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Encl

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 121, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

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January 7, 1957

Dr. L. A. Gossman
Surgical Advisor
The Acton Casualty and
Surety Company
Hartford 15, Connecticut

Dear Dr. Gossman:

Your letter of December 22, 1956 to the American Petroleum Institute was forwarded to me by Mr. Streep, with a copy of his letter to you of December 27. The published information which I have on the carcinogenic properties of cutting oils are contained in the references listed below:

1. Grisham, C.H.B. and J. R. Squires: Skin Cancer in the Engineering Industry from the Use of Mineral Oil. *BRIT. J. INDUSTRIAL MED.* 1:1-11 (1950).
2. Grisham, C.H.B. and A. Gourevitch: Skin Cancer of the Hand and Forearm. *BRIT. J. INDUSTRIAL MED.* 2:74-79 (1952).
3. Mastromatteo, E.: Cutting Oils and Squamous-Cell Carcinoma. Part I: Incidence in a Plant with a Report of Six Cases. *BRIT. J. INDUSTRIAL MED.* 12:240-243 (1955).
4. Gilman, J.F.W. and E. B. Vassilovitch: Cutting Oils and Squamous-Cell Carcinoma. Part II: An Experimental Study of the Carcinogenicity of Two Types of Cutting Oils. *BRIT. J. INDUSTRIAL MED.* 12:244-248 (1955).
5. Henny, S. A.: Cancer of the Scrotum in Relation to Occupation. 112 p. N. Y., Oxford University Press, (1946).
6. Harper, W. G.: Occupational Tumors and Allied Diseases. 396 p. Baltimore, Md., Charles C. Thomas, (1942).

Cushman, January 7, 1957, - 2 -

appear to me, from reviewing this literature, that certain cutting oils
carcinogenic, and it is certainly my impression that cancer of the scrotum
occupational in origin until definitely proven not to be occupational in origin.
My personal belief that cancer of the scrotum, or any other area of the skin,
from cutting oils or other mineral oils, should be easily prevented by the institution
of personal hygiene measures in the industry. This would include such
as the wearing of clean work clothes, the taking of showers and attempting to
keep the oil from getting on the individual, except if it is absolutely unavoidable.

If is anything further we can do to help you with this problem, do not hesitate
to ask us again.

Very yours,

WAST, M. D.

J. V. Stroop ✓

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. BOX 121, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

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CHIEF CLINICAL RESEARCH PHYSICIAN

January 11, 1957

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 17, New York

Dear Mr. Stroop:

I would greatly appreciate it if you would have the attached duplicated and distributed to the members of the Subcommittee on Carcinogenicity and to Dr. A. W. Horton of the Kettering Laboratories.

It is my understanding that the British are somewhat put out that they have not received anything from us in the past several years. I suggest that the subcommittee give serious thought as to what they are going to send the British so that we can discuss it at the next meeting of our subcommittee.

In addition, Dr. Newquist has suggested that perhaps Dr. Horton ought to summarize this, and all past reports received from the British. This occurs to me to be a good idea. In the event that Dr. Horton does not have some of the previous information received from England, if he would let me know I would be happy to see that he is brought up to date on anything that he may be lacking.

Very truly yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:cjh

Attach. - Six reports of the Committee on the Carcinogenic Action of Mineral Oils, Medical Research Council, London, attached to ltr to REE from Dr. Newquist, 1/2/57.

Copy From D. V. Stroop For Information Of And Consideration
By Members Of The Subcommittee On Carcinogenicity And Dr. A.
W. Horton

1/14/57

MEDICAL RESEARCH COUNCIL



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MRC.56/963
CAMO. Ag.21

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

AGENDA

for the Twenty first meeting to be held
at 38 Old Queen Street, Westminster, S.W.1,
on Tuesday, 18th December, 1956 at 2.30 p.m.

FWC
ARJ
JOY
FHP
JHF

LCM
MKS

JAN 3

1. Minutes of the previous meeting (MRC.56/727, CAMO.Min.20 - already circulated)

2. Progress Reports:-

- (a) No.XVII, November 1956 (Birmingham), by Dr. D.L. Woodhouse, (MRC.56/946, CAMO.56/9 - Enclosure A).
- (b) The 1955-56 Experiments with Mice at Leeds, by Dr. J.O. Irwin, (MRC.56/965, CAMO.56/12 - Enclosure B).
- (c) Report by Dr. W. Carruthers, Dr. J.W. Cook and Mr. A.G. Douglas, (MRC.56/958, CAMO.56/11 - Enclosure C).

3. Preparation of Kuwait fractions for 1957 to 1958 tests.

As picrate treatment on a large scale has proved impracticable Professor Morton will suggest preparation of fractions by chromatography on alumina from KX₅₋₆.

A Note by Professor Morton is enclosed (MRC.56/956, CAMO.56/10 - Enclosure D).

4. Proposal for including a single specimen of cutting oil, reported to be non-carcinogenic in the Birmingham tests.

Manchester Oil Refineries have prepared an oil which, according to the Twort Formula is non-carcinogenic, for Messrs. Ferranti, a big user of cutting oils. This oil satisfies all the requirements from the technical point of view, and it is now suggested that it might be tested in the laboratory to see if it is in fact relatively non-carcinogenic as far as animals are concerned. If it were so, then it could be, and perhaps should be, recommended for wider use as a cutting oil.

5. Any other business.

6. Date of next meeting.

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MRC. 56/94
CAMO. 56/9



COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Progress Report No. XVII, November, 1956 (Birmingham)

by

D.L. Woodhouse

The fractions listed in Table I were commenced on 28th February and have been applied for 37 weeks at the time of the report, when the tumours indicated were observed. Fuller details will be submitted at the end of the 52 week period, the present report being intended as a preliminary guide for future work.

Table I

<u>Fraction</u>	<u>Rabbit Tests</u>	<u>Tumours</u>
A. K ₄ S ₆ -8 Ari V	(53 ml.)	1
B. K ₄ S ₆ -8 Ari W	(53 ml.)	0
C. K ₄ S ₆ -8 Ari X	(53 ml.)	0
D. K ₄ S ₆ -8 Ari Y	(53 ml.)	0
E. K ₄ S ₆ -8 Ari Z (residue)	(53 ml.)	1
F. K ₄ S ₆ -8 Arii X	(15 ml.)	0
G. K ₄ S ₆ -8 Arii Y	(15 ml.)	0
H. K ₄ S ₆ -8 Arii Z (residue)	(15 ml.)	0
I. K ₄ S ₆ -8 Ariii X	(11 ml.)	0
J. K ₄ S ₆ -8 Ariii Y	(11 ml.)	0
K. K ₄ S ₆ -8 Ariii Z (residue)	(11 ml.)	0
L. K ₄ S ₆ -8 Ari (original pet. ether eluate)	(132 ml.)	0
M. K ₄ S ₆ -8 Arii (original benzene eluate)	(23 ml.)	0
N. K ₄ S ₆ -8 Ariii (original methanol eluate)	(17 ml.)	0
O. KX ₂ -4 (B.range 355-370 C)	(300 ml.)	3
P. KX ₅ -6 (B.range 370-380 C)	(300 ml.)	5
Q. KX ₇ -8 (B.range 380-390 C)	(300 ml.)	3
R. KX-Residue (Boiling above 390 C)	(300 ml.)	8
S. K ₄ S ₈ (original Stedman cut as standard)	(300 ml.)	0
T. D(2) Standard as agreed		0
U. D(1/2) Standard as agreed		0

See CAMO. 56/7 page 1.

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MRC.56/965
CAMO.56/12

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

The 1955-56 Experiments with Mico at Leeds

by

J. O. Irwin

The results for the Standards are given in Table 1, and for the Fractions in Table 2.

The Standards

The responses to D₁ were in good agreement with those obtained in previous years. In Table 1 these responses are compared with the results of the three experiments carried out at Birmingham in 1952-3, 1953-4 and 1954-5 and that carried out at Leeds in 1954-5.

The response to D₂ however seems to have been anomalous. The total number of tumours was 32 against an average of 38 in the Birmingham experience, but tumours occurred a great deal later, as shown by the expectation of tumourless life and date when 10% of survivors had tumours.

The Fractions

The Fractions tested were the eight Lagunillas L₄S₁A - L₄S₈A and the residue L₄Sp. In Table 2 these are compared with the corresponding Kuwait fractions tested at Birmingham in 1953-4.

With one exception to L fractions all gave a higher response than the corresponding K fractions. The difference was statistically significant for L₄S₅A, L₄S₆A, L₄S₇A, L₄S₈A, also these four fractions gave a higher response than the other L fractions. The residue L₄Sp gave a positive response while K₄Sp did not.

In view of the anomalous response to the standard these results should be interpreted with some caution. However, D₁ at Leeds in 1955-6 gave a lower response than D₂ at Birmingham in 1953-4 and D₂ at Leeds gave a much lower response than D₂ at Birmingham in the same year. This suggests that the Lagunillas really were more potent than the corresponding Kuwait fractions, for if they were compared relative to the standards tested at the same time, their relative difference would be enhanced.

Table 1. Results from Standards in Mice Experiments
(Leeds 1955-6)

<u>Fractions</u>	<u>Expectation of</u> <u>Tumourless Life</u> <u>(Limited to</u> <u>52 weeks)</u>	<u>Date when 10%</u> <u>of Survivors</u> <u>had Tumours</u>	<u>Total</u> <u>number of</u> <u>Tumours</u>
<u>Leeds Results (1955-6)</u>			
D ₂	32.5 ± 1.0	26.1 ± 0.4	32
D _{1/2}	23.3 ± 0.9	17.3 ± 0.6	42
<u>Leeds Results (1954-5)</u>			
D ₂	16.1 ± 1.8	10.1 ± 0.5	41
D _{1/2}	18.8 ± 0.9	12.2 ± 0.2	44
<u>Birmingham Results</u>			
D ₂ 1952-3	13.9 ± 0.4	11.4 ± 0.8	38
3-4	12.9 ± 0.6	8.7 ± 0.4	40
4-5	14.4 ± 2.0	6.6 ± 0.2	36
Mean	13.7 ± 1.2	8.9 ± 0.5	38
D _{1/2} 1952-3	24.9 ± 1.6	17.1 ± 0.6	25
3-4	18.1 ± 0.8	10.3 ± 0.6	45
4-5	17.9 ± 0.8	11.7 ± 0.3	43
Mean	20.3 ± 1.1	13.0 ± 0.5	38

Table 2. Results from fractions in Mice Experiments
Leeds (1955-6) Laquinillas and Birmingham (1953-4) Kuwait.

<u>Fractions</u>	<u>Expectation of</u> <u>Tumourless Life</u> <u>(Limited to</u> <u>52 weeks)</u>	<u>Date when 10%</u> <u>of Survivors</u> <u>had Tumours</u>	<u>Total</u> <u>number of</u> <u>Tumours</u>
L ₄ S ₁ A	48.0 ± 2.0	29.4 ± 2.9	4
K ₄ S ₁ A	50.1 ± 0.6	not reached	2
L ₄ S ₂ A	49.5 ± 1.2	32.7 ± 3.8	4
K ₄ S ₂ A	52	not reached	0
L ₄ S ₃ A	52	not reached	0
K ₄ S ₃ A	51.2 ± 0.6	not reached	3
L ₄ S ₄ A	48.2 ± 2.1	not reached	3
K ₄ S ₄ A	49.6 ± 1.3	not reached	4
L ₄ S ₅ A	42.2 ± 3.9	27.7 ± 0.6	4
K ₄ S ₅ A	51.2 ± 0.6	not reached	2
L ₄ S ₆ A	43.2 ± 3.0	19.7 ± 3.5	7
K ₄ S ₆ A	50.7 ± 1.0	46.3 ± 4.0	2
L ₄ S ₇ A	39.7 ± 4.1	17.6 ± 0.6	6
K ₄ S ₇ A	50.4 ± 1.0	43.9 ± 0.6	3
L ₄ S ₈ A	36.8 ± 4.0	17.7 ± 0.4	8
K ₄ S ₈ A	47.3 ± 1.6	28.6 ± 2.3	8
L ₄ SR	46.5 ± 1.7	24.3 ± 2.3	3
K ₄ SR	52	not reached	0

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MRC.56/958
CAMO.56/11

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

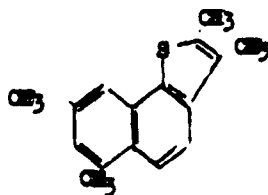
Report by Dr. W. Carruthers, Dr. J.W. Cook
and Mr. A.C. Douglas.

We are continuing with our investigation of fractions produced from the Kuwait Oil.

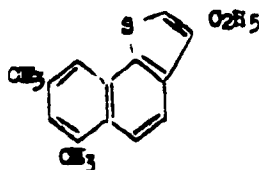
The distillates obtained by fractional distillation of the petroleum-ether aluates of picrate forming fractions have yielded a number of crystalline substances by crystallisation of molecular complexes and chromatography. Difficulty has arisen in purifying these substances, because of the small amounts available, but the ultra-violet absorption spectra of the crude materials shows that they belong to the class of phenanthrenes or of dibenzothiophenes. Two compounds have been obtained homogeneous; one is a tri- or tetra-methyldibenzothiophene, and the other is a tetra-methylphenanthrene.

One of the methanol aluates ($K_1S_7b_{4piv}$) obtained from the Kuwait fraction b.p. $382-385^\circ$ as outlined in the last Report, has yielded a crystalline compound, m.p. $179-181^\circ$. The ultra-violet absorption spectrum and elementary analysis of this substance indicate that it is a penta- or hexa-methylcarbazole, or the equivalent.

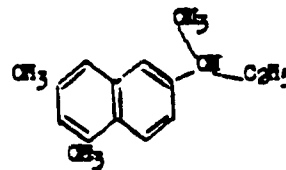
The compound $C_{16}H_{16}S$ isolated before from fraction $K_1S_6b_{4p}$ (see CAMO.54/4) has now been identified as 3-ethyl-6:8-dimethyl-naphtho (1:2-b) thiophene (II) (Ring-index nomenclature).



(I)



(II)



(III)

As outlined in previous Reports, the basic 6:7-benzothio-naphthen ring structure of the compound was shown by its ultra-violet absorption spectrum, and desulphurisation with Raney nickel afforded a naphthalene hydrocarbon $C_{16}H_{20}$. This has now been identified by synthesis as 1:3-dimethyl-6-secbutylnaphthalene (III). Two possible structures (I and II) thus remained for the parent sulphur compound. A decision was made in favour of II on the basis of the C-methyl analysis which showed the presence of only 3 C-methyl groups, as expected for (II). Compound I would have shown 4 such groups.

6th December 1956

API 06283

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MRC. 56/5/4
CAMO. 56/10

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Suggested Programme of Biological Tests at Birmingham

1957-58

Note by Prof. F. Morton

The following programme of tests for Dr. Woodhouse was discussed at Birmingham on 14 November by Professor Squire, Dr. Woodhouse, Dr. King and Professor Morton (Dr. Carruthers was unable to attend).

The reason for the modification in the original scheme, which was to prepare samples by the methods of separation developed by Dr. Carruthers, is our inability to handle large quantities of picric acid. Various industrial concerns have been approached but are not prepared to undertake this work.

We propose therefore to undertake the separation by liquid phase chromatography using alumina, following the publication by Mair et al (A.C.S. Pet.Div. Sept. 1956) which shows the same separation into polynuclear, di-nuclear and mono-nuclear aromatics is possible. The use of such technique on a large scale cannot be undertaken in our present laboratory (for safety reasons) and we therefore suggest a preliminary separation of the KX_{5-6} fractions (based on the interim report of Dr. Woodhouse) to provide samples for the 1957-58 series at Birmingham and some material for preliminary work by Dr. Carruthers.

The proposal involves firstly the acetone-water extraction of KX_{5-6} , to produce a more highly aromatic extract and a raffinate ($KX_{5-6} P$). The extract $KX_{5-6} A$ will then be chromatographed on alumina and the separation followed by refractive index measurements on the elutriates. By this means we expect to obtain some indication during the preparation of the Petroleum Ether, Benzene and Methanol elutriates of differences in the hydrocarbons used in each elutriate. Further separation of the Petroleum Ether and Benzene elutriates will be carried out if the refractive index measurements indicate that some further separation is possible. The Methanol elutriate will be studied only if biological results of the 1956 series indicate some activity. To check on possible loss of active components during chromatography the elutriates will be rebled in aliquot proportions and the blend included in the test samples.

In addition it is proposed to include:

1. The usual standards (D_2 and D_4).
2. KX_9 , a sample prepared by distilling the KX residues in a manner similar to the preparation of K_4S_9 .
3. At Professor Squire's request a cutting oil which has been offered as being non-potent.

The list of samples will not be completed until the examination of the elutriates has been discussed with Dr. Carruthers and Professor Squires, i.e. samples 12 - 21 may be prepared by further separation of $KX_{5-6} A_1$ and $KX_{5-6} A_{11}$, or alternatively Dr. Carruthers may wish to include some individual hydrocarbons in this series.

