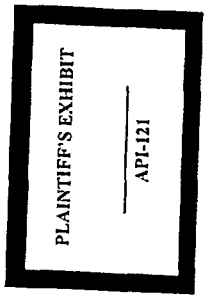
MEDICAL ADVISORY COMMITTEE MEETINGS
AND MINUTES THEREFROM 1956 - 1959



SC-API-2732

COPY

ESSO RESEARCH AND ENGINEERING COMPANY
(Formerly Standard Oil Development Company)
P. O. Box 121, Linden, N. J.

May 1, 1956

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

Dear Dr. Kehoe:

At the recent meeting of the Medical Advisory Committee in Philadelphia, the decision of the committee was to terminate the present epidemiological studies at the University of Cincinnati under the direction of Dr. Phair as of July 1, 1956. You will remember that in the report of the Subcommittee rendered one year ago, it was proposed that unless the reporting of cases improved during the past year there was probably little point in continuing these studies. It appeared to us at that time that you were in complete agreement with this idea. From Dr. Phair's report which indicated the accounting of cases in the calendar year 1955, it does not appear that any real significant improvement in reporting has occurred. It was the consensus of the Medical Advisory Committee that the present studies as currently being conducted should be discontinued as of the above date.

In addition, the Subcommittee was instructed through its Chairman to develop with interested members of the Medical Advisory Committee a proposed plan of epidemiological study which might be anticipated to be more productive of useful information to the members of the MAC. When such a plan has been developed, the function of the Subcommittee will then be to determine where such studies could be conducted. I can assure you that we will place your laboratories and Dr. Phair in a position of first consideration for doing these.

I discussed this whole situation with Dr. Phair on the phone yesterday, so that he is informed of the decision of the MAC. I would like at this time to re-emphasize that this decision by the MAC is not intended as a criticism of Dr. Phair or The Kettering Laboratory, but rather as a factual evaluation of where we are and where we may be going. Dr. Phair has had to work under extremely difficult and trying circumstances in connection with the epidemiological studies. The fact that he has been unable to successfully conduct satisfactory epidemiological studies, stands not as a criticism of him, but as a criticism of certain situations

which exist among the participating companies of the MAC. I believe, as does Dr. Phair, that his studies have accomplished some beneficial education among Medical Directors of the participating companies, but it must be recognized that the charge of the Subcommittee was for the development of more specific information than the general education of the Medical Directors concerning medical records.

It is hoped that when specific plans for a modified epidemiological study have been worked out, it will be possible to negotiate a satisfactory contract with you and Dr. Phair for the conduct of these studies. In the event that this does not work out, I am sure that the advice and guidance that Dr. Phair has given to the Medical Directors of the various participating petroleum companies will have been very useful and worthwhile.

Sincerely yours,

/s/

R. E. ECKARDT, M. D.

REE:mak

cc: Messrs. L. W. Adams
C. H. Hine
E. K. Linder
R. C. Mithoff
M. N. Newquist
A. C. Pabst
D. V. Stroop

AMERICAN PETROLEUM INSTITUTE

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

DEPARTMENT OF TECHNICAL SERVICES

ELMER O. MATTOCKS, DIRECTOR
JACK F. McKENNA, FIRE PROTECTION
FRANKLIN G. WILSON, SAFETY

October 11, 1957

Subject: Interim Report
Project MC-1

Ma-843-57

To Members
Medical Advisory Committee

Gentlemen:

You will find enclosed Interim Report for API Research Project MC-1, dated September 26, 1957, which has been received from The Kettering Laboratory in the Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati.

This is being sent for your information and files.

Very truly yours,

E. O. Mattocks

EOM:ed
Enclosure

AMERICAN PETROLEUM INSTITUTE

50 WEST 50TH STREET

NEW YORK 20, N. Y.

