepancies comparable to those reported by Shimkin and Andervont. Examples in the body of this text will show that combinations of systemic intoxication and intercurrent disease sufficient to cause significant aberration of the growth of the animals are capable generally of exercising an inhibitory effect upon the experimental induction of cancer of the skin of the mouse.

It has been our experience that neither the incidence of tumors nor the standard deviation of the latent period of their appearance will necessarily be changed by this slowing down of their growth. Hence, although appropriate statistical treatment of these data is useful and necessary, it may fail utterly to reveal the intrinsic error introduced by this variable. Along with all proper precautions to minimize the toxicity of the applied material and to prevent intercurrent disease of any type, the animals should be weighed at regular intervals. Then, before the results are used for quantitative comparison with those of other tests, the investigator must assure himself that the average growth of each group of animals was normal at least during the relevant periods of the experiments.

In the course of this experimental program, solutions of synthetic carcinogens in pure solvents have been used as external standards of reference. Results of these tests have been correlated to provide certain dosage-response relationships, discussed in the section on Reference Standards.

EXPERIMENTAL METHODS

The validity of the use of data obtained from experiments with small animals to provide some indication of potential hazards to men in specific occupations depends upon the extent of correlated experience. The use of mice in the estimation of the relative carcinogenic potency of various materials for the skin of men can be justified on such a basis. The similarity of response of the skin of these two species to carcinogenic materials, such as shale oils from Scottish refineries and certain spindle oils used in the spinning of cotton in Lancashire, is well documented (14,15,18,20).

To obtain reasonably close definition of relative potencies with a minimum number of mice in each experiment, males of the highly inbred C3H strain have been used in most of our work. The docility of this animal has proved important in obtaining reproducible results as compared to other work in this Laboratory with CFW and Swiss males. Thus, in experiments which were satisfactory from the standpoint of growth and survival, 20 C3H mice were usually sufficient to define the mean time of appearance of tumors within confidence limits of ±15 percent (95 percent probability).

The general procedure may be summarized briefly. Mice were received from the Jackson Memorial Laboratory at six to eight weeks of age. They were placed under observation for four weeks to eliminate any in which there was evidence of poor health.

The actual tests of various synthetic solutions and complex oils followed the time-honored procedure of repeated application upon the fur and skin in the interscapular region (see for example, 20). The usual schedule consisted of three 100 mg. applications each week. The average quantity used in each painting has proved a most important variable in the case of certain complex oils and, therefore, was kept within reasonable limits. In testing certain materials of

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moderate toxicity, it was necessary to reduce the severity of the exposure (dosage per application or frequency of application) to obtain satisfactory results.

On an unrestricted diet of Purina Laboratory Chow and water, the C3H mice in the satisfactory tests reached an average weight of 28 to 31 g. at six months of age. Experience has shown that, even when the mortality among an experimental group was low, the mean time of appearance of tumors was sometimes delayed seriously (as much as 50 percent) by conditions of variable or uncertain origin which also interrupted the normal growth of the animals. As a measure of such conditions, therefore, the mice were weighed at frequent intervals throughout the experiments. Precautions were taken to minimize infections and to prevent their spread from one group to another.

In general, under the conditions of these experiments one of two results has been obtained in response to repeated applications of any one of a long series of materials, i.e., most of the animals which lived long enough developed tumors of the skin at the site of the application, or none of them did so. The outcome of the experiments, therefore, has been essentially unequivocal, and the relative potencies of the different active materials could be expressed in terms of the relative rates of induction of tumors. For comparison, these rates may be conveniently expressed by what amounts to their reciprocals, the means[1] of the observed times of appearance of tumors. When deaths of tumor-free mice occur after the first tumor has appeared in a group, an improved estimate of the mean may be obtained by actuarial techniques ( ). A useful scale of relative carcinogenic potencies, based upon the relationship of these average times to the concentrations of carcinogen involved, is discussed in a later section.

CLASSIFICATION OF EXPERIMENTAL RESULTS ON THE BASIS OF THE HEALTH OF THE MICE

The success of a program aimed at the development of useful correlations between chemical composition and biological potency will depend largely upon the validity of the experimental data. Hence, it is essential to distinguish between the expected variation due to differences in the susceptibility of individual mice and occasional aberrant results due to other variables of unpredictable effect. Limits of confidence obtained by statistical methods (e.g., 5) usually provide an adequate measure of the possible error in a given determination. However, the toxicity of a complex oil, which is not directly related to its carcinogenic potency, and the occurrence of incidental disease among the animals may introduce important variables which cannot be given proper weight in the calculations.