<u>Sample No.</u>	<u>Description</u>
1	D2 Standard
2	D ₁ "
3	Cutting oil
4	KX ₉
5	KX ₅₋₆ (To repeat 1956 test)
6	KX ₅₋₆ A (Acetone extract)
7	KX ₅₋₆ P (Raffinate)
8	KX ₅₋₆ Ai (Petroleum Ether elutrate)
9	KX ₅₋₆ Aii (Benzene elutrate)
10	KX ₅₋₆ Aiii (Methanol elutrate)
11	Mix of KX ₅₋₆ Ai, ii and iii

Nos. 12 - 21 To be decided after examination of analysis of elutrates.

Standard strength of all KX₅₋₆ samples to be equal to KX₅₋₆ A.

Thus, the KX₅₋₆ Ai etc. will be diluted with liquid paraffin to the same volume as the KX₅₋₆ A from which they are prepared.

MEDICAL RESEARCH COUNCIL

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COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

meeting to be held at 2.30 p.m. on Tuesday
the 18th December 1956, at 38 Old Queen Street, S.W. 1.

FWC
ARJ
JDY
FHP
JHF

The attached report (MRC.56/969, C.A.O. 56/13), is for
discussion under item 2(b) of the Agenda.

LCM
WKS

173

15th December 1956.

R.C. MORRIS.

for review DVS for
information of & consideration
by members of S.C. on
Carcinogenicity & Dr.
A.W. Horton - Jan 14 1957

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MRC.56/969
CAMO.56/13

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Statistical Analysis of 1955-6 Experiments with Rabbits at Leeds

by J. O. Irwin

An experiment with 11 fractions was carried out. The fractions were L_4S_{1A} - L_4S_{8A} the residue L_4SP together with the two standards D_2 and $D_{1\frac{1}{2}}$.

The design of the experiment was the 11 x 5 Youden square shown in Table 1. There are 11 groups of 5 rabbits. In each group each rabbit was painted with the same 5 fractions one on each of the sites I, II, III, IV, VII. Each of the 11 sub-fractions was painted on each site in one and only one group. Each fraction was used in exactly five groups and every pair of fractions in just two groups.

The percentage of each group of animals which got tumours on each site was calculated. In this experiment there was an unusual number of tumourless deaths before the end of the year - 17 out of 55. Accordingly an allowance was made for them. The number of animal years of exposure was calculated for each group. For example in the sixth group there was one tumourless death 11 weeks from the beginning of the experiment. The number of animal weeks of exposure was therefore $11 + (4 \times 52) = 213$ and $219/52 = 4.2$. This was rounded off to the nearest unit i.e. 4 and the three tumours on site I were considered to have occurred in 4 animals exposed for a full year. The percentage was therefore taken to be 75% not 60%.

The method of analysis was to transform percentages to degrees by means of the angular transformation and then perform an analysis of variance of the results.

Table 2 shows the mean value of the transformed variables and the probabilities of getting a tumour, estimated for each fraction and standard. The corresponding values of the K series tested at Birmingham in 1953-4 are shown for comparison.

The Standards

The results for the standards are compared below with those of two previous years.

	<u>Leeds 1955-6</u>	<u>Leeds 1954-5</u>	<u>Birmingham 1953-4</u>
D_2	.627 (51.18)	.644 (52.27)	.643 (52.19)
$D_{1\frac{1}{2}}$	.521 (46.02)	.245 (31.84)	.156 (26.63)

The figure shown is the estimated probability of getting a tumour. (The transformed variable is shown in brackets. The standard errors are 4.2, 4.7, 5.0 respectively for 1955-6, 1954-5, 1953-4 respectively.) The result for $D_{1\frac{1}{2}}$ seems unusually high. For D_2 the agreement is good.

The fractions

L₄S₁A shows a rather low carcinogenicity, so does L₄SP, though the value for the latter is higher than for K₄SP; (the difference just about reaches the 5% level of significance). Otherwise there is little difference between the response of the different L fractions. The L fractions give a somewhat higher response than the corresponding K fractions and this result agrees with that obtained for the mice.

Analysis of Variance

The analysis of variance is shown in Table 3. There are significant differences between groups of rabbits, and the site differences are remarkably large. The observed percentage of tumours on the various sites is shown in Table 4. The highest incidence is again on sites I and II (ears) and VII (middle of the back nearest ears).

Table 1

Design for Experiment with Rabbits at Leeds (1955-6)

Rabbits	I	II	III	IV	VII
1 - 5	c	d	a	b	e
6 - 10	f	j	g	a	c
11 - 15	a	f	i	h	b
16 - 20	e	h	j	k	a
21 - 25	b	c	h	g	k
26 - 30	i	b	e	j	g
31 - 35	g	a	k	i	d
36 - 40	h	g	d	e	f
41 - 45	d	k	b	f	j
46 - 50	k	e	f	c	i
51 - 55	j	i	c	d	h

$L_4S_1A = c$

$L_4S_2A = a$

$L_4S_3A = j$

$L_4S_4A = h$

$L_4S_5A = e$

$L_4S_6A = b$

$L_4S_7A = i$

$L_4S_8A = k$

$L_4SP = g$

$D_2 = d$

$D_2^1 = f$

$a = L_4S_2A$

$b = L_4S_6A$

$c = L_4S_1A$

$d = D_2$

$e = L_4S_5A$

$f = D_2^1$

$g = L_4SP$

$h = L_4S_4A$

$i = L_4S_7A$

$j = L_4S_3A$

$k = L_4S_8A$

Table 2

Experiment with Rabbits at Leeds 1955-6Two Standards and eleven derived fractions

Mean Values corrected for Group differences

<u>Leeds 1955-6</u>				<u>Birmingham 1953-4</u>			
<u>Fraction or Standard</u>	<u>Transformed Variable</u>	<u>Probability of Tumour</u>	<u>Total Number of Tumours</u>	<u>Fraction or Standard</u>	<u>Transformed Variable</u>	<u>Probability of Tumour</u>	<u>Total Number of Tumours (out of 25)</u>
L ₄ S ₁ A	34.96	.299	⁸ /22 36%	K ₄ S ₁ A	43.68	.474	10 40%
L ₄ S ₂ A	52.03	.648	¹⁰ /17 59%	K ₄ S ₂ A	25.67	.141	5 20%
L ₄ S ₃ A	51.98	.642	¹⁴ /21 67%	K ₄ S ₃ A	41.88	.438	11 44%
L ₄ S ₄ A	47.16	.546	¹⁰ /18 56%	K ₄ S ₄ A	51.57	.631	14 56%
L ₄ S ₅ A	50.08	.606	¹¹ /19 58%	K ₄ S ₅ A	48.14	.563	14 56%
L ₄ S ₆ A	50.65	.618	¹¹ /18 61%	K ₄ S ₆ A	52.77	.654	16 64%
L ₄ S ₇ A	52.88	.664	¹³ /18 72%	K ₄ S ₇ A	38.35	.366	10 40%
L ₄ S ₈ A	51.58	.636	¹² /18 67%	K ₄ S ₈ A	49.35	.587	13 52%
L ₄ SP	34.52	.288	⁵ /20 25%	K ₄ SP	21.28	.077	2 8%
D ₂	51.18	.627	¹⁴ /20 70%	D ₂	52.19	.643	17 68%
D _{1/2}	46.02	.521	⁹ /19 47%	D _{1/2}	26.63	.156	6 24%
S.E. one mean	4.21				4.97		
Difference between two means	5.95				7.03		

Table 3

Experiment with Rabbits at Leeds 1955-6

Analysis of variance on angular transformation of
proportion of tumours

	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio
Sites	7478.43	4	1869.61	23.23 (P < .001)
Groups of Rabbits	3119.77	10	311.98	3.88 (.01 < P < .001)
Fractions	2565.98	10	256.60	
Error	2414.84	30	80.49	
	15579.02	54		

Table 4

Experiment with Rabbits at Leeds 1955-6

Number and Percentage of Tumours on the five
different sites

Site	Number of Tumours	% Tumours
I	33/42	79%
II	33/42	79%
III	12/42	29%
IV	13/42	31%
VII	26/42	62%

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MRC.56/969
SANC.56/13

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Statistical Analysis of 1955-6 Experiments with Rabbits at Leeds

by J. O. Irwin

An experiment with 11 fractions was carried out. The fractions were L_4S_1A - L_4S_8A the residue L_4SP together with the two standards D_2 and $D_{1/2}$.

The design of the experiment was the 11 x 5 Youden square shown in Table 1. There are 11 groups of 5 rabbits. In each group each rabbit was painted with the same 5 fractions one on each of the sites I, II, III, IV, VII. Each of the 11 sub-fractions was painted on each site in one and only one group. Each fraction was used in exactly five groups and every pair of fractions in just two groups.

The percentage of each group of animals which got tumours on each site was calculated. In this experiment there was an unusual number of tumourless deaths before the end of the year - 17 out of 55. Accordingly an allowance was made for them. The number of animal years of exposure was calculated for each group. For example in the sixth group there was one tumourless death 11 weeks from the beginning of the experiment. The number of animal weeks of exposure was therefore $11 + (4 \times 52) = 219$ and $219/52 = 4.2$. This was rounded off to the nearest unit i.e. 4 and the three tumours on site I were considered to have occurred in 4 animals exposed for a full year. The percentage was therefore taken to be 75% not 60%.

The method of analysis was to transform percentages to degrees by means of the angular transformation and then perform an analysis of variance of the results.

Table 2 shows the mean value of the transformed variables and the probabilities of getting a tumour, estimated for each fraction and standard. The corresponding values of the K series tested at Birmingham in 1953-4 are shown for comparison.

The Standards

The results for the standards are compared below with those of two previous years.

	<u>Leeds 1955-6</u>	<u>Leeds 1954-5</u>	<u>Birmingham 1953-4</u>
D_2	.627 (51.18)	.644 (52.27)	.643 (52.19)
$D_{1/2}$	.521 (46.02)	.245 (31.84)	.156 (26.63)

The figure shown is the estimated probability of getting a tumour. (The transformed variable is shown in brackets. The standard errors are 4.2, 4.7, 5.0 respectively for 1955-6, 1954-5, 1953-4 respectively.) The result for $D_{1/2}$ seems unusually high. For D_2 the agreement is good.

The Fractions

L₄S₁A shows a rather low carcinogenicity, so does L₄SP, though the value for the latter is higher than for K₄SP; (the difference just about reaches the 5% level of significance). Otherwise there is little difference between the response of the different L fractions. The L fractions give a somewhat higher response than the corresponding K fraction and this result agrees with that obtained for the mice.

Analysis of Variance

The analysis of variance is shown in Table 3. There are significant differences between groups of rabbits, and the site differences are remarkably large. The observed percentage of tumours on the various sites is shown in Table 4. The highest incidence is again on sites I and II (ear and VII (middle of the back nearest ears)).

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MRC.56/956
CAMO.56/10

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Suggested Programme of Biological Tests at Birmingham 1957-58

Note by Prof. F. Morton

The following programme of tests for Dr. Woodhouse was discussed at Birmingham on 14 November by Professor Squire, Dr. Woodhouse, Dr. King and Professor Morton (Dr. Carruthers was unable to attend).

The reason for the modification in the original scheme, which was to prepare samples by the methods of separation developed by Dr. Carruthers, is our inability to handle large quantities of picric acid. Various industrial concerns have been approached but are not prepared to undertake this work.

We propose therefore to undertake the separation by liquid phase chromatography using alumina, following the publication by Mair et al (A.C.S. Pet.Div. Sept. 1956) which shows the same separation into polynuclear, di-nuclear and mono-nuclear aromatics is possible. The use of such technique on a large scale cannot be undertaken in our present laboratory (for safety reasons) and we therefore suggest a preliminary separation of the KX_{5-6} fractions (based on the interim report of Dr. Woodhouse) to provide samples for the 1957-58 series at Birmingham and some material for preliminary work by Dr. Carruthers.

The proposal involves firstly the acetone-water extraction of KX_{5-6} , to produce a more highly aromatic extract and a raffinate (KX_{5-6} P). The extract KX_{5-6} A will then be chromatographed on alumina and the separation followed by refractive index measurements on the elutriates. By this means we expect to obtain some indication during the preparation of the Petroleum Ether, Benzene and Methanol elutriates of differences in the hydrocarbons used in each elutriate. Further separation of the Petroleum Ether and Benzene elutriates will be carried out if the refractive index measurements indicate that some further separation is possible. The Methanol elutriate will be studied only if biological results of the 1956 series indicate some activity. To check on possible loss of active components during chromatography the elutriates will be reblended in aliquot proportions and the blend included in the test samples.

In addition it is proposed to include:

1. The usual standards (D_2 and D_1^1).
2. KX_9 , a sample prepared by distilling the KX residues in a manner similar to the preparation of K_4S_9 .
3. At Professor Squire's request a cutting oil which has been offered as being non-potent.

The list of samples will not be completed until the examination of the elutriates has been discussed with Dr. Carruthers and Professor Squires, i.e. samples 12 - 21 may be prepared by further separation of KX_{5-6} Ai and KX_{5-6} Aii, or alternatively Dr. Carruthers may wish to include some individual hydrocarbons in this series.

<u>Sample No.</u>	<u>Description</u>
1	D ₂ Standard
2	D ₂ "
3	Cutting oil
4	KX ₉
5	KX ₅₋₆ (To repeat 1956 tests)
6	KX ₅₋₆ A (Acetone extract)
7	KX ₅₋₆ P (Raffinate)
8	KX ₅₋₆ Ai (Petroleum Ether elutrate)
9	KX ₅₋₆ Aii (Benzene elutrate)
10	KX ₅₋₆ Aiii (Methanol elutrate)
11	Blend of KX ₅₋₆ Ai, ii and iii

Nos. 12 - 21 To be decided after examination of analysis of elutrates.

Standard strength of all KX₅₋₆ samples to be equal to KX₅₋₆ A.

Thus, the KX₅₋₆ Ai etc. will be diluted with liquid paraffin to the same volume as the KX₅₋₆ A from which they are prepared.

7.12.56

- 2 -

API 06300

MEDICAL RESEARCH COUNCIL

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PRIVY COUNCIL

38 OLD QUEEN STREET,
WESTMINSTER,
LONDON, S.W.1

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Meeting to be held at 2.30 p.m. on Tuesday
the 18th December 1956, at 38 Old Queen Street, S.W.1.

The attached report (MRC.56/969,CALD.56/13), is for
discussion under item 2(b) of the Agenda.

13th December 1956.

R.C.NORTON.

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MRC.56/958
CAMO.56/11

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

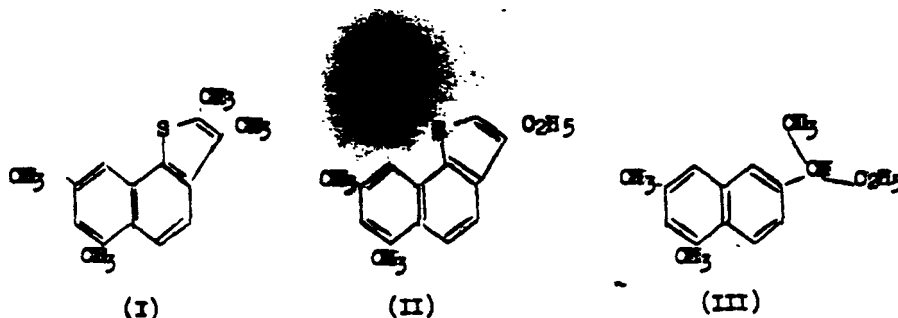
Report by Dr. W. Carruthers, Dr. J.W. Cook
and Mr. A.G. Douglas.

We are continuing with our investigation of fractions produced from the Kuwait Oil.

The distillates obtained by fractional distillation of the petroleum-ether alutes of picrate forming fractions have yielded a number of crystalline substances by crystallisation of molecular complexes and chromatography. Difficulty has arisen in purifying these substances, because of the small amounts available, but the ultra-violet absorption spectra of the crude materials shows that they belong to the class of phenanthrenes or of dibenzothiophenes. Two compounds have been obtained homogeneous; one is a tri- or tetra-methyldibenzothiophene, and the other is a tetra-methylphenanthrene.

One of the methanol alutes ($K_4S_7H_{41}Piv$) obtained from the Kuwait fraction b.p. $382^{\circ}-385^{\circ}$ as outlined in the last Report, has yielded a crystalline compound, m.p. $179-180^{\circ}$. The ultra-violet absorption spectrum and elementary analysis of this substance indicate that it is a penta- or hexa-methylcarbasole, or the equivalent.

The compound $C_{16}H_{16}S$ isolated before from fraction $K_4S_6H_{41}P$ (see CAMO.54/4) has now been identified as 3-ethyl-6:8-dimethyl-naphtho (1:2-b) thiophene (II) (Ring-index nomenclature).