DEPARTMENT OF TECHNICAL SERVICES

ELMER O. MATTOCKS, DIRECTOR
JACK F. McKENNA, FIRE PROTECTION
FRANKLIN G. WILSON, SAFETY

October 9, 1957

Subject: Unscheduled Meetings of Medical Advisory Committee

Ma-840-57

To Members
Medical Advisory Committee and
Technical Advisors

Gentlemen:

You will find attached a list of the meetings of the Medical Advisory Committee and its Subcommittees. All of these meetings are unscheduled except for the Group Session at 9:30 A. M. on Monday and the Medical Advisory Committee meeting on Wednesday afternoon.

It would be desirable for you to bring this list with you to Chicago in order to know the meeting rooms. We will have a few extra copies of this list in Chicago in case you forget your copy.

Very truly yours,

E O. Mattocks
E.O.

EOM:ed
Attachment

MEETINGS (UNSCHEDULED) OF THE
MEDICAL ADVISORY COMMITTEE AND ITS SUBCOMMITTEES

SATURDAY, NOVEMBER 9, 1957

2:00 P. M. — Subcommittee on C_9 - C_{12} Aromatics
Private Dining Room 9, Conrad Hilton Hotel

MONDAY, NOVEMBER 11, 1957

9:30 A. M. — (Scheduled-Open Meeting) Medical & Health Group Session
Parlor A, Conrad Hilton Hotel

2:00 P. M. — Medical Advisory Committee's Discussion Meeting
Private Dining Room 10, Conrad Hilton Hotel

6:00 P. M. — Operating Subcommittee
Private Dining Room 5, Conrad Hilton Hotel

8:00 P. M. — Petroleum Industrial Hygienist Round Table Conference
Room 18, Conrad Hilton Hotel

TUESDAY, NOVEMBER 12, 1957

9:00 A. M. — Subcommittee on Atmospheric Pollutants
Room 18, Conrad Hilton Hotel

9:00 A. M. — Subcommittee on Economic Poisons
Private Dining Room 10, Conrad Hilton Hotel

2:00 P. M. — Subcommittee on Toxicological Reviews
Private Dining Room 10, Conrad Hilton Hotel

2:00 P. M. — Subcommittee on Physical Agents
Room 18, Conrad Hilton Hotel

WEDNESDAY, NOVEMBER 13, 1957

9:00 A. M. — Subcommittee on Carcinogenicity
Private Dining Room 10, Conrad Hilton Hotel

9:00 A. M. — Subcommittee on Industrial Hygiene
Room 18, Conrad Hilton Hotel

2:00 P. M. — (Scheduled) Medical Advisory Committee
Beverly Room, Conrad Hilton Hotel

Chicago Trip Notes

TENTATIVE AGENDA
(Prepared by D. V. Stroop and subject to change by L. E. Curtis, M.D.)

API MEDICAL ADVISORY COMMITTEE
22nd Meeting
2:00 P.M. Monday - November 12, 1956
Room 19 - Fourth Floor - Conrad Hilton Hotel
Chicago, Illinois

I. Approval of minutes of 21st meeting
(As circularized with letter dated May 31, 1956)

II. Subcommittee Reports.

A.	Operating Subcommittee	- L.E. Curtis, M.D., Chairman
B.	Program Subcommittee	- B.B. Reeve, M.D., Chairman
C.	Atmospheric Pollutants	- John C. Ruddock, M.D., Chairman
D.	C_9-C_{12} Aromatics	- C.H. Hine, M.D., Chairman
E.	Carcinogenicity	- Robert E. Eckardt, M.D., Chairman
F.	Economic Poisons	- J.W. Osborn, M.D., Chairman
G.	Physical Agents	- Lamson Blaney, M.D., Chairman
H.	Toxicological Reviews	- H.W. Gerarde, M.D., Chairman
I.	Industrial Hygiene	- P.D. Halley, Chairman
J.	Dermatology	- Leo J. Wade, M.D., Chairman
K.	Medical Policies and Practices	- K.R. Fourcher, M.D., Chairman