A parallel examination of accumulated data on the growth and survival of the mice and the rate of induction of tumors in a large number of experiments on oils of widely varying composition and toxicity has proved most educational in this respect. The experience gained from this study has provided certain biological criteria for classifying a given test involving C3H mice as satisfactory (B) or unsatisfactory (X) for quantitative interpretation. Experiments have been placed in the X category if conditions resulted in excessive mortality or significant inhibition of growth during the critical period, the interval of about 15 weeks preceding the mean time of appearance of tumors. In tests on oils of moderately high potency, such conditions have frequently been accompanied by an increase in the mean of as much as eight weeks, equivalent to a reduction in relative potency of 40 to 50 percent (see discussion of potency scale below). An even more serious error may enter the interpretation of the results of Class X

1 Since recording of the times of appearance of tumors has been on an intermittent (Weekly) rather than a continuous basis, the calculated means have been arbitrarily reduced by one-half week.

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experiments on materials of relatively low carcinogenic activity ($P_{MC} \leq 0.1$). The tendency in such cases is toward high non-tumor mortality, sometimes to the degree that the improper assumption could easily be made that the material involved is of negligible potency to mice.

These considerations have led to the general use in our program of data sheets on the individual tests, which permit a direct visual comparison of the growth and survival of the mice and the distribution in time of the induced tumors[2], (as shown in Figures 1 and 2). The oil involved in these examples was a high boiling residuum from a catalytic cracking unit, from which benzo a pyrene has been isolated (19). The carcinogenic properties of similar materials have been the subject of a number of recent papers (see for example,).

In the two examples, the same frequency of mortality among mice which had not developed skin tumors was experienced. However, the growth of the surviving animals in Experiment 8A approximated that of normal controls, whereas in 8B recovery from an apparent infection in the 12th to 14th weeks of the test was shortlived and there was a general decline after the 20th week. The accompanying increase in the mean time of appearance of tumors has been typical of tests in which this pattern of growth is observed. As in this instance, the standard deviation was unusually large in the majority of such experiments, although the reverse was the case in a few. The latter result might have been expected in Experiment 8B had the onset of the infection occurred two to three weeks earlier.

From the experimental data of Shimkin and Andervont, it is evident that a similar increase in the mean latent period to sarcoma after single subcutaneous injections of carcinogens in C3H mice may occur if infection interferes during critical periods. In a series of experiments on MC, BP, and DBA, reported in 1940 ( ), an intercurrent infection caused seven deaths among mice exposed to the latter carcinogen. The mean latent period after injection of 0.5 mg of DBA was 23.3 weeks. In a test performed a year later ( ) with the same dosage of DBA, no animals died before developing sarcomas and the mean latent period was 16.6 weeks. On the other hand, no discrepancy occurred in parallel experiments on 0.5 mg. doses of MC. Since the means in the latter tests were only 9.5 weeks, it is probable that the infection in the 1940 series occurred after most of the MC mice had developed tumors. Information on the growth curves of the mice injected with BP would be necessary to judge the relative significance of the mean latent periods obtained in the 1940 tests with this carcinogen.

To sum up, the results of tests on small populations may be seriously biased by variables not directly related to carcinogenic potency. Hence, it is important that data be collected on the health as well as on the survival and frequency of tumors among the test animals. Quantitative comparisons of biologically unsatisfactory data are unwarranted and may be quite misleading if not properly qualified.

2 The cumulative frequency plots were based upon general principles outlined by Bliss (4). The normal distribution in time, shown for Experiment 8A, is typical. Logarithmic transformation of the time scale (3) has not been required.

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Appendix C

INTERIM REPORT TO THE API MEDICAL ADVISORY COMMITTEE

RESEARCH PROJECT MC-1

April 5, 1955

The importance of long-chain compounds as accelerators of the action of polycyclic carcinogens on the skin of mice has been emphasized in previous reports. Recent work on coal tars has provided further data that point to the importance of these compounds in the development of the occupational cancers of the skin which have resulted from exposure to slack wax and certain spindle oils (Mule spinners' cancer). The following comparisons of experimental data with human experience may be significant.

			Mice	Human Experience
Material	Relative Carcinogen Content	Maximum Probable Percentage of Long-chain Accelerators	Average Latent Period* (weeks)	Average Exposure Period (years)
Paraffin Distillate (Slack Wax)	Low	60	20-35	20 or more
Spindle Oil	Low	40	60	40 (Henry)
Coal Tar	High	Negligable	12-27	23 (Henry)
Pitch	Very High	Negligable	-	
Heavy Catalytic Cycle Oil	Low to Medium	75	10-25	no data
Catalytically Cracked Residua	Medium to high	10-60	6-20	no data

* Three applications per week.