As outlined in previous Reports, the basic 6:7-benzothio-naphthen ring structure of the compound was shown by its ultra-violet absorption spectrum, and desulphurisation with Raney nickel afforded a naphthalene hydrocarbon $C_{16}H_{20}$. This has now been identified by synthesis as 1:3-dimethyl-6-secbutylnaphthalene (III). Two possible structures (I and II) thus remained for the parent sulphur compound. A decision was made in favour of II on the basis of the C-methyl analysis which showed the presence of only 3 C-methyl groups, as expected for (II). Compound I would have shown 4 such groups.

6th December 1956

API 06302

Table 2. Results from Fractions in Mice Experiments
Leeds (1955-6) Laquinillas and Birmingham (1953-4) Kuwait.

<u>Fractions</u>	<u>Expectation of</u> <u>Tumourless Life</u> <u>(Limited to</u> <u>52 weeks)</u>	<u>Date when 10%</u> <u>of Survivors</u> <u>had Tumours</u>	<u>Total</u> <u>number of</u> <u>Tumours</u>
L ₄ S ₁ A	48.0 ± 2.0	29.4 ± 2.9	4
K ₄ S ₁ A	50.1 ± 0.6	not reached	2
L ₄ S ₂ A	49.5 ± 1.2	32.7 ± 3.8	4
K ₄ S ₂ A	52	not reached	0
L ₄ S ₃ A	52	not reached	0
K ₄ S ₃ A	51.2 ± 0.6	not reached	3
L ₄ S ₄ A	48.2 ± 2.1	not reached	3
K ₄ S ₄ A	49.6 ± 1.3	not reached	4
L ₄ S ₅ A	42.2 ± 3.9	27.7 ± 0.6	4
K ₄ S ₅ A	51.2 ± 0.6	not reached	2
L ₄ S ₆ A	43.2 ± 3.0	19.7 ± 3.5	7
K ₄ S ₆ A	50.7 ± 1.0	46.3 ± 4.0	2
L ₄ S ₇ A	38.7 ± 4.1	17.6 ± 0.6	6
K ₄ S ₇ A	43.4 ± 1.0	43.9 ± 0.6	3
L ₄ S ₈ A	35.8 ± 4.0	17.7 ± 0.4	8
K ₄ S ₈ A	47.3 ± 1.6	28.6 ± 2.3	8
L ₄ S _R	46.5 ± 1.7	24.3 ± 2.3	3
K ₄ S _R	52	not reached	0

Table 1. Results from Standards in Mice Experiments
(Leeds 1955-6)

<u>Fractions</u>	<u>Expectation of</u> <u>Tumourless Life</u> <u>(Limited to</u> <u>52 weeks)</u>	<u>Date when 10%</u> <u>of Survivors</u> <u>had Tumours</u>	<u>Total</u> <u>number of</u> <u>Tumours</u>
<u>Leeds Results (1955-6)</u>			
D ₂	32.5 ± 1.0	26.1 ± 0.4	32
D _{1/2}	23.3 ± 0.9	17.3 ± 0.6	42
<u>Leeds Results (1954-5)</u>			
D ₂	16.1 ± 1.8	10.1 ± 0.5	41
D _{1/2}	18.8 ± 0.9	12.2 ± 0.2	44
<u>Birmingham Results</u>			
D ₂ 1952-3	13.9 ± 0.4	11.4 ± 0.8	38
3-4	12.9 ± 0.6	8.7 ± 0.4	40
4-5	14.4 ± 2.0	6.6 ± 0.2	36
Mean	13.7 ± 1.2	8.9 ± 0.5	38
D _{1/2} 1952-3	24.8 ± 1.6	17.1 ± 0.6	25
3-4	18.1 ± 0.8	10.3 ± 0.6	45
4-5	17.9 ± 0.8	11.7 ± 0.3	43
Mean	20.3 ± 1.1	13.0 ± 0.5	38

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MRC.56/965
CAMO.56/12

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

The 1955-56 Experiments with Mice at Leeds

by

J. O. Irwin

The results for the Standards are given in Table 1, and for the Fractions in Table 2.

The Standards

The responses to D₁ were in good agreement with those obtained in previous years. In Table 1 these responses are compared with the results of the three experiments carried out at Birmingham in 1952-3, 1953-4 and 1954-5 and that carried out at Leeds in 1954-5.

The response to D₂ however seems to have been anomalous. The total number of tumours was 32 against an average of 38 in the Birmingham experience, but tumours occurred a great deal later, as shown by the expectation of tumourless life and date when 10% of survivors had tumours.

The Fractions

The Fractions tested were the eight Lagunillas L₄S₁A - L₄S₈A and the residue L₄SR. In Table 2 these are compared with the corresponding Kuwait fractions tested at Birmingham in 1953-4.

With one exception to L fractions all gave a higher response than the corresponding K fractions. The difference was statistically significant for L₄S₅A, L₄S₆A, L₄S₇A, L₄S₈A, also these four fractions gave a higher response than the other L fractions. The residue L₄SR gave a positive response while K₄SR did not.

In view of the anomalous response to the standard these results should be interpreted with some caution. However, D₁ at Leeds in 1955-6 gave a lower response than D₂ at Birmingham in 1953-4 and D₂ at Leeds gave a much lower response than D₂ at Birmingham in the same year. This suggests that the Lagunillas really were more potent than the corresponding Kuwait fractions, for if they were compared relative to the standards tested at the same time, their relative difference would be enhanced.

Table II
Mouse Tests

<u>Fraction</u>	<u>Tumours</u>
G) K ₄ S ₆₋₈ Arii Y	1
H) K ₄ S ₆₋₈ Arii Z	1
O) KX ₂₋₄	1
P) KX ₅₋₆	1
Q) KX ₇₋₈	1
T) D(2)	35
U) D($\frac{1}{2}$)	25

All other fractions have produced no tumours.

Notes

- 1) For comparison of fractions O, P, Q with K₄S₂ to 8 see
 Birmingham Report No. XII.

K ₄ S ₂	= 6 tumours	
K ₄ S ₃	= 6 tumours	In rabbits
K ₄ S ₄	= 7 tumours	all at 37
K ₄ S ₅	= 4 tumours	weeks.
K ₄ S ₆	= 5 tumours	
K ₄ S ₇	= 3 tumours	
K ₄ S ₈	= 2 tumours	
- 2) Compare R with K₄S₉ = 3 tumours at 37 weeks (Birmingham Progress Report XVI).
- 3) Compare S = K₄S₈ with results in Birmingham Progress Reports XI and XII, i.e. 2 tumours at 37 weeks, 3 at 44 weeks and 6 at 52 weeks.
- 4) In 1954 - 55 (Birmingham Progress Report XVI)

Standard D(2)	gave	15	tumours	at	37	weeks
Standard D($\frac{1}{2}$)	"	2	"	"	37	"

 In 1953 - 54 (Report XII)

Standard D(2)	gave	10	tumours	at	37	weeks
Standard D($\frac{1}{2}$)	"	6	"	"	37	"

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MRC.56/946
CAMO.56/9

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Progress Report No. XVII., November, 1956 (Birmingham)

by

D.L. Woodhouse

The fractions listed in Table I were commenced on 28th February and have been applied for 37 weeks at the time of the report, when the tumours indicated were observed. Fuller details will be submitted at the end of the 52 week period, the present report being intended as a preliminary guide for future work.

Table I

<u>Fraction</u>	<u>Rabbit Tests</u>	<u>Tumours</u>
A) K ₄ S ₆₋₈ Ari V	(53 ml.)	1
B) K ₄ S ₆₋₈ Ari W	(53 ml.)	0
C) K ₄ S ₆₋₈ Ari X	(53 ml.)	0
D) K ₄ S ₆₋₈ Ari Y	(53 ml.)	0
E) K ₄ S ₆₋₈ Ari Z (residue)	(53 ml.)	1
F) K ₄ S ₆₋₈ Arii X	(15 ml.)	2
G) K ₄ S ₆₋₈ Arii Y	(15 ml.)	0
H) K ₄ S ₆₋₈ Arii Z (residue)	(15 ml.)	0
I) K ₄ S ₆₋₈ Ariii X	(11 ml.)	0
J) K ₄ S ₆₋₈ Ariii Y	(11 ml.)	0
K) K ₄ S ₆₋₈ Ariii Z (residue)	(11 ml.)	0
L) K ₄ S ₆₋₈ Ari (original pet. ether eluate)	(132 ml.)	0
M) K ₄ S ₆₋₈ Arii (original benzene eluate)	(23 ml.)	0
N) K ₄ S ₆₋₈ Ariii (original methanol eluate)	(17 ml.)	0
O) KX ₂₋₄ (B.range 355-370 C)	(300 ml.)	3
P) KX ₅₋₆ (B.range 370-380 C)	(300 ml.)	5
Q) KX ₇₋₈ (B.range 380-390 C)	(300 ml.)	3
R) KX _{Residue} (Boiling above 390 C)	(300 ml.)	8
S) K ₄ S ₈ (original Stedman cut as standard)	(300 ml.)	2
T) D(2) Standard as agreed		11
U) D($\frac{1}{2}$) Standard as agreed		8

See CAMO. 56/7 page 1.

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MRC.56/963
CAMO. Ag.21

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COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

AGENDA

for the Twenty first meeting to be held
at 38 Old Queen Street, Westminster, S.W.1,
on Tuesday, 18th December, 1956 at 2.30 p.m.

1. Minutes of the previous meeting (MRC.56/727, CAMO.Min.20 - already circulated)
2. Progress Reports:-
 - (a) No.XVII, November 1956 (Birmingham), by Dr. D.L. Woodhouse,
(MRC.56/946, CAMO.56/9 - Enclosure A).
 - (b) The 1955-56 Experiments with Mice at Leeds, by Dr. J.O. Irwin,
(MRC.56/965, CAMO.56/12 - Enclosure B).
 - (c) Report by Dr. W. Carruthers, Dr. J.W. Cook and Mr. A.G. Douglas,
(MRC.56/958, CAMO.56/11 - Enclosure C).
3. Preparation of Kuwait fractions for 1957 to 1958 tests.

As picrate treatment on a large scale has proved impracticable Professor Morton will suggest preparation of fractions by chromatography on alumina from KX5-6.

A Note by Professor Morton is enclosed (MRC.56/956, CAMO.56/10 - Enclosure D).
4. Proposal for including a single specimen of cutting oil, reported to be non-carcinogenic in the Birmingham tests.

Manchester Oil Refineries have prepared an oil which, according to the Twort Formula is non-carcinogenic, for Messrs. Ferranti, a big user of cutting oils. This oil satisfies all the requirements from the technical point of view, and it is now suggested that it might be tested in the laboratory to see if it is in fact relatively non-carcinogenic as far as animals are concerned. If it were so, then it could be, and perhaps should be, recommended for wider use as a cutting oil.
5. Any other business.
6. Date of next meeting.

Lawrence

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

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

CABLE ADDRESS: KETLAB. CINCH
TELEPHONE: CAMTOL 1414

January 14, 1957

Subcommittee on Carcinogenicity
API Medical Advisory Committee

Gentlemen:

In connection with the proposed investigation of petroleum waxes, we have given serious consideration to the desirability of dividing the program into two phases, the first of which would involve a relatively rapid screening of pertinent waxes used to coat meat wrapping paper or milk cartons. If positive biological evidence of the presence of carcinogens is obtained in this first phase, a second developmental phase to estimate the hazard of internal cancers would be recommended. Dr. Eckardt has asked us to circulate the attached memorandum, which presents in some detail the reasons for the suggested phasing of the proposed investigation.

Dr. Eckardt has also raised the question of the desirability of renewing the exchange of information with Research Committee No. 2 of the Institute of Petroleum. We have indicated our whole-hearted agreement with such a policy and have suggested that it might be appropriate to send copies of our annual reports on Project MC-1 for 1955 and 1956, together with reprints of the papers on the determination of benzo(a)pyrene and carcinogenesis of the skin.

Sincerely yours,

A. Wesley Horton

A. Wesley Horton

AWH:mjg
CC: Mr. D. V. Stroop
Attachment

SUPPLEMENTARY PROPOSAL FOR
THE INVESTIGATION OF POTENTIAL CANCERIGENIC PROPERTIES
OF PETROLEUM WAXES

Further consideration has been given to methods for the development of information with which to answer, in at least a preliminary way, questions about the carcinogenicity of waxes which may occur in human food. With this purpose in mind, a previous proposal involving four or five years of investigation may be divided into two parts. The first of these, if pursued vigorously, should provide some basis for the relief of apprehension, on the one hand, or point the way toward corrective measures, on the other, within 15 months, or possibly less, after the start of the biological tests.

A significant question, selected for prompt investigation because it is susceptible to direct experimental attack without the necessity of developing any new techniques or concepts, is that of whether waxes used to coat wrapping paper for meat or various cartons for other foods do or do not contain polycyclic carcinogens. The skin of the mouse provides a sensitive instrument for detecting the presence of such compounds. Further, the rate of response, on the part of the skin of the mouse, may reveal the relative amounts of carcinogenic substances of this type in those waxes which do not prove to be free of them. API 06310

To obtain these answers as expeditiously as possible, concentrates of the fluorescent components of the waxes should be tested in an accelerating solvent (since the waxes are largely normal paraffins, the use of n-dodecane for this

purpose is indicated). Appropriate parallel experiments with the solvent alone (negative controls) would be an essential part of the experimental program, as would also be tests with solutions of benzopyrene in n-dodecane.

It should be noted that, in such experiments, the skin of the mouse would merely be used as a sensitive and reproducible means of determining the presence of polycyclic carcinogens. If no tumors are produced by fluorescent components of the refined waxes, the safety of their continued use in containers for food will have gained a significant degree of support. If, on the other hand, fractions of certain of the waxes do prove to be carcinogenic, the precise significance of such results will have to be determined by further investigation. This should not prove to be very difficult, if positive results can be related to polycyclic impurities in the products tested. In any case, it should be understood that the examination of appropriate materials by such means is recommended, not because of any notion that the use of refined waxes presents a potential hazard of cancer of the human skin, but rather because such evidence of the presence or absence of polycyclic carcinogens would be of immediate practical value.

Information on the sources and properties of the waxes under investigation should be collected carefully for this initial phase of the program. Particular characteristics, such as crude source and oil content, have been discussed previously.

Should it become apparent from the initial observations that some of the important waxes have carcinogenic potentialities, then a supplementary experimental program should probably be undertaken. Its objective would be the development of a biological technique for estimating the capacity of materials to induce internal cancers if ingested by human beings. Since this type of test has been sought by experienced investigators for many years without success, it would be presumptuous to suggest that a satisfactory procedure would be forthcoming promptly.

Date: January 14, 1957

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 121, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

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BERTRAND E. BENNISON, M. D.
CHIEF CLINICAL RESEARCH PHYSICIAN

January 11, 1977

Dr. Phillip Drinker
Harvard School of Public Health
55 Shattuck Street
Boston 15, Massachusetts

Dear Dr. Drinker:

Mr. Stuep has advised me that it is not necessary for you to receive written authorization to proceed with the revision of the toxicological review. The \$6000 authorized at the last meeting will be available July 1, 1977. It is my understanding that there is a balance of \$4000 from a previous appropriation that is available now for this work.

For your information, I am enclosing a copy of the approved recommendations made by the Toxicology Sub-Committee at the last meeting.

If you have any questions on the above, please contact me.

Very truly yours,

R. V. CHAMBER, M. D.

ENC: new

Enc. 1 Appendix C, Minutes of 2nd MRS Meeting, November 12, 1976.
cc: 1 Mr. David V. Stuep - wa/enc.

Mr. L. E. Curtis
Mr. V. C. Baird
Mr. E. Davis

STANDARD OIL COMPANY

(INDIANA)

910 SOUTH MICHIGAN AVENUE

CHICAGO 80, ILLINOIS

MEDICAL DEPARTMENT

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MORGE M. GOLDEN, M. D.

PAUL D. HALLEY
INDUSTRIAL HYGIENIST

January 21, 1957

Room 3-
1:00-5:00 P.M.

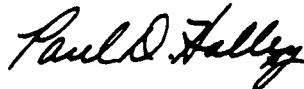
Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Dave:

In answer to your inquiry of January 11, I should like to request space Saturday, April 20, 1957 1:00 to 5:00 P. M. for a meeting of the Subcommittee on Industrial Hygiene.

If this request should be in conflict with other meetings, however, then it will be alright with me if you set us up for a morning meeting on the same day.

Yours truly,



Paul D. Halley

cc: L. E. Curtis, M. D.

R I C H F I E L D O I L C O R P O R A T I O N

R I C H F I E L D B U I L D I N G • L O S A N G E L E S 1 7 • C A L I F O R N I A

JOHN C. RUDDOCK, M.D.
Medical Director

January 22, 1957

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

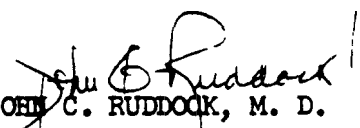
Room 4
1:00 - 3:00 P.M.