III. Reports by Liaison Members
- A. Dermatitis Survey - Leo J. Wade, M.D.
- B. American Standards Association
  - Z-4 - Industrial Sanitation - Allan E. Dooley
  - Z-37 - Toxic Dusts and Gases - Allan E. Dooley
  - Z-62 - Industrial Hygiene Standards - N.V. Hendricks
- C. Asphalt Institute - Robert E. Eckardt, M.D.
- D. American Medical Association - J.W. Osborn, M.D.
- E. Smoke and Fumes - John C. Ruddock, M.D.
- F. Labeling - C.H. Hine, M.D. & M.N. Newquist, M.D.
- G. First Aid Training - T.M. Frank, M.D.

(Ten minute recess)

IV Executive Session
- A. Budget Estimates for 1957 - 58
- B. Organization and Procedures
- C. Time and Place of 23rd Meeting

V New Business

VI Adjournment

11-1-56

October 31, 1956

Dr. L. E. Curtis
Medical Director
Standard Oil Company of California
225 Bush Street
San Francisco 20, California

Dear Doctor Curtis:

Copies of the enclosed proposal for the investigation of paraffin waxes are being sent to each member of the Subcommittee on Carcinogenicity. In the event that you may wish a broader distribution of this proposal to the members of the Medical Advisory Committee prior to your November meeting, we are putting an additional 50 copies in Mr. Stroop's hands for the purposes of such distribution.

Sincerely yours,

A. Wesley Horton

AWH:mjg
CC: Mr. David V. Stroop
enc:

A PROGRAM FOR THE INVESTIGATION OF INTERMEDIATE AND REFINED WAXES

OBJECTIVES: Certain crude paraffinic distillates have been associated with the development of scrotal cancer in wax pressmen. By further refining (essentially deoiling and decolorization processes) the waxy components of these distillates are purified until they meet the specifications for their particular use.

The major objective of the proposed investigation is the determination by suitable biological tests of the stage in the refining process at which the concentration of the components of the paraffinic distillates responsible for their carcinogenic potency for the human skin has been reduced to a negligible level. A correlated and equally important goal will be the development of biological techniques which will yield some estimate of the relative cancer hazard incurred by human beings through the ingestion of these partially or fully refined waxes. Pertinent information on composition obtained in the course of the research on cracked oils and straight run distillates (API Research Project MC-1) will be applicable to the various waxes. Analytical techniques based on these findings will serve as a further check on the extent of the reduction in the concentration of carcinogens present in the crude distillates from which the waxes were derived.

PROCEDURE:

I. Selection of materials

A. Process variables to be considered (partial assembly of this information from individual producers has been carried out in an early phase of Project MC-1)

1. Crude source
2. Preparation of feed to the wax plant
3. Method of deoiling the wax

B. Types of materials under consideration

1. Correlated series of samples
   a. Feed to the wax plant (straight run or extracted paraffinic stocks)
   b. Intermediate scale waxes resulting from sweating or solvent deoiling operations
   c. Refined waxes after final deoiling and decolorization (e.g., MEK-benzol or adsorbents)
2. Waxes of increasing molecular weight (melting point), including those referred to as "microcrystalline"
3. Suitable composites of closely related materials from different producers

C. Pertinent properties by which selected materials may be described

1. Oil content
2. Melting range or molecular weight
3. Content of fluorescent materials (chromatographic)
4. Absorption and mass spectra

II. Biological testing

A. Criteria for selection of experimental conditions

1. Control animals subjected to the administration of vehicles alone, with no added carcinogens, should have a low, essentially negligible incidence of the cancer to be reproduced
2. Positive results should be obtainable if a known carcinogenic hydrocarbon is introduced into the animal under the conditions of the investigation