Chemical and biological experiments on coal tars and fractions thereof have indicated that long-chain accelerators are absent. Although these materials regularly contain higher concentrations of polycyclic carcinogens than do catalytically cracked oils, they are frequently less potent when applied upon the skin of mice. It is also notable that Henry's investigation of the occurrence of cancer of the skin among workmen who handled coal tar or pitch in British industries indicated that the latent period of tumor formation was about the same as that observed among wax pressmen in two petroleum refineries in the United States. Since it may be estimated conservatively that coal tar contains at least ten times as much carcinogen as paraffin distillates, the role of the long-chain accelerators in the latter appears to be a highly important factor in their induction of tumors.

Experimental data indicate that there is a considerable variation from one straight run distillate to another in the accelerating activity of the fraction which distills over between 480 and 660°F. Fortunately, useful quantitative

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correlations between the physical properties of these fractions and this activity are being found. These variations may help to explain partially, at least, the differences in the incidence of scrotal cancer among wax pressmen in different refineries.

Further experimental work aimed at learning more about the role which may be played by personal hygiene in bringing about these apparent differences, has been carried out. It was found that the average period of exposure to the wax distillate, API-56, required to induce tumors in control C3H mice (32 weeks) was about doubled (63 weeks), when the skin of the animals was washed with detergent solution 7 hours after each application.

In 1951, similar observations on the effect of washing suggested that the use of medium distillates to rinse off most of the carcinogenic oil, before using the detergent, actually decreased the latent period of cancer induction, as compared with that associated with washing with detergent solution alone. The influence of accelerators, as demonstrated subsequently, furnished a possible explanation of this surprising result. It seemed questionable, therefore, that any petroleum distillate should be used for this purpose. The results of tests which were started last fall to answer this question are summarized in the attached Table.

Two conclusions from these data seem warranted. The use of distillates in the 500-700° range as rinses tends to accelerate the experimental induction of epithelial cancers. Kerosene or oils containing less than 10 percent of hydrocarbons which boil below 700°F. do not seem to exert this effect to a demonstrable degree, but they do not contribute to the capacity, possessed by the detergent alone, of diminishing the rate of cancer induction. Waterless cleansers should be examined by similar means for their content of accelerators in the 500-700° range.

API EXPERIMENT NUMBER	DESCRIPTION OF EXPERIMENT	DOSAGE PER APPLICATION[1] (mg.)	MAXIMUM INCIDENCE OF TUMORS (T.I./weeks)	AVERAGE LATENT PERIOD OF TUMOR INDUCTION (weeks)	RELATIVE CARCINOGENIC POTENCY, P_{MC}
8	F.C.C. Cracked Residuum (No washing)	100	89/7	5.4	> 0.6
8	F.C.C. Cracked Residuum (No washing)	15	100/18	12.5	0.25
321	API-8, after 1 hour, 45 min. washed with detergent solution	100	100/21	16.4	0.17
319	API-8, after 1 hour, 25 min. rinsed with refined kerosene, washed with detergent solution	100	89/18	16	0.17
320	API-8, after 1 hour, 35 min. rinsed with API-80, technical white oil (95 SSU at 100°F) washed with detergent solution	100	100/16	11	0.30
318	API-8, after 1 hour, 15 min. rinsed with medicinal white oil (340 SSU at 100°F.) washed with detergent solution	100	95/21	17	0.16

1 Three applications per week on the skin of C3H mice.

EXHIBIT B

REPORT OF SUBCOMMITTEE ON ATMOSPHERIC POLLUTANTS
E. P. Luongo, M. D., Chairman

The last report of this committee pointed out the deficiency of scientific knowledge on the health effects of community atmospheric pollution. There has been very little change in this situation except for a remarkable increase in public interest and in the interest of Public Health agencies.

I. Summary of Present Status of Knowledge of the Effects on Health by Air Pollutants. According to the current thinking on atmospheric pollution, the possible effects of air pollution on man may be grouped under four categories.

A. Mortality There have been four occurrences of reported increased mortality in certain localities due to the acute effects of community air pollution - Donora, London, Poza Rica , Meuse Valley. In London and Donora a careful clinical and pathological investigation has failed to establish any specific cause of death in man or animal due to any specific agent or the smog as a whole.

Per se: To date there are no other reported authentic cases either acute or chronic due to community air pollution.

B. Morbidity To date there are no reported authenticated cases of disease caused by contact with community air pollution. However, it is possible that there are as yet undetermined accumulative adverse effects on health.