Dear Dave:

The Atmospheric Pollutants Subcommittee has recently had a full day's meeting in Los Angeles, and there is a great deal for us to do prior to the meeting of the Medical Advisory Committee in order to make a report, which will require various modifications if we do not get the \$20,000 for setting up a project on the effects of air pollution (for which the petroleum industry is responsible) on the human being.

I would therefore like to request at least two hours sometime on Saturday, April 20, 1957, in one of the rooms that have been assigned for that purpose at the Sheraton Jefferson Hotel in St. Louis, Missouri.

Sincerely,


JOHN C. RUDDOCK, M. D.
Chairman, Subcommittee on
Atmospheric Pollutants,
Medical Advisory Committee to API

JCR:ldb



SHELL DEVELOPMENT COMPANY

EMERYVILLE, CALIFORNIA

TELEPHONE OLYMPIC 3-2100

January 18, 1957

MEETINGS - 4 - 20 - 57

Room 3
9:00 - 12:00

AIR MAIL

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

In reply to your letter of January 11, I would appreciate your arranging to have a meeting room available for use of the Subcommittee on C₉-C₁₂ Aromatics on Saturday, April 20, from 9:00 A.M. to 12:00 noon.

While the subcommittee has only ten members, our policy will be to open the meeting to other interested members of the Medical Advisory Committee, and we will therefore appreciate having space suitable for 30 persons.

Very truly yours,

Charly

C. H. Hine, M.D., Ph.D.
Consultant in Occupational
Health & Industrial Toxicology

CHH/jck

The Standard Oil Company

(The Ohio Corporation)
Midland Building
Cleveland, Ohio

INDUSTRIAL RELATIONS DEPARTMENT
JAMES W. OSBORN, M.D.
MEDICAL DIRECTOR

January 17, 1957

*Room 4
9:00 - 11:00*

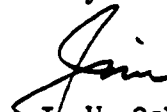
Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

In reply to your letter of January 11,
I will definitely want a meeting of the Subcommittee
on Economic Poisons of at least two hours for
Saturday, April 20, 1957, preferably starting at
9:00 A.M.

I will notify the other subcommittee
members as soon as you let me know the definite
time.

Very truly yours,



J. W. Osborn, M.D.
Chairman
Subcommittee on Economic Poisons

JWO:amd

CC: Dr. L. E. Curtis

STANDARD OIL COMPANY

(INDIANA)

910 SOUTH MICHIGAN AVENUE

CHICAGO 80. ILLINOIS

MEDICAL DEPARTMENT

BRYCE B. REEVE, M. D.
MEDICAL DIRECTOR

NELSON W. BOLDYARD, M. D.
ASSISTANT MEDICAL DIRECTOR

GEORGE M. GOLDEN, M. D.

PAUL D. HALLEY
INDUSTRIAL HYGIENIST

January 15, 1957

*Room 4
300 - 500*

Dr. David Stroop
American Petroleum Institute
50 West 50th Street
New York 20, N.Y.

Dear Dave:

I would like to arrange for a meeting of the Program Committee to be held on Saturday April 20, 1957. At least two hours should be scheduled for either the morning or afternoon, preferably the afternoon.

Yours truly,

B. B. Reeve M.D.

Medical Director

BBR:mb

STANDARD-VACUUM OIL COMPANY
1000 WESTCHESTER AVENUE
WHITE PLAINS, NEW YORK

ROCKWELL 1-1000

January 16, 1956

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

Dear Mr. Stroop:

Your advice was received regarding the Medical Advisory Committee meeting April 20 - 22, 1957.

Unless something unusual arises between now and the time of the meeting, I do not expect to call a Sub-Committee Meeting on Policies and Practices.

Very truly yours,



K. R. Fourcher, M.D.

KRF:ml



DD Stroy

AMERICAN PETROLEUM INSTITUTE

February 10, 1957

Dr. E. M. Adams
Biochemical Research Department
The Dow Chemical Company
Midland, Michigan

Dear Dr. Adams:

Your letter of November 1, 1956 to Paul Halley has been referred to me as Chairman of the API's Medical Advisory Committee's Subcommittee on Carcinogenicity, for answer. In answering your inquiry, I would like to discuss two phases of the problem separately.

First, I would like to discuss the relationship of fluorescence to carcinogenicity. The original concept that fluorescence is a good measure of carcinogenicity came out of the work done on the isolation of benzpyrene from coal tar. It was, perhaps, fortuitous, that the chemists engaged in this problem found that those fractions which were carcinogenic to mice fluoresced in ultraviolet light. Thus, they were able to use fluorescence as a guide to select fractions which they had prepared for biological testing. In brief, the non-fluorescent fractions were non-carcinogenic, and among the fluorescent fractions, one or more was found to contain the biological activity, i.e., carcinogenicity. In this way, they were able ultimately to isolate benzpyrene from coal tar. Note, however, that they did not maintain that all fluorescent fractions were carcinogenic, but only that all non-fluorescent fractions were non-carcinogenic. Parodying a well-known statement, all carcinogenic fractions are fluorescent, but not all fluorescent fractions are carcinogenic. That this is true is well known, since certain pure compounds, such as chrysene, which fluoresce intensely, nonetheless, are completely devoid of carcinogenic activity.

Second, I would like to discuss the carcinogenicity of U.S.P. mineral oils. From an experimental standpoint, U.S.P. mineral oils have probably been used more extensively as a solvent or vehicle for carcinogens in experimental carcinogenic work than any other material with the exception of benzene and acetone. In practically all such cases, the mineral oil has been independently tested for its carcinogenicity as a control. To my knowledge, not one of these investigators has ever reported carcinogenic activity for the U.S.P. mineral oil he used. I may add, that these investigators probably all used a U.S.P. mineral oil which they purchased in their local drug store and, hence, undoubtedly, U.S.P. mineral oils from all segments of the petroleum industry have been tested in the course of these tests.

Dr. E. M. Adams, February 1st, 1957, - 2 -

In addition, several U.S.P. mineral oils have been tested for their carcinogenicity at the Kettering Laboratory under the auspices of the Subcommittee of which I am Chairman. No evidence of carcinogenicity has been obtained in such tests. Independently, several individual petroleum companies have had their U.S.P. mineral oil tested for carcinogenicity, with results confirming those obtained at the Kettering Laboratory.

Medicinally, U.S.P. mineral oil has been consumed in enormous quantities. In individual cases this may be as high as 30 cc. three times a day, consumed daily for 20-30 years. To my knowledge, no clinical reports have arisen out of such usage which would suggest that U.S.P. mineral oil is carcinogenic to humans.

Cosmetically, U.S.P. mineral oils have been daubed and patted daily on the skin of hundreds of thousands of humans over extended periods of time, again with no clinical suggestion of a carcinogenic effect.

U.S.P. mineral oils have been injected subcutaneously into hundreds, if not thousands, of humans when used as an adjuvant for certain vaccines, again without the slightest clinical evidence of a carcinogenic effect.

I may add, that such medicinal and cosmetic uses of U.S.P. mineral oil undoubtedly have encompassed U.S.P. mineral oils originating from all petroleum industry sources of this material, and not just one manufacturer.

Finally, a recent regulation in England has made it necessary to lubricate spindles with white oils in order to eliminate the occupational cancer hazard in the weaving industry. This is recognition by the British authorities that even industrial white oils, which are similar to, but not as highly refined as, U.S.P. mineral oils, are devoid of carcinogenic activity.

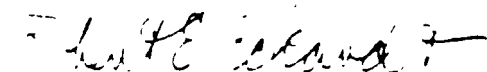
U.S.P. mineral oils are highly acid-treated. The quantity and strength of acid used are far in excess of that used in treating, let us say, lubricating oils. This acid treatment removes unsaturates, which are responsible for the distinctive color and taste of less refined petroleum oils. The unique characteristic of U.S.P. mineral oils is their lack of color (hence, the name white oils) and taste, characteristics which must be maintained even after long periods of storage.

Thus, it appears that the weight of experimental biological, clinical epidemiological, and chemical evidence all substantiate the non-carcinogenicity of U.S.P. mineral oils. These data must, of course, be weighed against the opinion of the cancer

Mr. E. M. Adams, February 18, 1957, - 3 -

expert whom you cite, whose opinion is obviously based on rather archaic thinking about the relationship of fluorescence to carcinogenicity.

Very truly yours,



ROBERT E. ECKARDT, M. D., Chairman
Subcommittee on Carcinogenicity
Medical Advisory Committee

E. W. Adams
C. H. Hine, M. D.
E. K. Linder, M. D.
R. C. Mithoff, M. D.
M. N. Newquist, M. D.
A. C. Pabst

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 121, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH., M.D.
DIRECTOR

N. V. HENDRICKS, CH. E.
HEAD INDUSTRIAL HYGIENIST

MORACE W. GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST

BERTRAND E. BENNISON, M.D.
CHIEF CLINICAL RESEARCH PHYSICIAN

February 19, 1957

Messrs: E. W. Adams R. C. Mithoff
 C. H. Hine* M. N. Newquist
 E. K. Linder A. C. Pabst

Gentlemen:

I am attaching a tentative draft of the minutes of our last meeting.

I would appreciate any comments, suggestions, or additions which you make to these minutes before I prepare them in final form.

It might appear advisable to circulate these minutes to the MAC after they are prepared in final form.

Sincerely yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ejh

Attach. - Minutes of the Meeting of the Subcommittee on Carcinogenicity,
Held at the Biltmore Hotel, Los Angeles on January 31 - February 1, 1957
R. E. Eckardt, M. D. (February 18, 1957).

cc: Dr. L. E. Curtis ✓
Mr. D. V. Streep ✓

* - In Duplicate

49

MINUTES OF THE MEETING OF THE
SUBCOMMITTEE ON CARCINOGENICITY

Held at the Biltmore Hotel, Los Angeles

January 31 - February 1, 1957

The meeting was called to order at 10:00 a.m., January 31 in Dr. R. E. Eckardt's suite at the Biltmore Hotel.

In attendance were the following:

R. E. Eckardt, M. D. - Chairman
N. W. Bolyard (representing E. W. Adams)
E. K. Daniels (representing A. C. Pabst)
C. H. Hine, M. D.
E. K. Linder, M. D.
M. N. Newquist, M. D.
R. C. Mithoff, M. D.

First order of business of the Subcommittee was to review the proposals of the Lewis laboratories for the study of carcinogenicity of petroleum waxes. Copies of the proposals obtained from each laboratory were given to each of the members of the Subcommittee and the Subcommittee then adjourned for an hour to permit each individual an opportunity to review each proposal.

When the Subcommittee reconvened, Dr. Hine had prepared a summary of the items which each laboratory planned to study for comparative purposes. It was then decided by the Subcommittee, after reviewing each of the proposals, that any one of the laboratories could probably conduct a satisfactory study, but some proposals showed more imagination than others. Each Subcommittee member was asked to express his opinion as to his first choice of a laboratory in which the studies should be conducted. On this basis, four of the laboratories were selected and three were eliminated. Next, each Subcommittee member was asked to rank the four laboratories so selected and one of the four laboratories was eliminated in this fashion. Since there wasn't a unanimous opinion concerning which of these should be recommended, it was decided to recommend all three, but to rank them in accordance with the preferences of the Subcommittee, based upon a proportional representation vote to be undertaken the following day, after each Subcommittee member had an opportunity to re-review the proposals of the three laboratories concerned.

Results indicated preferences in the following order:

1. Dr. Philippe Shubik's laboratory
2. The Hazleton Laboratories
3. Dr. Morton Nelson's laboratory

- A. Status report by Dr. Horton
- B. Final report by Dr. Phair
- C. Budget proposals for the interval of July 1, 1958 to June 30, 1959 from Dr. Kehoe

This information has been transmitted to the Kettering Laboratory representatives and the above meeting date and desire for the reports expressed in the letter from the Chairman.

The final order of business discussed was a meeting of the Subcommittee at the time of the Industrial Health Conference in St. Louis. It was agreed that an open meeting at which all MAC members would be welcomed, will be scheduled for Saturday, April 20 at 8:00 p.m. at the Sheraton-Jefferson Hotel in St. Louis. The plan will be to have the draft report of the Subcommittee to the MAC prepared and distributed to all members of the MAC and to have the discussion at the meeting on April 20, simply be a whipping up into final form of the report for the MAC.

There was also some discussion by the Subcommittee of the possible carcinogenic effects of air-blowing asphalt and oil mists which might occur within the refinery. In this connection, Dr. Eckardt reported to the Subcommittee, the work which Esso Research and Engineering Company had sponsored at NYU. This work had shown that the condensate of the fume obtained with air-blowing of asphalt was highly carcinogenic to the skin of the mouse and that the material scrapped off a fan blade which was used to ventilate a slurry oil pump, was also carcinogenic to the skin of the mouse. Dr. Eckardt warned that only one fume of an asphalt had been tested and it was not, therefore, possible to say that all asphalt blowing fumes are carcinogenic. The consensus of the Subcommittee on these problems seemed to be that it probably represented an individual company problem, but that if there was enough general interest in it, perhaps the Subcommittee could consider experimental work on it at some future date.

The Subcommittee was of the opinion that the work at the Kettering Laboratory had essentially fulfilled its purposes and that the work probably would be terminated as of July 1, 1959. The Subcommittee meeting continued into the morning of February 1 and about one-half an hour before the Subcommittee adjourned, Dr. Kehoe was asked to join the Subcommittee meeting. At this time, he was informed about the meeting on April 2 and the desire of the Subcommittee for the reports by March 25. In addition, he was informed that it was the feeling of the Subcommittee that the carcinogenic work at Kettering Laboratory would be terminated as of July 1, 1959. Hope was expressed to Dr. Kehoe that an adequate final report of the work at Kettering Laboratory would be made available to the Subcommittee at the time of the termination of the work on July 1, 1959.

Minutes Prepared By
R. E. Eckardt, M. D. - Chairman
February 18, 1957

The next order of business discussed was how to implement a survey of wax uses for the guidance of the biological work. It was the consensus of the Subcommittee that our recommendations on this were cleared at the April meeting of the MAC and that we had no further responsibility in this direction.

The next order of business concerned the draft letter by the Chairman which he proposed to be sent to Dr. E. M. Adams of the Dow Chemical Company. Apparently the Subcommittee members did not understand that this letter was to be cleared through Mr. Stroop's office and therefore would receive clearance by Mr. Stroop through Mr. Porter before it was sent out. When this situation was explained, the Subcommittee was in unanimous agreement that the letter should be sent to Dr. Adams under the signature of the Chairman of the Subcommittee, acting as Chairman of the Subcommittee, assuming that there were no objections to his course of action by Mr. Stroop. Upon returning to New York, the Chairman called Mr. Stroop and was informed that there were no objections to sending out this letter and, hence, arrangements have been made to obtain API stationery and forward this letter to Dr. Adams on API Stationery as a statement of the Subcommittee, signed by the Subcommittee Chairman.

The next order of business was a discussion of what should be sent to the Institute of Petroleum in Britain by our Subcommittee. There was a general consensus that we should send Dr. Horton's 1955 and 1956 reports along with the minutes of the Subcommittee meetings during the years 1955 and 1956. It was felt desirable that this information sent to Great Britain should be sent from Mr. Stroop's office and that future correspondence from the Institute of Petroleum in Britain be forwarded to our Subcommittee through Mr. Stroop's office. In other words, it should be addressed to Mr. Stroop to the attention of the Chairman of the Subcommittee on Carcinogenicity. In this way, even though changes occur in the chairmanship of the Subcommittee, it will be possible to see that the information gets to the Subcommittee Chairman. At the same time, the question of summarizing the British work was brought up and it was deemed undesirable to have Dr. Horton prepare such a summary. It was proposed that a member of the Subcommittee prepare such a summary and it was further suggested that Dr. Hine be so appointed. Therefore, I am making this appointment as Chairman now.

The next order of business discussed was the next meeting of the Subcommittee. It was agreed that this should be held on April 2 in Chicago. An attempt will be made by the Chairman to reserve a suite at the Blackstone Hotel so that the meeting can be held in his suite on April 2. It was suggested that it would be extremely helpful to the Subcommittee members if they could obtain by March 25 from the Kettering Laboratory the following:



AMERICAN PETROLEUM INSTITUTE

30 WEST 50TH STREET
NEW YORK 20, N. Y.

March 1, 1957

SECTION OF MARKETING
J. J. RUMOSHSKY DIRECTOR

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Mr. D. T. Staples
Tidewater Oil Company
79 New Montgomery Street
San Francisco 20, California

Dear Mr. Staples:

With regard to your letter of February 12th, I have no objection to the proposed continuation of a study of carcinogenicity and concur that the sum of \$50,000 be made available to cover the cost of carcinogenic testing of waxes by an independent laboratory.