B. Materials to be tested

1. Solutions of fluorescent fractions (chromatographic) of the waxes, in selected concentrations in the appropriate vehicles
2. Solutions of benzopyrene (BP) or methylcholanthrene (MC) in the same vehicle
3. Vehicles alone
4. Solid solutions of BP or MC in the non-fluorescent fraction (chromatographic) of selected waxes

C. Species of animals to be used

1. Inbred mice for induction of skin cancer
2. Selected species, including mice, which are available from healthy stocks, for induction of cancer of small intestine or other internal organs

II. Biological testing (continued)

D. Experiments involving the induction of skin cancer

1. Tests to determine the relative potencies of liquid fractions of slack waxes which differ with respect to the variables shown in I.A. or I.C.

2. Subsequent tests to determine the relative potencies of liquid fractions, or solutions of fluorescent fractions of related samples of slack wax, intermediate scale waxes, and fully refined wax

E. Experiments involving the induction of intestinal tumors

1. Attempted duplication of published method of induction of intestinal tumors by solutions of MC in olive oil

2. Subsequent attempts to induce similar tumors by solutions of fluorescent fractions of waxes

3. Determination of relative potency to intestine of solid solutions of MC in non-fluorescent fractions of waxes

III. Application of analytical techniques from Project MC-1 to paraffinic oils and separated waxes

Kettering Laboratory
November 1, 1956

MEMORANDUM ON A MEANS OF APPRAISING THE POTENTIAL CANCEROGENIC HAZARD OF THE USE OF PETROLEUM WAXES UNDER CONDITIONS THAT MAY RESULT IN THEIR INTRODUCTION INTO HUMAN FOOD AND BEVERAGES

The question of the safety of the use of refined waxes on food containers was apparently raised in Rome this past summer. According to Dr. Arnold Lehman of the F.D.A., the potential problem was not discussed by Dr. Hueper in his formal paper. (It has since been referred to briefly, among many other sources of contamination of food, in an article in the Saturday Review of literature.) At the same time, the reports in the popular press are sufficient evidence that the subject was discussed informally by some members of the conference. In any event, it seems highly probable that the question will have to be answered eventually by the acquisition and publication of convincing experimental evidence.

On October 4, the following persons participated in an informal discussion of a suitable approach to the problem: Drs. Lehman, Nelson and Voss of the Food and Drugs Administration and Drs. Kehoe and Horton of the Kettering Laboratory. There was unanimous agreement that the somewhat conventional experiment of feeding test materials to rats over a period of two years is not particularly applicable. It was further agreed that the experimental approach to the testing of materials in terms of the responses of animals, must be or, at least, should be controlled in a positive answer by some experimental procedure in which a known carcinogenic hydrocarbon will produce malignant tumors of relevant type and location. In keeping with the sense of the foregoing discussion, and following careful consideration of the entire problem, we propose to investigate the carcinogenic potentialities of

selected materials by introducing them into the forestomach and small intestine of mice (see publications of Lorenz and Stewart of National Cancer Institute) after choosing a suitable solvent for the appropriate experimental material or fraction thereof. The use of positive controls, exposed in corresponding manner to methylcholanthrene in the same solvent, and negative controls, comparably exposed to the solvent alone, would form a necessary part of such a program. (Dr. Lehman and his associates indicated that they would be in substantial agreement with this approach. Dr. Lehman suggested further that, since the methods for developing cancer of the skin from liquid solutions had been worked out, it might be expeditious to apply some of the solutions to the skin, at least in the preliminary phases of the program. The data from the skin, in combination with those from the gastro-enteric tract, would provide a much higher level of confidence in the interpretation of the results then would be possible if only one or the other of the tissues was involved.)

In considering the proper scope of such an investigation, the opinion was general that there is a lack of the data necessary to present a clear picture of the situation rather than an actual or imminent hazard to the public health. Hence, although a fairly detailed examination of the problem seems warranted, it should be carried out in a carefully considered manner and at a logical speed, rather than after the manner of an emergency.