C. Irritative Effects There are definite acute irritative effects in certain localities. Acute irritation of the mucous membrane of the eye and upper respiratory tract do occur during certain periods of community air pollution. These effects disappear when the individual is removed from exposure without known residual effects.

D. Psychologic Effects Because of reduced visibility, and certain anxiety associated with odor and other manifestations, there are psychologic effects. A polluted atmosphere may make people unhappy for a variety of reasons.

II. Investigations as to effects of Community Air Pollution on health.

A. Investigations now in progress.

1. Stanford Research - Irritation effects of smog on the eyes (completed or near completion).

2. Kettering Laboratory, University of Cincinnati - Effects of Air Pollutants on persons chronically ill with cardiac and respiratory diseases.

3. U. S. Public Health Services and related public health agencies. Epidemiological studies in a number of areas, the latest reported by State Department of Public Health, California (March 1955).

4. University of Southern California (Research grant from U. S. Public Health Service) - Under direction of Dr. P. V. Kotin. Carcinogenic studies on animals relating to community atmospheric pollution.

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B. Future or projected investigations:

1. The Surgeon General (U. S. Public Health Service) has recently stated that a considerable sum of money would be made available for support of research on health effects of community air pollution. This will be in the form of grants-in-aid and contract research with universities and research centers in the U. S. and also by the U. S. Public Health itself.

III. Areas of Deficiency in Knowledge of the Problem.

A. Does prolonged exposure to community air pollution cause an increase in morbidity and mortality in human beings?

B. What is the mechanism of irritative effects of community air pollutants?

C. By what mechanism do air pollutants cause psychologic effects?

D. It has been assumed that 3, 4, benzpyrene is a constituent of smog and it is a suspected carcinogenic agent in man. How much of the 3, 4, benzpyrene that is in the smog is the petroleum industry responsible for?

E. Are there any substances in community air pollution that will cause pulmonary malignancy in man?
To what extent does the petroleum industry contribute either indirectly or directly in producing these substances.

IV. Summary

If the Committee on Smoke and Fumes deems it desirable to actively investigate any of the problems mentioned above, the Medical Advisory Committee, through this sub committee, is available for consultation. We feel that preventive engineering now in effect in the petroleum and automotive industry may solve any or all problems before there is time to do any medical investigation.

April 25, 1955

EXHIBIT C

INTERIM REPORT TO THE API MEDICAL ADVISORY COMMITTEE

DERMATITIS SURVEY

April 22, 1955

Mr. M. D. Gjerde and I visited the Industrial Hygiene Foundation on April 14th, where we met with Dr. Walmer and his associates. After exploratory discussions, it was agreed that they would give the problem thought and provide us with a proposed plan for action in the very near future.

Several points of particular interest developed during the talks:

1. State records are probably of no value. Such records as are available would be confined to compensable cases and hence represent only a small portion of the total cases.

2. Insurance company (several are members of the Institute) records would be reliable and provide diversification of industry, geographic location, and both technical and medical information of high caliber.

3. Entree to smaller operators of many sorts could be secured through contacts in larger industries represented among the membership of the Institute.

4. Observations should be confined to the shortest and most recent interval of time compatible with a sound and reliable result.

5. A small group (3 or 4) of A.P.I. representatives should be appointed as liaison group to work with the investigators if the job is done by the Institute.

6. Unless the study is published by the investigators in a reputable scientific journal, none of the acquired data or information may be used by the A.P.I. or its members for advertising or propaganda purposes.

Under the circumstances, we doubted the wisdom of seeking consultation with others until the Industrial Hygiene Foundation has submitted its suggestions.

LWade:oh

/s/ Leo J. Wade

EXHIBIT D

REPORT OF THE SUBCOMMITTEE ON ECONOMIC POISONS
C. H. Hine, M. D., Chairman

1. Liaison has been established with the Medical Committee of the National Agricultural Chemical Association thru Dr. Curtis who recently has been appointed to membership in this organization.

2. Attention of the Medical Advisory Committee members has been called to the publication on the allowable limit of pesticides set forth by the Federal Food and Drug Administration.

3. Attention of the Medical Advisory Committee members is directed to the increased activity in dissemination of professional information concerning the diagnosis and treatment of acute poisoning by the following organizations.

   A. American Academy of Pediatrics

      This group is helping establish poison centers locally. Such centers are now active in New York City, Boston, Chicago, San Francisco, Seattle and Durham, North Carolina

   B. U. S. Public Health, Technical Service Branch, Savanah, Ga.

   C. California Spray Company.

   D. Local health departments recommend the subcommittee continue its role of disseminating information on economic poisons of interest to the Medical Advisory Committee. No funds are required for this purpose.