I believe that this action should not be linked in the manner shown in the draft letter to Dr. Burney, Surgeon-General of the U. S. Public Health Service. From the discussions in the Subcommittee on Carcinogenicity, it is apparent that there was misquotation and misinterpretation of the statements made by Dr. Hueper. These misinterpretations did lead to unfortunate publicity. However, I believe it would be a mistake to tie this in any way as a basis for the further cancer research proposal by the Medical and Health Committee of the API.

Therefore, it is my recommendation that the letter to Dr. Burney be omitted.

Cordially,

D. T. Colley

cc: Mr. Frank M. Porter

API 06329

UNION OIL COMPANY OF CALIFORNIA

UNION OIL BUILDING

LOS ANGELES 17, CALIFORNIA

RICHARD CALL, M.D.
MEDICAL DIRECTOR

March 4, 1957

Mr. David Stroop
American Petroleum Institute
50 W 50th Street
New York 20, N. Y.

Dear Mr. Stroop:

I am in receipt of your kind letter of February 5, 1957 in reference to closing out of your inventory. Would you please send me a copy of :

1. "Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," (58)
2. Report of Progress in the Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," (4)

Thanking you for your consideration, I remain,

Sincerely yours,

Richard Call

Richard Call, M.D.

RC:d

*Done
go. - 3-7-57*

INVENTORY OF MAC CIRCULARS, REPORTS, ETC. ON HAND - FEBRUARY, 1957

1. of
copies

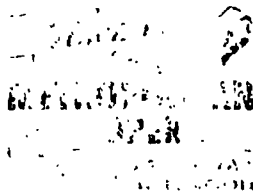
- 100 "Occupational Cancer - A Challenge to the Physician," by the Office of Public Health Education, N. Y. State Department of Health.
- 58 "Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," Report of the Progress in the Epidemiological Studies, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 70 "Tabular Summary of Current and Completed Biological Experiments," API Res. Project MC-1, September 1, 1953, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 38 "Skin Cancer of the Hand and Forearm," by C. N. D. Cruickshank and A. Gourevitch.
- 4 "Report of Progress in the Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 20 "Thermal Burns," Revised draft by Dr. A. O. Seeler.
- 7 "Report of Progress in the Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," - The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 16 "The Cutting Oil Dermatoses - A Review," by Bertrand C. Kriete, A. B., Harvard School of Public Health, March 15, 1950.
- 100 "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, 1954 - June 30, 1955."
- 25 "American Petroleum Institute Medical Advisory Committee Report for Period 1945 - 1952."
- 75 "Tabular Summary of Current & Completed Biological Experiments, September 1, 1953," The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 45 "BAL," by Raymond V. Randall, M. D., and Albert O. Seeler, M. D. API 06334
- 11 "Interim Report API Research Project MC-1, October 1, 1955," by The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 20 "Cutting Oil Dermatoses," by Harry Shapiro, M. D., N. Y. State Dept. of Labor Monthly Review, Division of Industrial Hygiene & Safety Standards.
- 3 "Supervisory Development Services Available from Public and Private Agencies and Institutions," compiled by the API Comm. on Supervisory Development.

No. of
Copies

- 80 "Determination of Benzo(a) - pyrene in Complex Mixtures, Use of Catalytic Iodination on Activated Alumina," by Russel Tye, Mary Jane Graf, and A. Wesley Horton, Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio, Reprinted from ANALYTICAL CHEMISTRY, Vol. 27, Page 248, February, 1955.
- 185 "Carcinogenesis of the Skin. A Re-examination of Methods for the Quantitative Measurement of the Potencies of Complex Materials," by A. Wesley Horton and Dorothy T. Denman, reprinted from CANCER RESEARCH, Vol. 15, No. 11, pp. 701-09, December, 1955.
- 28 "Phosphate Ester Insecticides," by D. O. Hamblin, M.D., H. H. Golz, M. D., F.A.C.P., and C. B. Shaffer, Ph.D.
- 35 Revised manuscript of paper entitled "Carcinogenesis of the Skin," by Dr. A. Wesley Horton and Dorothy Templeton Denman.
- 12 Committee on the Carcinogenic Action of Mineral Oils, Meeting held May 2, 1955, at 38, Old Queen Street, Westminster, London, S.W.1, three Progress Reports.

THE TEXAS COMPANY
135 EAST 42ND STREET
NEW YORK 17, N Y

API 06336



Mr. D. V. Strop
American Petroleum Institute
50 West 50 Street
New York, N. Y.

INVENTORY OF MAC CIRCULARS, REPORTS, ETC. ON HAND - FEBRUARY, 1957

No. of
Copies

- 100 "Occupational Cancer - A Challenge to the Physician," by the Office of Public Health Education, N. Y. State Department of Health.
- 58 "Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," Report of the Progress in the Epidemiological Studies, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 70 "Tabular Summary of Current and Completed Biological Experiments," API Res. Project MC-1, September 1, 1953, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 38 "Skin Cancer of the Hand and Forearm," by C. N. D. Cruickshank and A. Gourevitch.
- 4 "Report of Progress in the Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 20 "Thermal Burns," Revised draft by Dr. A. O. Seeler.
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- 16 "The Cutting Oil Dermatoses - A Review," by Bertrand C. Kriete, A. B., Harvard School of Public Health, March 15, 1950.
- 100 "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, 1954 - June 30, 1955."
- 25 "American Petroleum Institute Medical Advisory Committee Report for Period 1945 - 1952."
- 75 "Tabular Summary of Current & Completed Biological Experiments, September 1, 1953," The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 45 "BAL," by Raymond V. Randall, M. D., and Albert O. Seeler, M. D. API 06337
- 11 "Interim Report API Research Project MC-1, October 1, 1955," by The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 20 "Cutting Oil Dermatoses," by Harry Shapiro, M. D., N. Y. State Dept. of Labor Monthly Review, Division of Industrial Hygiene & Safety Standards.
- 3 "Supervisory Development Services Available from Public and Private Agencies and Institutions," compiled by the API Comm. on Supervisory Development.

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- 35 Revised manuscript of paper entitled "Carcinogenesis of the Skin," by Dr. A. Wesley Horton and Dorothy Templeton Denman.
- 12 Committee on the Carcinogenic Action of Mineral Oils, Meeting held May 2, 1955, at 38, Old Queen Street, Westminster, London, S.W.1, three Progress Reports.

*the 7 copies marked in margin for
Dr. J. E. Riddick*

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RICHFIELD BUILDING • 555 SOUTH FLOWER STREET
LOS ANGELES 17, CALIFORNIA

AIR MAIL

API 06339

VIA AIR MAIL



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

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

MEDICAL RESEARCH DIVISION

ROBERT E ECKARDT PH. D M D
DIRECTOR

N V HENDRICKS CH E
HEAD INDUSTRIAL HYGIENIST

HORACE W GERARDE PH D M D
HEAD TOXICOLOGIST

BERTRAND E BENNISON M D
CHIEF CLINICAL RESEARCH PHYSICIAN

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

In response to your letter of February 25, I would greatly appreciate receiving 25 reprints of the two papers by Dr. Horton. One of which appeared in ANALYTICAL CHEMISTRY and the other in CANCER RESEARCH.

Sincerely yours,

R.E. Eckardt

R. E. ECKARDT, M. D.

REF: cjh

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1957

PHILLIPS PETROLEUM COMPANY

BARTLESVILLE, OKLAHOMA

February 28, 1957

MEDICAL DEPARTMENT

KIEFFER DAVIS, M. D.
MEDICAL DIRECTOR

CAMP S. HUNTINGTON, M. D.
ALBERT M. MERY, M. D.
ASST. MEDICAL DIRECTORS

LUCIAN E. RENES
INDUSTRIAL HYGIENIST

J.S.
Planned
one of each
as marked
one for
3-5-57

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

Dear Dave:

Received your letter of February 25, 1957 and am returning
the list of circulars, marking the ones that I would appreciate
receiving.

Sincerely yours,

Kieffer
Kieffer Davis, M. D.
Medical Director

KD:tmd

Enclosure

API 06341

INVENTORY OF MAC CIRCULARS, REPORTS, ETC. ON HAND - FEBRUARY, 1957

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- ✓ 100 "Occupational Cancer - A Challenge to the Physician," by the Office of Public Health Education, N. Y. State Department of Health.
- 58 "Appraisal of the Potential Carcinogenic Properties of American Petroleum Products," Report of the Progress in the Epidemiological Studies, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
- 70 "Tabular Summary of Current and Completed Biological Experiments," API Res. Project MC-1, September 1, 1953, The Kettering Laboratory, Dept. of Preventive Medicine & Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
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- ✓ 16 "The Cutting Oil Dermatoses - A Review," by Bertrand C. Kriete, A. B., Harvard School of Public Health, March 15, 1950.
- 100 "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, 1954 - June 30, 1955."
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Plum

BCY 950, BAYTOWN, TEXAS

Line 3-5-57

[illegible]

Dear Mr. Stroop:

Very truly yours,

J. W. Hammond
J. W. HAMMOND

API 06347

INVENTORY OF MAC CIRCULARS, REPORTS, ETC. ON HAND - FEBRUARY, 1957

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June 17, 1957

AIR MAIL

Professor T. Ferguson
University of Glasgow
Department of Public Health
and Social Medicine
6 University Gardens
Glasgow W. 2, SCOTLAND

Dear Sir:

Most thoughtfully, Col. Auld has given me a copy of the letter he addressed to you under date of 7th June, 1957.

If you should confirm the arrangements outlined in his letter, we should like to have Mr. Horton's post office address so that we may be assured of proper transmittal for our communications.

Very truly yours,

YV:ed

cc: E. E. Edwards, M. D.

ALCO PRODUCTS EXPORT COMPANY, INC.

With
LT. COL. S. J. M. AULD'S
Compliments.

25, VICTORIA STREET,
LONDON, S.W.1.

7th June, 1967.

Professor T. Ferguson,
University of Glasgow,
Dept. of Public Health & Social Medicine,
6, University Gardens,
GLASGOW, W. 2.

Dear Professor Ferguson:

Carcinogenicity of Petroleum.

American relationships.

Talks in U.K. with one or two people concerned on this subject and particularly with Dr. D.V. Streep of American Petroleum Institute, (with whom I had been in correspondence) and Dr. R.E. Schmidt, Chairman of the A.P.I. Medical Advisory Committee, have led me to believe that the slowing up of exchange of thought and information with our American friends is likely to have been due to two causes. The first is that Dr. Hargrave who recently retired from the A.P.I. Medical Committee Chairmanship did not take perhaps the same interest in exchange of data as his predecessor and this subject is clearly one where the personal touch is of great importance.

Conditions in this respect will undoubtedly revive with the appointment to the Chairmanship of Dr. Schmidt. For R.R.C. record purposes he is :

Robert E. Schmidt, M.D.,
Basic Research and Engineering,
Research Division,
P.O. Box 211,
Linden, New Jersey.
Telephone MAhesh 8-1600
extension 8104.

Subject to your confirmation I have arranged to meet Dr. Schmidt's suggestions (a) that outgoing material from U.K.A. side should come to us through A.P.I. (Mr. Streep) and to

/cont...

addressed directly to Dr. Norton. (b) that material from the U.K. side (either from N.R.C. or from individual members of the N.R.C. Committee) be sent directly to Dr. Eckardt. He in turn is in the closest touch with Mr. Streep, who would thus know of anything that was going on. (c) that encouragement be given to the exchange of visits between individuals and laboratories.

The second cause of the slowing up of information from U.S.A. is more fundamental. You will remember that the Sloan lettering work at University of Cincinnati was supported liberally by the American Oil Industry, chiefly through the channel of A.P.I. This was largely because of the widely popular concern at the believed relationship of exposure to petroleum and incidence of skin cancer.

The large scale work consequently embarked upon was largely based on the potential dangers and examination of individual products, chiefly catalytic cracked materials of mid-distillate origin. These were (and are still) strongly suspected, as also are the aromatic extracts.

The search for carcinogens was guided by such special cases and with much of the work, the N.R.C. is well equipped.

It seems now to appear that the interest of A.P.I. is waning since public alarm has been quietened. This it would seem is partly because of the close attention being paid to personal cleanliness and other prophylactic measures and possibly also no doubt because of the counter-irritant of the cigarette-cancer scare. Introduction of the filter tip cigarettes on a wide scale (to the ultimate benefit of the cigarette makers who are enabled to give less and inferior tobacco for more money) is saving the public conscience in that respect.

This does not mean that the medical interest in petroleum as a source of hydrocarbon or other carcinogens is being given up; but it may mean a re-evaluation and re-direction of the effort. This reaction is intensified by reason of the feeling amongst the American biologists that the matter is becoming far more involved and vague than was originally imagined. That refers in particular to the work which has been going on in connection with co-carcinogenic action.

Dr. Eckardt is keen that the workers in America should continue and retain their contact with the British team and will do everything he can to that end.

I think it would be a good thing therefore, if you and perhaps Professor Squire would write to Dr. Eckardt and open the ball with some concrete suggestions or exchanges of experience.

Kind regards,

S.J.M. Auld

John Sikora
Please let me
have the file on
this subject

OK
5-10-57

S J M AULD

TELEPHONE
ABBEY 3775

25. VICTORIA STREET
LONDON.

SW 1

5th April, 1957

D.V. Stroop Esq.,
American Petroleum Institute,
50 West 50th Street,
New York. 20. N.Y.

Dear Mr. Stroop,

I am greatly obliged for your letter of March 18th on the subject of exchange of information between the A.P.I., and the Groups concerned over here in studying the carcinogenicity of petroleum.

This is very timely as I shall be arriving in New York on the 16th April and shall be on the North American continent for about three weeks after that. I would therefore like to come and have a talk with you on the subject but I am not certain what actual date to suggest. However, I will get in touch with you on arrival and fix a date. In the meantime you may care to make a note that I can be contacted c/o Mr. Manuel Alonso, Alco Products Inc., 30 Church Street, New York. 8 N.Y. U.S.A.

Canterland 7-8660

Called - left message 4/20/57

OS

Yours very truly,

S.J.M. Auld

SJ MA/gbm

S.J.M. Auld

*Dr. Auld 10th
Called - May 10th
Said to send
material to
Dr. Norton
Medical Research Council*

Council
OS

File: MAC

March 18, 1957

Colonel S. J. M. Auld, President
Institute of Petroleum
26 Portland Place
London, W. 1., England

Dear Colonel Auld:

Some years ago, an informal liaison was maintained between the chairman of A. P. I. and I. P. committees having a common interest in the carcinogenicity of petroleum.

More recently the flow of information has become concentrated in one direction - westward.

We should like to restore the flow to the east if you will give us the name and address of the man to whom such matters should be addressed.

Very truly yours,

DVB:js

API 06356

UNIVERSITY OF GLASGOW
Department of Public Health and Social Medicine

Professor
Thomas Ferguson



6 University Gardens
Glasgow, W.2
Telephone: Kelvin 2231

AIR MAIL.

21st June, 1957.

Dear Mr. Stroop,

Thank you very much for your
note. Dr. Norton's address is 38 Old
Queen Street, Westminster, London, S.W.1.,
and I have written to him following Col.
Auld's letter to me.

Yours very sincerely,

T. Ferguson.

D.V. Stroop, Esq.,
Executive Assistant,
American Petroleum Institute,
50 West 50th Street,
New York 20, N.Y.,
U.S.A.

DL

API 06358

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 121, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKHARDT, PH. D., M. D.
DIRECTOR

N. V. HENDRICKS, CH.
HEAD INDUSTRIAL HYGIENE

HORACE W. GERARDE, PH. D., M. D.
HEAD TOXICOLOGIST

BERTRAND E. BENNISON, M. D.
CHIEF CLINICAL RESEARCH PHYSICIAN

Copy From D. V. Stroop For Information Of
Members Of Medical Advisory Committee
3/18/57

March 11, 1957

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

Dear Mr. Stroop:

I am sending you copies of all the minutes of the Subcommittee on Carcinogenicity for the years 1955-1956 in response to your request of March 6, 1957. In addition, I am sending you some information obtained from the Medical Research Council in Britain which probably ought to be duplicated and distributed, at least to the Subcommittee members and to the group at Kettering Laboratory.

Finally, I do not believe there is any rush to reproduce the British report which you mentioned in your letter and I am sure you can do this at your leisure.

Sincerely yours,

R. E. Eckhardt

R. E. ECKHARDT, M. D. *gh*

HEE:cjh

- Attach. - Minutes of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council. MRC.57/176 CAMO.Min.21.
- Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated April 25, 1955.
 - Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated October 31, 1955.
 - Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated April 23, 1956.
 - Minutes of the Subcommittee on Carcinogenicity for their meeting on September 6, 1956.
 - Proposed Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee for its Meeting on November 12, 1956, dated November 5, 1956.