In general, the problem arises out of the fact that refined waxes, as marketed, are faintly to strongly fluorescent under ultraviolet light. While not all fluorescent hydrocarbons are carcinogenic, the converse apparently is true. There is, for example, evidence that the carcinogens responsible for the development of scrotal cancer in wax pressmen are fluorescent.

Since the refined waxes derive from the distillates associated with these occupational skin cancers, the obvious question is raised, since the waxes still fluoresce, whether the carcinogens have been eliminated or to what extent their concentration has been reduced. A program aimed at a qualitative understanding of the composition of the carcinogens in the wax distillates and a quantitative measure of the desired decrease in their concentration during the refining processes seems to be called for.

Although API Research Project MC-1 has been directed primarily at cracked oils, the general principles and techniques developing in that work should be applicable to the wax problem. Biological testing of solutions of suitable fractions of the intermediates and final products in parallel with chemical research on the composition of the fluorescent components should provide the information needed for the long term answer to this problem.

This question concerns every oil company engaged in the production or distribution of petroleum waxes. Since the inclusion of even selected materials from each of these companies would quickly multiply the experimental effort beyond the scope warranted by the nature of the problem, it would seem appropriate to follow the mechanism for sampling used in Project MC-1 in

1949-50. The general boundaries of the investigation would be described by the advisory committee. Guided by this outline, the Kettering Laboratory should assume the responsibility for assembling the necessary confidential information from the individual producers and selecting a representative group of samples. The experience along this line and contacts already established should make this a fairly efficient process of arriving at the desired goal.

As to the general level of the overall effort, an annual expenditure in the neighborhood of $35,000 to $40,000 for about five years would produce the information needed in the most economical and satisfactory manner. It is doubtful in our mind that a higher rate of expenditure initially would be wise or necessary. It will probably be desirable to be able to indicate an early date for the initiation of the investigation. The staff of the Laboratory would be prepared to start the necessary groundwork for the sampling program at a moderate cost, as soon as the decision to proceed has been arrived at.

Robert A. Kehoe

Robert A. Kehoe, M. D.

October 11, 1956

STANDARD OIL COMPANY OF CALIFORNIA

STANDARD OIL BUILDING

L. E. CURTIS, M. D.
CHIEF, MEDICAL DEPARTMENT
SAN FRANCISCO 20, CALIFORNIA

July 3, 1956

RICHARD DILLON, M. D.
REGIONAL PHYSICIAN
LOS ANGELES 54, CALIFORNIA

Dr. A. Wesley Horton
The Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Doctor Horton:

I suggest that you send the additional copies of your manuscript to Mr. Stroop at this time so that he can have them prepared for distribution as soon as we are ready to submit the question to the Medical Advisory Committee.

Obviously time is important to you and we will try to hurry the matter as much as possible.

Sincerely yours,

L. E. Curtis

L. E. CURTIS, M.D.

cc: Dr. R. C. Mithoff
Dr. R. E. Eckhardt
Mr. D. V. Stroop

AGENDA

Research Project (MC-1) Advisory Committee Meeting
Kettering Laboratory, Cincinnati, Ohio

July 10, 1952, 9:30 a.m. to 4:00 p.m. EST

1 - Summary of April 1952 Progress Report	Dr. A. W. Horton
2 - Comments on the Progress Report	Dr. R. E. Eckardt et al
3 - Progress of studies since April 1952 and future plans	Dr. A. W. Horton
4 - Effect of viscosity on potency and the use of embodying agents to modify viscosity	R. M. Shepardson L. C. Beard
5 - (a) Need for additional studies on straight-run, uncracked distillates and residua	
(b) Appraisal of British literature and the magnitude of the hazard in Great Britain	L. C. Beard
6 - Plans of the Sub-panel on Lubricants and Process Products Hygiene of the API Lubrication Committee	R. M. Landon K. G. Mackenzie L. C. Beard
7 - Report on mid-year meeting, General Committee, Division of Refining, May, 1952, with respect to the RPA Committee's report of April 30, 1952, to Mr. T. J. Sullivan	R. M. Landon
8 - Epidemiological Surveys (a) Among employees of petroleum companies	Dr. J. J. Phair Dr. E. K. Linder
(b) Among employees of customers	Dr. M. N. Newquist
9 - Other business	
10 - Date and place of next meetings of (a) Subcommittee on Carcinogenicity (b) RPA Committee	