April 25, 1955

EXHIBIT E

REPORT OF SUBCOMMITTEE ON PHYSICAL AGENTS
J. W. Osborn, M. D. Chairman

The subcommittee on Physical Agents met at Buffalo, N. Y., on April 25, 1955 with Chairman J. W. Osborn, M. D., presiding. Present were Messrs. Osborne, Potts, Reeve, Hendricks and Halley.

This being the first meeting of this new subcommittee, discussion revolved around the functions and scope of the committee. The committee agreed that two physical agents most worthy of consideration at this time were noise and radiations.

On the subject of noise the following action was taken:

1. The committee wishes to go on record as recognizing that that noise problems do exist in the petroleum industry, that some such noise exposures in the industry will produce loss of hearing in exposed employees while other exposures are borderline, and to recommend that the MAC approve the subcommittee's beginning a study of the noise problem in the petroleum industry.

2. Mr. Hendricks will contact the Industrial Hygiene Foundation to determine whether they will make available to the subcommittee copies of their recent compilation of state laws pertaining to hearing loss. If such can be obtained, they will be distributed to MAC members.

3. The committee wishes to call to the attention of members of the MAC a Noise Reduction Program or course of instruction being given at the Massachusetts Institute of Technology, August 15-26 of this year.

   Further, the committee feels that if any member companies send representatives to this meeting that a report from such persons to the Subcommittee on Physical Agents would be invaluable to the work of the subcommittee. Consequently, the subcommittee wishes to advise the members of the MAC at this time that they will later be contacted by letter inquiring as to whether their companies are sending any representatives to this meeting and if so, whether such persons could report in writing and in person to the subcommittee, the proceedings of that meeting.

On the subject of radiation, the committee wishes to go on record as recognizing that potential radiation hazards do exist in the petroleum industry and that such radiations include those from radioactive materials and gases from same, x-rays and ultra-violet radiations from such sources as shielded arc welding.

The subcommittee takes cognizance of the need for medical departments of the individual companies to be familiar with the hazards and uses of x-ray and nuclear radiations peculiar to their company. The subcommittee suggests the establishment within the individual companies of a Radioactivity Committee or similar group, with medical representation, as a means of keeping abreast of

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the problem.

The Subcommittee on Physical Agents will welcome suggestions as to the need for activity or study pertaining to other physical agents such as heat, cold, vibration and ultrasonics but has no specific recommendations to make along these lines at this time.

April 25, 1955

EXHIBIT "F" - ITEM 1

Exhibit F

REPORT OF MEDICAL AND HEALTH COMMITTEE

M. J. Rathbone, Chairman

As authorized by the Board of Directors on November 9, 1954 a representative special committee made a study and has reported recommendations on the organization of an Institute committee to handle problems incidental to precautionary labeling of petroleum products.

The committee has reported six findings as follows:

(1) Recent regulatory developments have created an urgent need for a committee representative of oil company operations to consider problems of national significance incidental to precautionary labeling of petroleum products.

(2) At this time the most urgent problem relates to the labeling of products packaged for sale.

(3) The most important phase of this problem is the development of standards for the design and use of the labels.

(4) Such standards will depend upon specific knowledge of the physiological and other properties of petroleum products included in the package.

(5) The adoption and use of the standards will be accomplished only by close cooperation between regulated and regulatory agencies.

(6) Compliance with labeling regulations primarily is a function and responsibility of oil company sales and marketing departments.

Based upon these six findings the committee made eight recommendations as follows:

(1) The American Petroleum Institute should have a committee representative of the industry's responsibilities in precautionary labeling of petroleum products packaged for sale.

(2) The committee should comprise members representative of those responsible in the industry for:

(a) Manufacturing
(b) Marketing
(c) Medical
(d) Research and development
(e) Transportation

Exhibit "I" - Item 17 (Cont'd)

(3) The committee should develop necessary information and should formulate API recommended standards on the design and use of precautionary labels for petroleum products.

(4) As may be necessary, the committee should recommend research and experimental work to develop physiological and other properties of petroleum relating to labeling.

(5) The committee should establish and maintain cooperative relationship with other national agencies concerned with precautionary labeling of products packaged for sale.

(6) The committee should work with the American Petroleum Industries Committee in its guidance of state petroleum industries committees on state laws and state regulations in this field.

(7) The committee chairman should have the benefit of legal guidance in the conduct of meetings.

(8) Information developed by or through the committee should be disseminated widely to interested members of the Institute.

I concur in these recommendations and request authority for the Chairman of the Medical and Health Committee to organize the labeling committee as recommended and to supervise its activities from time to time as outlined in this report.