Dictated, but not read

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.57/176
CAMO.Min.21

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the twenty-first meeting held at 38 Old Queen Street, London, S.W.1, on Tuesday, 18th December, 1956 at 2.30 p.m.

Present:- Professor T. Ferguson (Chairman), Col. S.J.M. Auld, Dr. J.W. Cook, Dr. I. Hieger, Dr. J.O. Irwin, Professor F. Morton, Professor R.D. Passey, Professor J. R. Squire, Dr. D. L. Woodhouse, with Dr. R.C. Norton (Secretary).

Attended: Dr. Philip J. King, and Dr. W. Carruthers.

An apology for absence was received from Professor H.N. Green.

1. Minutes

Dr. Irwin suggested that the Minutes of the previous meeting might be amended by re-numbering the paragraphs under item 3, "Progress Reports", so that they agreed with the numbering of the corresponding items of the agenda for that meeting. The numbering of the paragraphs under min.3, of the twentieth meeting should therefore be as follows:-

Min.3.(a) by Dr. W. Carruthers and Dr. J. W. Cook (MRC.56/543, CAMO.56/4) to be re-numbered 3.(1)(a),

Min.3.(b) by Professor F. Morton (CAMO.56/7) to be re-numbered 3.(1)(b),

Min.3.(c) by Dr. D.L. Woodhouse - Progress Report No. XVI (May 1956), (MRC.56/542, CAMO.56/3) to be re-numbered 3.(11)(a),

Min.3.(d) Data tables on mineral oil fractions, submitted by Dr. D.L. Woodhouse (CAMO.56/3) to be included in 3.(11)(a),

Min.3.(e) Experiments with mice at Leeds (MRC.56/548, CAMO.56/5 and MRC.56/549, CAMO.56/6 to be re-numbered 3.(11)(b) and (c).

It was further suggested that in the first line of paragraph 3.(c) in the Minutes (before amendment) of the previous meeting the word 'importance' should be substituted for 'significance'. The beginning of this paragraph should therefore read "Dr. Irwin said that a point of great importance emerging from the report was the failure"

The Committee agreed to these amendments and the Minutes of the twentieth meeting were then signed by the Chairman.

2. Matters arising

API 06360

Professor Squire said that he had now heard from Dr. W. E. Smith (Min.2 of the 20th meeting) who was anxious to carry out further tests by his rapid screening

method of oil samples already tested under the Committee's programme. After discussion it was agreed to send Dr. Smith further samples, although any results which he might obtain would not be likely to be of great assistance in the present phase of the Committee's programme.

In this connection Col. Auld suggested that it was desirable to build up a more direct association with American workers in the field and it was agreed that he and Professor Morton should investigate further methods of doing this.

3. Progress Reports

- (a) No. XVII, November 1956 (Birmingham), by Dr. D.L. Woodhouse, (MRC.56/946, CAMO.56/9).

Dr. Woodhouse gave some further figures for the incidence of tumours at 42 weeks in his series of rabbit tests. These were for each fraction shown in Table I:-

(A) 2	(H) 0	(O) 7
(B) 0	(I) 0	(P) 7
(C) 0	(J) 1	(Q) 7
(D) 1	(K) 0	(R) 8
(E) 1	(L) 1	(S) 5
(F) 3	(M) 1	(T) 14
(G) 0	(N) 0	(U) 8

He also said that in Table II 'Mouse tests', fraction (T) D(2) should read D($\frac{1}{2}$) and that fraction (U) D($\frac{1}{2}$) should read D($\frac{1}{4}$).

Since fractions A-E (with parent fraction L) and F-H (with parent fraction M) were more active than I-K (with parent fraction N), these results showed that chromatography on alumina is a promising method of separation, the active substance(s) being eluted by petroleum ether (A to E + L), though some remained for subsequent elution with benzene (F to H + M).

- (b) The 1955-56 Experiments with Mice at Leeds, by Dr. J.O. Irwin, (MRC.56/965, CAMO.56/12).

Dr. Irwin pointed out that with the standard D₂ at Leeds, tumours had occurred much later than expected. There also appeared to be a small, but genuine difference between the potency of the L and K series.

It was noted that in the second sentence of the last paragraph of the first page of this paper, the first "D₂" should read "D $\frac{1}{2}$ " so that the whole sentence should read: "However, D $\frac{1}{2}$ at Leeds in 1955-56 gave a lower response than D $\frac{1}{2}$ at Birmingham in 1953-4 and D₂ at Leeds gave a much lower response than D₂ at Birmingham in the same year."

Commenting on the statistical analysis of the 1955-56 experiments with rabbits at Leeds (MRC.56/969, CAMO.56/13), Dr. Irwin drew attention to the unusual number of tumourless deaths, and, referring to the standards, he said that D₂ appeared to be normal but that the results with D $\frac{1}{2}$ had been unusual. Again the L series appeared to be slightly more carcinogenic than the corresponding K's.

In both papers the fractions referred to as L₄SR and K₄SR should be L₄SP and K₄SP respectively, and when referred to in the text the word 'raffinate' should be substituted for 'residue'.

- (c) Report by Dr. W. Carruthers, Dr. J. W. Cook and Mr. A. G. Douglas,
(MRC.56/958, CAMO.56/11).

Dr. Carruthers introduced his Report by remarking that attempts to isolate homogeneous compounds from the Kuwait picrate-forming fractions were continuing. A synthetic programme based on the results so far obtained was about to be started.

The 6:7-benzothionaphthene derivative discussed in his Report was the first example of this particular ring system to be detected in mineral oil.

It now seemed desirable to do tests for carcinogenicity on some of the pure compounds isolated; it was agreed to include several in the 1957-58 Birmingham tests if adequate amounts could be provided.

4. Preparation of Kuwait fractions for 1957 to 1958 tests.
(MRC.56/956, CAMO.56/10).

Professor Morton said that he had tried to find suitable areas in which to carry out the picrate separations with his own resources, but that he had been unsuccessful. He had therefore approached several commercial firms in an attempt to get them to carry out the separations, but they had been unwilling to do so. He therefore proposed that as the best possible alternative in the time available he should try to provide separate fractions from K_4 and KX_{6-8} by chromatography carried out in his existing laboratory. He hoped to have completed this stage by the end of February and it was agreed that he should hold a discussion with Professor Squire and Dr. Woodhouse in early March to work out details for the next stage of the work at Birmingham. He confirmed that he would be able to provide the necessary 12 fractions by that time.

It was noted that Professor Morton would include in the samples for testing a blend of eluates as well as original material in an attempt to account for the apparent loss of carcinogenicity noted at the previous meeting.

In view of the results on the spinning band column, Professor Morton said that he was now building the equivalent of a molecular still - a 'spinning brush' column - which was capable of operating at pressures down to 0.2 mm, which enabled the work to be carried into a boiling range which had not hitherto been looked at. He was proposing to supply Dr. Carruthers with specimens of K_4S_9 and K_4X_9 . He also reported that he had received \$500 from I.C.I. for the installation of a Vapour Phase Chromatographic Column to work at temperatures of about 300°C, which would enable separations to be made in the middle range of residues.

5. Proposal for including in the Birmingham tests a single specimen of cutting oil,
reported to be non-carcinogenic.

Professor Squire said that he had heard of the oil prepared by Manchester Oil Refineries which according to the Twort Formula was said to be non-carcinogenic, through an informal letter from Dr. Schilling. It was proposed that a sample of this oil might be included in the 1957 to 1958 tests.

After discussion it was agreed that the inclusion of such an oil might involve the Council in difficulties with other commercial firms producing similar oils, and it was felt that before the proposal could be considered further a case must be made out for doing so as part of the normal scientific programme sponsored by the Committee. Dr. Norton pointed out that there were precedents for the Council undertaking such tests on the products of commercial firms, but that they were always done on the

condition that the results obtained would not be the exclusive property of the individual firm and that they could be freely published. An alternative method whereby the oil in question might be tested would be for a request to this effect to be sent to the Council through H.M. Inspectorate of Factories.

Professor Squire said that he would consider the matter further in view of these procedural difficulties and it was agreed to defer consideration of the matter until he had done so.

7. Date of next meeting

It was tentatively suggested that this might be in July 1957, but that a final decision would have to be deferred until the meeting between Professor Morton, Professor Squire and Dr. Woodhouse proposed for the beginning of March (Min.4) had taken place.

ESSO RESEARCH AND ENGINEERING COMPANY

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P. O. Box 121, LINDEN, N. J.

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CHIEF CLINICAL RESEARCH PHYSICIAN

Copy From D. V. Stroop For Information Of
Members Of Medical Advisory Committee
3/18/57

March 11, 1957

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

Dear Mr. Stroop:

I am sending you copies of all the minutes of the Subcommittee on Carcinogenicity for the years 1955-1956 in response to your request of March 6, 1957. In addition, I am sending you some information obtained from the Medical Research Council in Britain which probably ought to be duplicated and distributed, at least to the Subcommittee members and to the group at Kettering Laboratory.

Finally, I do not believe there is any rush to reproduce the British report which you mentioned in your letter and I am sure you can do this at your leisure.

Sincerely yours,

R. E. Eckardt
R. E. ECKARDT, M. D. *gh*

REK:cjh

- Attach. - Minutes of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council. MRC.57/176 CAMO.Min.21.
- Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated April 25, 1955.
 - Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated October 31, 1955.
 - Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee dated April 23, 1956.
 - Minutes of the Subcommittee on Carcinogenicity for their meeting on September 6, 1956.
 - Proposed Report of the Subcommittee on Carcinogenicity to the Medical Advisory Committee for its Meeting on November 12, 1956, dated November 5, 1956.

Dictated, but not read

MEDICAL RESEARCH COUNCIL



"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.57/176
CAMO.Min.21

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the twenty-first meeting held at 38 Old Queen Street, London, S.W.1, on Tuesday, 18th December, 1956 at 2.30 p.m.

Present:- Professor T. Ferguson (Chairman), Col. S.J.M. Auld, Dr. J.W. Cook, Dr. I. Hieger, Dr. J.O. Irwin, Professor F. Morton, Professor R.D. Passey, Professor J.R. Squire, Dr. D.L. Woodhouse, with Dr. R.C. Norton (Secretary).

Attended: Dr. Philip J. King, and Dr. W. Carruthers.

An apology for absence was received from Professor H.N. Green.

1. Minutes

Dr. Irwin suggested that the Minutes of the previous meeting might be amended by re-numbering the paragraphs under item 3, "Progress Reports", so that they agreed with the numbering of the corresponding items of the agenda for that meeting. The numbering of the paragraphs under min.3, of the twentieth meeting should therefore be as follows:-

- Min.3.(a) by Dr. W. Carruthers and Dr. J.W. Cook (MRC.56/543, CAMO.56/4) to be re-numbered 3.(i)(a),
- Min.3.(b) by Professor F. Morton (CAMO.56/7) to be re-numbered 3.(i)(b),
- Min.3.(c) by Dr. D.L. Woodhouse - Progress Report No.XVI (May 1956), (MRC.56/542, CAMO.56/3) to be re-numbered 3.(ii)(a),
- Min.3.(d) Data tables on mineral oil fractions, submitted by Dr. D.L. Woodhouse (CAMO.56/3) to be included in 3.(ii)(a),
- Min.3.(e) Experiments with mice at Leeds (MRC.56/548, CAMO.56/5 and MRC.56/549, CAMO.56/6 to be re-numbered 3.(ii)(b) and (c).

It was further suggested that in the first line of paragraph 3.(o) in the Minutes (before amendment) of the previous meeting the word 'importance' should be substituted for 'significance'. The beginning of this paragraph should therefore read "Dr. Irwin said that a point of great importance emerging from the report was the failure"

The Committee agreed to these amendments and the Minutes of the twentieth meeting were then signed by the Chairman.

2. Matters arising

Professor Squire said that he had now heard from Dr. W.E. Smith (Min.2 of the 20th meeting) who was anxious to carry out further tests by his rapid screening method of oil samples already tested under the Committee's programme. After discussion it was agreed to send Dr. Smith further samples, although any results which he might obtain would not be likely to be of great assistance in the present phase of the Committee's programme.

In connection Col. Auld suggested that it was desirable to build up a more direct association with American workers in the field and it was agreed that he and Professor Morton should investigate further methods of doing this.

3. Progress Reports

- (a) No. XVII, November 1956 (Birmingham), by Dr. D.L. Woodhouse, (MRC.56/946, CAMO.56/9).

Dr. Woodhouse gave some further figures for the incidence of tumours at 42 weeks in his series of rabbit tests. These were for each fraction shown in Table I:-

(A)	2	(H)	0	(O)	7
(B)	0	(I)	0	(P)	7
(C)	2	(J)	1	(Q)	7
(D)	1	(K)	0	(R)	8
(E)	1	(L)	1	(S)	5
(F)	3	(M)	1	(T)	14
(G)	0	(N)	0	(U)	8

He also said that in Table II 'Mouse tests', fraction (T) D(2) should read D($\frac{1}{2}$) and that fraction (U) D($\frac{1}{2}$) should read D($\frac{1}{4}$).

Since fractions A-E (with parent fraction L) and F-H (with parent fraction M) were more active than I-K (with parent fraction N), these results showed that chromatography on alumina is a promising method of separation, the active substance(s) being eluted by petroleum ether (A to E + L), though some remained for subsequent elution with benzene (F to H + M).

- (b) The 1955-56 Experiments with Mice at Leeds, by Dr. J.C. Irwin, (MRC.56/965, CAMO.56/12).

Dr. Irwin pointed out that with the standard D₂ at Leeds, tumours had occurred much later than expected. There also appeared to be a small, but genuine difference between the potency of the L and K series.

It was noted that in the second sentence of the last paragraph of the first page of this paper, the first "D₂" should read "D $\frac{1}{2}$ " so that the whole sentence should read: "However, D $\frac{1}{2}$ at Leeds in 1955-56 gave a lower response than D $\frac{1}{2}$ at Birmingham in 1953-4 and D₂ at Leeds gave a much lower response than D₂ at Birmingham in the same year."

Commenting on the statistical analysis of the 1955-56 experiments with rabbits at Leeds (MRC.56/969, CAMO.56/13), Dr. Irwin drew attention to the unusual number of tumourless deaths, and, referring to the standards, he said that D₂ appeared to be normal but that the results with D $\frac{1}{2}$ had been unusual. Again the L series appeared to be slightly more carcinogenic than the corresponding K's.

In both papers the fractions referred to as L₄SR and K₄SR should be L₄SP and K₄SP respectively, and when referred to in the text the word 'raffinate' should be substituted for 'residue'.>

- (c) Report by Dr. W. Carruthers, Dr. J.W. Cook and Mr. A.G. Douglas, (MRC.56/958, CAMO.56/11).

Dr. Carruthers introduced his Report by remarking that attempts to isolate homogeneous compounds from the Kuwait picrate-forming fractions were continuing. A synthetic programme based on the results so far obtained was about to be started.

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The 6:7-benzothionaphthene derivative discussed in his Report was the first example of this particular ring system to be detected in mineral oil.

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It now seemed desirable to do tests for carcinogenicity on some of the pure compounds isolated; it was agreed to include several in the 1957-58 Birmingham tests if adequate amounts could be provided.

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or each

4. Preparation of Kuwait fractions for 1957 to 1958 tests.
(P.O. 56/956, C.A.O. 56/10).

Professor Morton said that he had tried to find suitable areas in which to carry out the picrate separations with his own resources, but that he had been unsuccessful. He had therefore approached several commercial firms in an attempt to get them to carry out the separations, but they had been unwilling to do so. He therefore proposed that as the best possible alternative in the time available he should try to provide separate fractions from K₆ and KX₆₋₈ by chromatography carried out in his existing laboratory. He hoped to have completed this stage by the end of February and it was agreed that he should hold a discussion with Professor Squire and Dr. Woodhouse in early March to work out details for the next stage of the work at Birmingham. He confirmed that he would be able to provide the necessary 12 fractions by that time.

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It was noted that Professor Morton would include in the samples for testing a blend of eluates as well as original material in an attempt to account for the apparent loss of carcinogenicity noted at the previous meeting.

Irwin,

In view of the results on the spinning band column, Professor Morton said that he was now building the equivalent of a molecular still - a 'spinning brush' column - which was capable of operating at pressures down to 0.2 mm, which enabled the work to be carried into a boiling range which had not hitherto been looked at. He was proposing to supply Dr. Carruthers with specimens of K₆S₉ and K₆X₉. He also reported that he had received £500 from I.C.I for the installation of a Vapour Phase Chromatographic Column to work at temperatures of about 300°C, which would enable separations to be made in the middle range of residues.

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5. Proposal for including in the Birmingham tests a single specimen of cutting oil, reported to be non-carcinogenic.

Professor Squire said that he had heard of the oil prepared by Manchester Oil Refineries which according to the Twort Formula was said to be non-carcinogenic, through an informal letter from Dr. Schilling. It was proposed that a sample of this oil might be included in the 1957 to 1958 tests.