Prepare 1953-1954 budget for next meeting

RPA Committee Sept 24 morning

MAC Thurs Sept 25 Chicago - Conrad Hilton

We feel it would be in order to request Kettering to make a realistic appraisal of the British literature and advise us of the magnitude of this hazard. Place should be provided for a brief presentation of the plans of the Sub-Panel on Lubricants and Process Products Hygiene of the API Lubrication Committee of which Messrs. Landon, Mackenzie and I are members.

I feel that closer liaison with the British workers is in order. The minutes attached to your letter of May 17, 1952, are not very helpful. Privately I have learned - "that fractions from Oklahoma bright crudes were tested biologically at Birmingham University and yielded interesting results, amongst them the finding that the most active carcinogens are concentrated in a fraction whose initial boiling point is 600 to 625°F. The upper limit of distillation was not so sharply defined as the carcinogenicity fell off gradually. Whether this effect was due to a decrease in specific activity with increase in molecular weight, or to a lower concentration of active hydrocarbon types was not clear".

The quotation above gives in my opinion some substantiation to a point that has been stressed by Drs. Eckardt and Shepardson - to the effect that viscosity appears to lessen carcinogenicity. Over the years wur have noticed that our most violent dermatitis complaints deal with products of relatively low viscosity but a boiling range higher than conventional solvents.

This would suggest that the product must be sufficiently non-volatile to stay on the skin and of sufficiently low viscosity to penetrate - and, of course, be irritant or carcinogenic. I repeat a suggestion made some time ago that it might be in order to take one of our relatively non-viscous active carcinogenic fractions and dissolve therein several percent of a material to increase viscosity without materially changing composition and then test this material of increased viscosity to determine if its carcinogenicity is lower. Thought should be given to the use of Vistanex, Alkylated Poly Styrene and Acryloids in the order mentioned; also, aluminum stearate or silica flour dispersion (run through a colloid mill) might well prove effective thickening agents for this purpose.

Very truly yours,

L. C. BEARD, JR.

LCB:EHL

cc: R. E. Eckardt, M.D.; E. K. Linder, M.D.; G. M. Saunders, M.D.
Dr. R. M. Shepardson

awh

MEMORANDUM FROM THE KETTERING LABORATORY

THIRD MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

July 10, 1952

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

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

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

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

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

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

C. Results on API-83-2 indicate that mild air oxidation of catalytically cracked residua not useful for reduction of concentration of carcinogens.

D. Effects on rate of tumor induction of decreasing severity of tests by decreasing dosage per application.

1. For solutions of methylcholanthrene, same rate of tumor induction by 20 mg. and 100 mg. applications (results to be rechecked on Heston sub-line with purified methylcholanthrene). True for either 9,10 or DDB solutions of it

2. For fuel oil blends (probably relatively low concentration of accelerating constituents), preliminary data indicates rate of tumor induction same for 5 mg., 20 mg., or 100 mg. applications.

3. For API-8 (catalytically cracked residuum of high potency) rate for 20 mg. applications significantly slower than for 100 mg. applications, possibly indicating a critical dosage level for action of accelerating constituents.

E. Correlation of potencies of finished lubricants with their ultraviolet absorption spectra.

1. API-99, spectrum type C (0.5), weakly acid treated naphthenic stock containing 0.2 percent antioxidant, P_{MC} 0.07. Consider antioxidant properties of BP & M But 0.07 typical of Mideast SR distillates.