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After discussion it was agreed that the inclusion of such an oil might involve the Council in difficulties with other commercial firms producing similar oils, and it was felt that before the proposal could be considered further a case must be made out for doing so as part of the normal scientific programme sponsored by the Committee. Dr. Morton pointed out that there were precedents for the Council undertaking such tests on the products of commercial firms, but that they were always done on the condition that the results obtained would not be the exclusive property of the individual firm and that they could be freely published. An alternative method whereby the oil in question might be tested would be for a request to this effect to be sent to the Council through H.M. Inspectorate of Factories.

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Professor Squire said that he would consider the matter further in view of these procedural difficulties and it was agreed to defer consideration of the matter until he had done so.

7. Date of next meeting

It was tentatively suggested that this might be in July 1957, but that a final decision would have to be deferred until the meeting between Professor Morton, Professor Squire and Dr. Woodhouse proposed for the beginning of March (Min.4) had taken place.

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ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 45, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH. D., M. D.
DIRECTOR

BERTRAND E. BENNISON, M. D.
ASSISTANT DIRECTOR

N. V. HENDRICKS, CH. E.
HEAD INDUSTRIAL HYGIENIST

MORACE W. GERARDE, PH. D., M. D.
HEAD TOXICOLOGIST

June 21, 1957

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

Dear Mr. Stroop:

I am attaching some information forwarded
to me from Dr. H. H. Newquist by Mr. A. E. Dooley.
Perhaps you would like to have this duplicated and
distributed to the members of the Subcommittee on
Carcinogenicity and also to Dr. Horton and Dr. Kahoe.

Sincerely yours,

R. E. Eckardt
R. E. ECKARDT, M. D. *ejh*

REE:cjh

Attach. - Institute of Petroleum. Research Group No. 2.
Minutes of Meeting No. 17 held at 26, Portland
Place, W.I. on the 12.3.57.

Copy From D. V. Stroop For Information Of Members Of
Subcommittee on Carcinogenicity 6/25/57

RESEARCH GROUP NO. 2.

Minutes of Meeting No. 17 held at 26, Portland
Place, W.I. on the 12.3.57.

ATTENDANCE

IN THE CHAIR:

F. Morton

MEMBERS:

S.J.M. Auld
G.A. Dickins
J.N. Haresnape
C.F. McCue
H.W. Stevenson

APOLOGIES FOR ABSENCE:

B.G. Banks
J.W. Barrett
J.W. Cook
A. McLean

SECRETARY:

E. Herbert

1. MINUTES OF MEETING NO. 16. 23.10.56:

These were signed as correct, subject to the addition of "pages 146-155" "The Transactions of the Institution of Chemical Engineers" Vol. 34 No. 2. (See Minute No. 7) and the alterations of "Research No. 2 Committee" to "Research Group No. 2."

2. MATTERS ARISING:

(a) The Chairman mentioned that the paper for publication in the IP Journal is continuation of that presented at the World Petroleum Congress had been prepared (See Minute 3 of Meeting 15).

(b) The disappearance of activity referred to by Dr. Irwin was being studied the present series of tests at Birmingham (See Minute No. 5 and Minutes No. 4 para. 2 of M.R.C. Minutes M.R.C.57/176 and C.A.M.O. Minute 21).

3. CONSIDERATION OF FINANCE FOR FUTURE PROGRAMME:

The Chairman's memorandum and the report on the Constitution and Biologic Activity of Mineral Oils which had been circulated was noted.

The Chairman mentioned that there was no great urgency for additional financial support as the I.C.I. and the Salter Research Institute had made contributions of £500 each and the M.R.C. Current Budget included a grant similar to that made last year. It appeared that there was sufficient finance available to complete the present work. During general discussion, it was evident that development of methods was of more interest to industry than actual results and that a biological testing unit for use of industry would be welcome. The Chairman undertook to prepare a memorandum of suggestions for future work which would include (a) programme for Middle Distillate and (b) Oxidation.

Members were asked to write their comments to the Chairman after consideration of his memorandum so that recommendations which were likely to receive industry's financial support could be forwarded, through the Research Committee, to IP Council early in 1958.

4. DATE OF NEXT MEETING:

To be arranged by the Chairman.

May, 1957. JB.

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. BOX 45, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH. D., M. D.
DIRECTOR

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ASSISTANT DIRECTOR

N. V. HENDRICKS, CH. E.
HEAD INDUSTRIAL HYGIENIST

HORACE W. GERARDE, PH. D., M. D.
HEAD TOXICOLOGIST

June 21, 1957

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

Dear Mr. Stroop:

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Perhaps you would like to have this duplicated and
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Carcinogenicity and also to Dr. Horton and Dr. Kehoe.

Sincerely yours,

R. E. Eckardt
R. E. ECKARDT, M. D. *cjh*

REE:cjh

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Minutes of Meeting No. 17 held at 26, Portland
Place, W.I. on the 12.3.57.

Copy From D. V. Stroop For Information Of Members Of
Subcommittee on Carcinogenicity 6/26/57

RESEARCH GROUP NO. 2.

Minutes of Meeting No. 17 held at 26, Portland
Place, W.I. on the 12.3.57.

ATTENDANCE

IN THE CHAIR: F. Horton

MEMBERS: S.J.M. Auld
G... Dickins
J.N. Haresnapo
C.F. McCue
H.W. Stevenson

APOLOGIES FOR ABSENCE: B.G. Banks
J.W. Barrett
J.W. Cook
A. McLean

SECRETARY: E. Herbert

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Members were asked to write their comments to the Chairman after consideration of his memorandum so that recommendations which were likely to receive industry's financial support could be forwarded, through the Research Committee, to IP Council early in 1958.

1. DATE OF NEXT MEETING:

To be arranged by the Chairman.

May, 1957. JB.

June 25, 1957

ALL MAIL

Dr. E. C. Burton, Secretary
Committee on the Cardiovascular Action of Mineral Oils
National Research Council
38 Old Queen Street
Washington, London, E.C. 1, ENGLAND

Dear Dr. Burton:

We regret circumstances have delayed our transmittal to you of several reports, as follows:

- 1) Report of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, dated April 25, 1957.
- 2) Report of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, dated October 3, 1956.
- 3) Report of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, dated April 25, 1957.
- 4) Minutes of Meeting of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, held September 6, 1956.
- 5) Report of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, dated November 3, 1956.
- 6) Report of Subcommittee on Cardiovascularity of AVE Mineral Activity Committee, dated April 25, 1957.
- 7) Interim Report - AVE Research Project 22-1, October 1, 1956.
- 8) Interim Report - AVE Research Project 22-1, November 1, 1956.
- 9) Interim Report - AVE Research Project 22-1, April 25, 1957.

These reports are being mailed to you under separate cover. We hope they will be delivered in good order.

If you or your colleagues desire additional information, please let us know.

Very truly yours,

Respectfully,

cc: E. E. Schmidt, M. D.
Professor Thomas Ferguson
Col. S. J. E. Auld
L. E. Curtis, M. D.
(without enclosure)

~~CC~~ WO/E R E Eckardt M.D.

CC WO/E Professor Thomas Ferguson - ^{AIR MAIL} Univ of Glasgow -

CC WO/E Col. S. J. M. Auld ^{AIR MAIL} [get address from his letter]

CC WO/E L. E. Curtis M.D. ^{AIR MAIL}

Dr. R. C. Norton, Secretary

Committee on the Carcinogenic Action of Mineral Oils

Medical Research Council

38 Old Queen Street

Westminster, London, S.W.1.

Dear Dr. Norton

We regret circumstances have delayed our transmittal to you of several reports as follows:

- ✓ 1) Report of Subcommittee on Carcinogenicity of API Medical Advisory Committee dated April 25 1955
- ✓ 2) Report of Subcommittee on Carcinogenicity of API Medical Advisory Committee dated October 31 1955
- ✓ 3) Report of Subcommittee on Carcinogenicity of API Medical Advisory Committee dated April 23 1956
- 4) Minutes of Meeting of Subcommittee on Carcinogenicity of API Medical Advisory Committee held Sept 6 1956

API 06376

^{Handing D}
^{MAC Minutes} ✓ 5) Report of Subcommittee on Carcinogenicity of API Medical Advisory Committee dated November 5 1956

^{Handing G to}
^{MAC Minutes} ✓ 6) Report of Subcommittee on Carcinogenicity of API Medical Advisory Committee dated April 20 1957

7) Interim Report - API Research Project MC-1. Oct 1 1955

- 8) Interim Report - API Research Project MC-1 November
- 9) Interim Report - API Research Project MC-1 April 10

These reports are being mailed to you under separate cover. We hope they will be delivered in good order.

If you or your colleagues desire additional information please let me know

J by
D/2

This is not
complete - There should be
a appendix with it.
see if you have copies
attached to HSC
minutes for April 1955

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 benzantracenes, 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

MAC MURPHY NOV 12 '55

PROPOSED REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY
TO THE MEDICAL ADVISORY COMMITTEE
for its meeting on November 12, 1955
to be held at the Conrad Hilton Hotel in Chicago

Recent newspaper publicity concerning the carcinogenicity of waxes which may be used on milk cartons, have lead the Subcommittee on Carcinogenicity to consider it advisable to conduct biological testing which will help establish the non-carcinogenicity of waxes. In addition, it is the belief of the Subcommittee on Carcinogenicity that waxes, other than milk carton waxes which might also be used in the food industry, should also be included in this testing program in order to develop a more complete picture of the situation concerning waxes. In view of this, the subcommittee recommends the following courses of action to the Medical Advisory Committee:

- 1) A survey of the types of waxes which are used in the food industry should be undertaken in order that a complete understanding of the types of waxes which come in contact with food can be had by the subcommittee.
- 2) Following the above survey a selection of samples from these waxes should be made in order to provide a potential range of carcinogenic activity in the waxes sampled, which will be determined by the following factors:

- a) The crude source.
 - b) The oil content.
 - c) The degree and type
of refining.
- 3) The available biological methods for carcinogenic testing of materials, comparable to waxes which find their way into food usage, should be reviewed and from them a selection of biological methods to be used in the testing program should be made, but these should probably include:
- a) Feeding.
 - b) Skin applications.
- 4) The subcommittee has received from Dr. Kahoe, at the Kettering Laboratory, a proposal for such studies. However, the subcommittee does not believe that Dr. Kahoe's proposal is completely realistic with the problem being faced concerning wax carcinogenicity and, therefore, requests approval of the Medical Advisory Committee to survey other toxicological laboratories for their proposals concerning carcinogenicity, their facilities for conducting such tests and their budget estimates on the costs of such tests. Such laboratories to be surveyed

4) would include, but not necessarily be limited to, the following:

- a) The Hazleton Laboratories.
- b) The Institute of Industrial Medicine of New York University.
- c) The Department of Pharmacology of the University of Miami Medical School, under Dr. William Deichmann.
- d) The laboratories of Dr. Phillip Shubik of the Chicago Medical School.
- e) Industrial Bio-Test Laboratories, Incorporated, under the direction of Dr. Joseph Colandra in Chicago.
- f) Stanford Research Institute, Department of Biology, M. V. Velde, M. D., and G. H. Newall, Ph.D., directors.
- g) UCLA, Department of Medicine, Dr. F. Bryan, director.

5) The Subcommittee on Carcinogenicity recommends that the Medical Advisory Committee appropriate funds in the amount of \$50,000 to cover the costs of such carcinogenic testing of waxes, at a laboratory to be determined at a later date. In order that funds can be available beginning July 1, 1957

- 5) for such carcinogenic testing, it is proposed that this \$50,000 be set aside, but not definitely earmarked at this time, for these studies. The Subcommittee believes that an equivalent amount of money will be needed each year for the next 3-4 years in order to study the problem adequately.
- 6) The Subcommittee recommends that a letter similar to the attached be sent by the proper authority of the API.

RESPECTFULLY SUBMITTED,

Members of the Subcommittee on Carcinogenicity

R. E. Bekardt, M. D. - Chairman

E. W. Adams

C. H. Hime, M. D.

E. K. Linder, M. D.

R. C. Mithoff

M. H. Newquist, M. D.

A. C. Pabst

R. E. Bekardt, M. D./eja
Chairman, Subcommittee on Carcinogenicity
November 5, 1956

Attachment - Proposed letter to Leroy E. Burney, Surgeon-General, September 13, 1956

use appendix E - MAC minutes
April 1957



Socony Mobil Oil Company, Inc.

150 EAST 42ND STREET NEW YORK 17, N. Y.

August 20, 1977

Subcommittee on Cardiovascularity

Dr. R. E. Roberts, Chairman
Dr. E. V. Adams
Dr. C. E. Kins

Dr. E. E. Lindsay
Mr. E. G. Mithoff
Dr. M. E. Neupigist

U. S. PHARMACOPEIA: SPECIFICATIONS

I have just noticed the following announcement in a recent issue of
CHEMICAL AND ENGINEERING NEWS:

UNP REVISION

The revision program leading to publication of the 16th
revision of the U. S. Pharmacopoeia has begun. Selection
of drugs to be included is going on and the list is well
under way. A call will be issued shortly for volunteers
to read UNP proof. Meanwhile, constructive suggestions
for changes in the present UNP general tests chapters
are invited. They should be addressed to the UNP
headquarters at 45 Park Avenue, New York 16, New York.

It seems like this would be a good opportunity to investigate the possibility
of revising UNP requirements for paraffin. As you know, present requirements
are obsolete and do not list tests presently used by the industry for main-
taining quality.

In our opinion, the specifications could be considerably improved by
changing the melting point range, requiring an ASTM color test, and oil
content. Also, eliminating the UNP acid color test.

Sincerely yours,

A. C. Fabst
Industrial Hygienist
National Department

API 06386

COPY

COPY

S o c c n y M o b i l O i l C o m p a n y, I n c.
150 East 42nd Street, New York 17, N. Y.
August 20, 1957

Subcommittee on Carcinogenicity

Dr. R. E. Eckardt, Chairman	Dr. E. K. Linder
Mr. E. W. Adams	Mr. R. C. Mithoff
Dr. C. H. Hine	Dr. M. N. Newquist

U. S. PHARMACOPEIA REVISION

I have just noticed the following announcement in a recent issue of
CHEMICAL AND ENGINEERING NEWS:

USP REVISION

The revision program leading to publication of the 16th revision of the U. S. Pharmacopeia has begun. Selection of drugs to be included is going on and the list is well under way. A call will be issued shortly for volunteers to read USP proof. Meanwhile, constructive suggestions for changes in the present USP general tests chapters are invited. They should be addressed to the USP headquarters at 46 Park Avenue, New York 16, New York.

It seems like this would be a good opportunity to investigate the possibility of revising USP requirements for paraffin. As you know, present requirements are archaic and do not list tests presently used by the industry for maintaining quality.

In our opinion, the specifications could be considerably improved by changing the melting point range, requiring an ASTM color test, and oil content. Also, eliminating the USP acid color test.

Sincerely yours,

/s/ A. C. Pabst

A. C. Pabst
Industrial Hygienist
Medical Department

ACP:lgp

cc: E. G. Mattocks

API 06387

Sub on Carcinogenicity

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. Box 43, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH.D., M.D.
DIRECTOR

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ASSISTANT DIRECTOR

V. V. HENDRICKS, CH.E.
HEAD INDUSTRIAL HYGIENIST

MORACE W. GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST

October 1, 1957

Dr. R. A. Kehoe
University of Cincinnati
Lettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

I would greatly appreciate it if you could arrange to send a copy of Dr. Horton's Interim Report dated September 26, 1957 to each member of the Medical Advisory Committee. This could probably be arranged through Mr. E. O. Mattheck's office of the API, if you could provide him with the master stencils of this report.

I am sending you three copies of the minutes of our meeting in Chicago. I would be very interested in your comments or criticisms of these minutes, as well as those of Dr. Horton and Dr. Phair. Most important, however, it would be of great interest to me as Chairman of the Subcommittee, to learn of your response and/or reaction to the suggestion that you be retained by the MAC as a consultant following the completion of the work with Dr. Horton. Your answer to this will of course, in great part, influence the ultimate recommendations of our Subcommittee to the MAC. It is our hope that you will look with favor upon this suggestion if such a proposal is formally made to you by the MAC, since we believe that you could bring valuable advice and guidance to the MAC in years to come. Certainly we have found that Prof. Drinker has provided us with this advice and guidance and I would anticipate that you could do the same on a slightly different standpoint.

Unfortunately we did not have time in Chicago to discuss this with you prior to our departure, but it was the consensus of the Subcommittee that they would like to know your feelings towards such a possible future arrangement to guide them in making their advice to the MAC. I would therefore greatly appreciate it if you would let me have your comments concerning this.

Very truly yours,

R. E. ECKARDT, M. D.

API 06388

RHE/cjh

Enc. - Minutes of the Subcommittee on Carcinogenicity Held at the Blackstone Hotel in Chicago Friday, September 27, 1957 (October 1, 1957). (3)

cc: Mr. E. O. Mattheck

MINUTES OF THE MEETING OF THE SUBCOMMITTEE ON CARCINOGENICITY

Held at the Blackstone Hotel, Chicago

Friday, September 27, 1957

A meeting of the Subcommittee on Carcinogenicity of the Medical Advisory Committee of the American Petroleum Institute was convened in Dr. R. E. Eckardt's suite at the Blackstone Hotel at 9:30 a.m. on September 27, 1957. The full Subcommittee was in attendance, plus Mr. Paul Halley of the Standard Oil Company (Indiana) as a guest.

The Subcommittee discussed preliminarily the work at the Kettering Laboratory and wishes to point out that work now being performed by Dr. Horton is far more fundamental in nature than was originally anticipated by the Subcommittee. For this reason the Subcommittee believes that its decision to discontinue sponsoring this research under its direction has been a correct one, and the Subcommittee plans to continue with the recommendation that this work be discontinued as of July 1, 1959. However, the Subcommittee does wish to point out that there are fundamental aspects in the petroleum chemistry now being conducted by Dr. Horton, which might warrant a continuation of this type of research, either at Kettering Laboratory or some other laboratory, under the sponsorship of the Committee for Fundamental Research of the API. The methodology now being pursued by Dr. Horton is primarily chemical in nature rather than biological and might therefore well be considered by the Committee for Fundamental Research. In addition, the Subcommittee discussed in a preliminary fashion, the possibility of suggesting to the MAC that Dr. Kehoe be put on a retainer fee at the conclusion of the work at the Kettering Laboratory on July 1, 1959, in order that Dr. Kehoe might attend all meetings of the MAC and offer us his advice and guidance in some of the problems which the petroleum industry is facing now and might face in the future. It is the Subcommittee's belief that Dr. Drinker's attendance at and participation in the affairs of the MAC have been highly worthwhile and if Dr. Kehoe were willing to accept such a retainer agreement, his participation in the affairs of the MAC would also be worthwhile.

At 11 a.m. the group was joined by Dr. R. A. Kehoe, Dr. A. W. Horton and Dr. J. J. Phair of the Kettering Laboratory. Dr. Horton began by presenting a progress report of the work at the Kettering Laboratory during the past five months. He indicated that all the experimental work for the past five months has been in the field of analytical methods. He divided this work into two sections: that work done on carcinogens and that work done on accelerators.

Carcinogens

To date the work of the Kettering Laboratory suggests that the most significant carcinogens in petroleum oils are polycyclic aromatic compounds, most hydrocarbons.

He emphasized the difference in concept between the basic carcinogenic potency of an oil, which is that due to the presence of carcinogens vs. the actual carcinogenic potential of the oil, which is the carcinogenic activity resulting from both the presence of carcinogens and of accelerators and inhibitors. He indicated that certain data developed at the Kettering Laboratory have suggested that some sulfur compounds may act as accelerators but that they only do so in the presence of other accelerators. Thus, if there are sulfur-containing accelerators they would not be active as accelerators in the absence of hydrocarbon accelerators. Present data at the Kettering Laboratory indicated that the accelerators are probably long-chained hydrocarbons.

Suggestive evidence at the Kettering Laboratory indicates that there may be inhibitors present in petroleum oils. These inhibitors do not inhibit the carcinogens, but rather inhibit only the accelerators. This evidence has arisen from some work done by the Kettering Laboratory with two different white mineral oils which were used as diluents of accelerators. It is important to emphasize that these inhibitors are inhibitors of the accelerating action, rather than inhibitors of the basic carcinogenic activity due to the carcinogens.

In the past five months almost all of the work done by the Kettering Laboratory on carcinogens has been done on what they have previously identified in the April 1957 report, as 3 1/2-ring aromatics. These consist of pyrenes, fluoranthrenes, cyclopentanophenanthrenes, and benzfluorenes. Dr. Horton believes that these 3 1/2-ring aromatics are probably the most important class of carcinogens in most petroleum oils.

The work has been done principally on API-8 and fractions of API-8, as diagrammatically indicated in the attached diagram. Descriptively, API-8 was subjected to a theoretical 80 plate distillation. Examination of the 660°F fraction suggested that only 0.001% of carcinogens was present in this fraction but that it contained a very high concentration of accelerators. This evidence is supported in part by the fact that tumors appear rapidly but only at a very low total incidence of tumors.

Following the work on this fraction, Dr. Horton next concentrated his attention on three fractions which boiled in the range of 730°F to 760°F. These fractions contain very little accelerators. These three fractions were subjected to maleic anhydride treatment in order to remove the anthracenes and their derivatives. Testing suggested that .03 out of .21 of the carcinogens present in this fraction was due to carcinogens of this type. Roughly, therefore, 1/7 of the basic carcinogenic activity of these three fractions is due to anthracenes and their derivatives. The raffinate from the maleic anhydride treatment of these three fractions was next combined and chromatographed, and two fractions were obtained, one of which contained the benzfluorenes and experimental work has suggested

that these are unimportant in the total carcinogenicity of these three fractions. The other fraction contains the remaining three classes of carcinogens, namely, pyrenes (and their methyl and dimethyl derivatives) cyclopentanophenanthrenes, and fluoranthrenes (principally the dimethyl derivatives). At the present time, Dr. Horton is working on the separation of these three types of aromatic hydrocarbons in the raffinate from the maleic anhydride treatment of the 730°F to 760°F cuts of API-8. This is being done by liquid-liquid partition between 99% sulfuric acid and iso-octane at -30°F. Dr. Horton says that this treatment will separate the pyrenes from the other two classes of compounds. The raffinate of this extraction then is chromatographed and treated with picric acid which may lead to the separation of the cyclopentanophenanthrenes from the fluoranthrenes.

Dr. Horton did indicate that of seven oils carried through the maleic anhydride extraction step, only one was found to have much benzanthrane which contributed to carcinogenic activity. This one oil was from a coker gas oil (API-33) in which 7/11 of the basic carcinogenicity was due to benzanthrane-type compounds. This contrasted with other types of oils in which only 1/7 of the basic carcinogenicity is due to this type of compound.

In work which Dr. Horton did with a thermally cracked, cat cracked, oil he found that the benzpyrene and 4-ring carcinogens almost doubled in concentration but the activity of the oil decreased. This result might be due to the destruction of accelerators or to the destruction of the 3 1/2-ring carcinogens. It is Dr. Horton's belief that possibly this reduction in activity is most likely due to the destruction of the accelerators rather than to the destruction of the 3 1/2-ring carcinogens.

Accelerators

At the present time, Dr. Horton is following clues which have been provided for the presence of inhibition of accelerators in petroleum oils. He believes that these inhibitors probably fall into a class of compounds referred to as polycycloparaffins. These have essentially the same structure as the aromatic carcinogens except that they are saturated compounds. In partial support of this, Dr. Horton pointed out that Zechmeister and Kotin reported about a year ago in SCIENCE, that hydrogenated aromatics inhibit sarcoma production when injected subcutaneously. However, they used ethyl laurate as a solvent for their carcinogens and ethyl laurate would be expected to be a highly accelerating solvent. Therefore it was not clear from their work whether they were inhibiting carcinogens or inhibiting accelerators. It is Dr. Horton's belief that the inhibition they observed is most likely the inhibition of the ethyl laurate as an accelerator rather than true inhibition of the carcinogens.

In discussing the so-called preconditioning of an animal by accelerators, it is Dr. Horton's belief that this occurs through an accelerator "setting up" the animal for other accelerators. In other words, preconditioning does not precondition the animal for carcinogenic activity but only for accelerating activity. Support for this belief is contained in the fact that if the animal is painted with an oil essentially free of accelerators following preconditioning it is not possible to demonstrate the preconditioning effects, but if an oil high in accelerators is used after the preconditioning treatment, the preconditioning effect can be demonstrated.

The white oils being studied by Dr. Horton for so-called inhibiting effects (principally API-80) are free of n-paraffins. They contain some iso-paraffins and condensed cycloalkanes which represent the greatest amount of material present. The suggestion at the moment, therefore, is that these condensed cycloalkanes are inhibitors of accelerators.

In an attempt to separate these inhibitors from other compounds present in the white oils, Dr. Horton is going to use distillation, thiourea separation, and liquid thermal diffusion. In addition, he may possibly consider the use of molecular sieves.

Dr. Horton submitted his Interim Report on his work dated September 26, 1957 which was distributed to the Subcommittee at this meeting.

Epidemiology

Next, Dr. J. J. Phair gave a progress report on the epidemiological work. Dr. Phair indicated that he had completed the coding and punching of the cases. In this process he felt it necessary to discard some cases since the information contained on the report was inadequate. Hence, the total number of cases reported in his final report will not be the same as in previous reports from Dr. Phair. At the moment, the status of this final report is that the introduction, the objectives, and so forth have already been written up and the data tables are now being prepared and the comparisons and correlations will be made. It is hoped by both Dr. Phair and Dr. Kehoe that this final report can be made available to the Subcommittee by the first of the year.

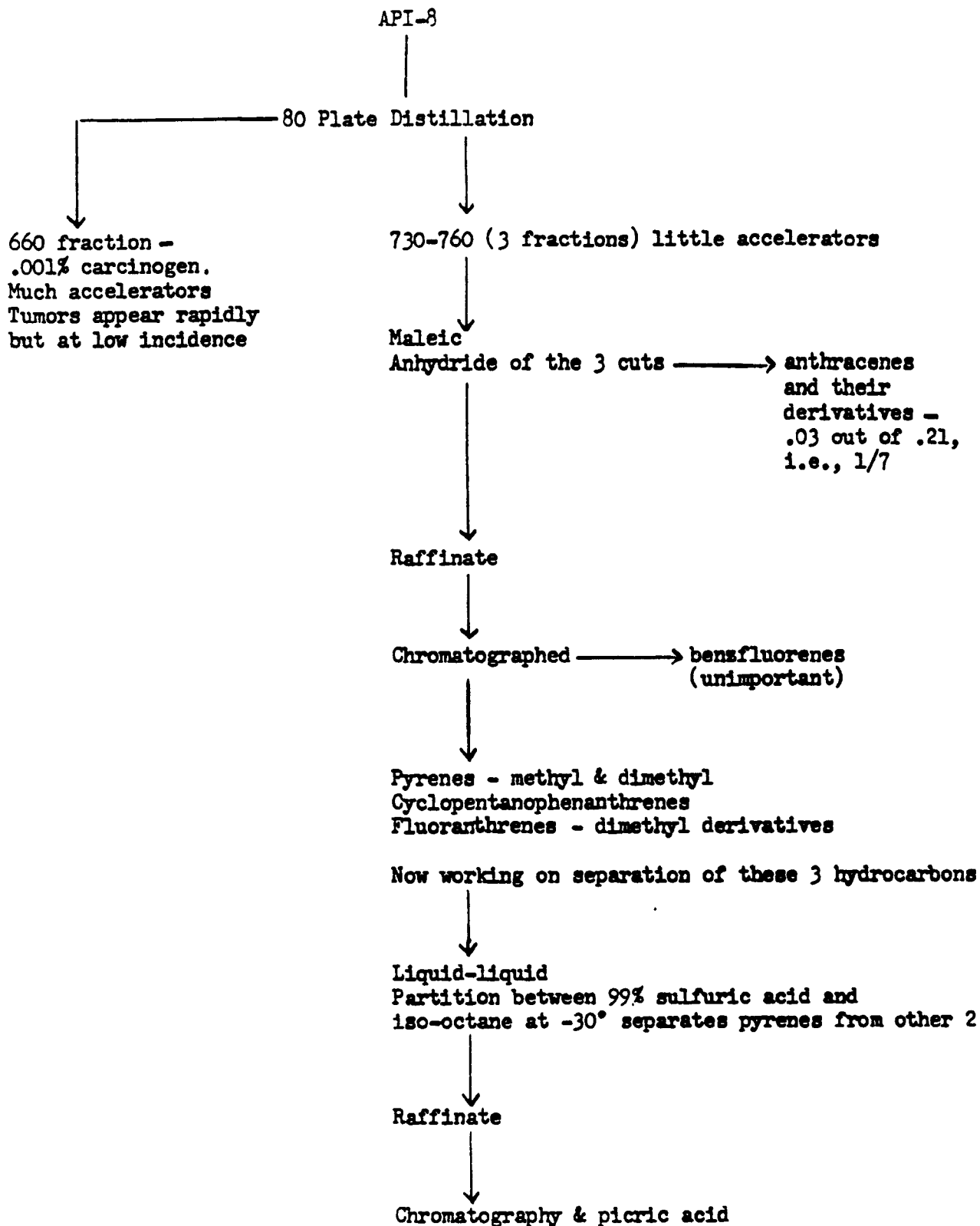
In Dr. Phair's work he pointed out that in the cases occurring after 1950, 28% of the tumors have been found to be skin tumors, whereas, only 15.3% of the cases prior to 1950 were skin tumors. In general population figures available, 16.6% tumors are skin tumors. Whether this increase in the relative number of skin tumors in the post-1950 group of cases is significant, is not now known. Dr. Phair is at present making age, geographic location, primary site and occupational-group breakdowns of the cases which he analyzed.

Following Dr. Phair's presentation, the Subcommittee discussed in private with Dr. Kehoe certain phases of the relationships between the Subcommittee and the Kettering Laboratory and it was concluded that these relationships remain on a friendly, amiable, and professional level.

The Subcommittee meeting broke up at approximately 4 p.m. on September 27, 1957, without having set a date for its next meeting.

R. E. ECKARDT, M. D./cjh
Chairman, Subcommittee on Carcinogenicity
October 1, 1957

Attachment



MINUTES OF THE MEETING OF THE SUBCOMMITTEE ON CARCINOGENICITY

Held in the Conrad Hilton Hotel in Chicago

Wednesday, November 13, 1957

The Subcommittee on Carcinogenicity held a meeting at the Conrad Hilton Hotel in Chicago at 9 a.m. on Wednesday, November 13, 1957. The following members were in attendance:

E. W. Adams
C. H. Hine, M. D.
E. K. Linder, M. D.
M. N. Newquist, M. D.
A. C. Pabst
R. E. Eckardt, M. D. - Chairman

In addition, the following individuals attended the meeting as guests:

R. D. Bent
Lamson Blaney, M. D.
C. F. Boys, M. D.
C. T. Brown
R. C. Cole
L. E. Curtis, M. D.
T. M. Frank, M. D.
H. W. Gerarde, M. D.
N. J. Gothard
J. H. Hege, M. D.
R. M. Landon
B. B. Reeve, M. D.
F. J. Sanders
L. J. Wade, M. D.

The purpose of the meeting was to discuss the report of the Subcommittee to the MAC that afternoon. In addition to the three points mentioned in the Chairman's letter to the Subcommittee, it was decided to add a fourth point; namely, that the Subcommittee solicit comments and criticisms from all members and advisors of the MAC about the outline of the final report of the work at Kettering Laboratory which was attached to Dr. Horton's Interim Report dated September 26, 1957.

The Chairman of the Subcommittee then summarized for those in attendance the present status of the wax situation. Briefly, the situation is that a Mr. Kellogg of the Milk Industry Foundation in Washington had collected 40 wax samples from dairies which he had forwarded to Dr. Hueper. Twenty-four of these were forwarded to Dr. Shubik and UV absorption data on these 24 samples obtained by Dr. Shubik's chemist indicated that the UV absorption at 290 millimicrons varied from 0.04 to infinity. From one sample, in which the total absorption at 290 had been greater than 3.0, he chromatographed and isolated 4 micrograms of 1,2,5,6-dibenzanthracene

per gram of wax. It was the considered opinion of Dr. Shubik that he believed this quantity of the known carcinogen, 1,2,5,6-dibenzanthracene, in milk carton wax is undesirable and that the petroleum industry should establish an immediate standard which does not permit this much carcinogen in the finished product. Long range work then would attempt to establish a standard based upon biological testing.

In discussions which the Chairman had with Dr. Hueper at the recent Lung Cancer Workshop at the American Cancer Society, Dr. Hueper indicated that he was willing to sit still as long as the industry was willing to approach this problem with a reasonable, rational attitude, and as long as he was kept informed of the results of any work which was done. The Chairman indicated to the Subcommittee that the Three-Man Wax Committee appointed by the Medical and Health Committee of the Board, had met in Chicago on October 24 and unanimously recommended to the Medical and Health Committee, that work be done on waxes to the extent of approximately \$100,000 a year for the next three to five years in Dr. Shubik's laboratory. Copies of the report of the Three-Man Wax Committee will be made available to the members of the MAC through Mr. E. O. Mattocks' office of the API.

The meeting was adjourned at approximately 10:30 a.m.

R. E. ECKARDT, M. D./cjh
Chairman, Subcommittee on Carcinogenicity
November 14, 1957