2. API-100, spectrum type B (0.3), blended, solvent extracted lube containing no additives, yield of papillomas zero after 41 weeks of painting (3 applications per week, C3H mice).

F. Tumor yield from white oils, API-80 and 95, zero after one year of painting.

Incidentally - retardation of tumor inducting by Varex not sufficient to justify use

G. Fractionation studies to determine classes of 3- and 4-ring compounds responsible for carcinogenicity.

1. Exhaustive Diels-Alder reaction (maleic anhydride) on API-8 yielding anthracenes, benzanthracenes, dibenzanthracenes (?), naphthacenes, naphthopyrenes (?), and nitrogen bases (?). These classes separated by solubility properties of their succinic acid adducts and adsorption properties (on alumina) of the recovered parent compounds to prepare samples for biological testing.

2. Indications from results of biological and analytical tests on API-8-19 and 8-20 that pyrenes and anthracenes not contributing to potency of distillate fractions, boiling 700-800°F. (vacuum corrected), from API-8.

3. Fraction boiling lower than chrysene of aromatic compounds from API-12, F.C.C. residuum, being treated to remove pyrenes and anthracenes; fraction thus prepared for mouse testing to contain alkylphenanthrenes, alkylbenzfluorenes, benzphenanthrene (?), etc.

4. Further chromatographic fractionation of distillate fractions of API-8 corresponding to 8-10, 8-11, and 8-12 to separate 4-ring compounds into classes for biological tests.

H. Accelerating constituents of cracked oils.

1. Further evidence that colorless fraction from chromatography of API-8 has accelerating effect on rate of tumor induction. Potency of API-8-21 (50:50 blend of 8 with white oil from 8) not significantly different from that of API-8, whereas comparable 50:50 blends with sec-amylbenzene (see 8-16) or with white oil and reduced crude (see 8-4) demonstrated marked reduction in potency. Note also same $\bar{X}$ for 20 and 20-1

2. Resin removed from API-71, T.C.C. residuum, not responsible for high potency of this relatively low boiling catalytically cracked product. Testing and further fractionation of colorless chromatographic fraction of API-71 to be carried out.

3. Low dosage tests on cracked sidestreams for further evidence on possible contribution of accelerating constituents to their moderately high potency when tested in 100 mg. applications.

I. Pure HC's for analytical purposes

1. 1-ϕdecane and 1-cyclohexyldecane recd from API RP 45

2. all monomethylbenz(c)-phenanthrenes to be obtained from Dr Mel Newman.

J. S.R. Distillates

1. Tests on British fractions not far enough for PMC. Some have produced tumors in mice.

2. Sample of Penna lube dist. correlated with API-71 available.

Future individual data sheets on multilith with complete graph lines

AWH

LEGEND FOR DATA SHEETS ON INDIVIDUAL EXPERIMENTS

~ sign on P_{MC} for 2x/wK exps. will be used until further confirmation of reference curve is obtained

Symbols used in connection with average weight curves:

- $\overline{\nabla}$ Time of death (from disease) of i th tumor-free mouse.
- i Time of death (from disease) of i th tumor-bearing mouse.
- $\overline{\overline{\nabla}}$ or $\overline{i}$ Time mouse killed.
- $\overset{\vee}{\nabla}$ Mouse missing from cage.

Weight curves not connected in periods where more than 2 weeks elapsed between weighings. Currently weighed each week.

Gross and microscopic pathology:

- $\boxed{i}$ Time of appearance of first papilloma in i th mouse. When this symbol is first used for a given mouse after its death, the presence of non-invading carcinoma (intra-epithelial) or small areas of benign neoplasm was determinable only by histopathology.
- $\boxed{i}$ Time of appearance of papilloma which regressed later or was not confirmed by histopathology.
- $\textcircled{i}$ Time of appearance of gross changes indicative of malignancy in tumor of i th mouse. Diagnosis confirmed except in cases where no tissue section available. When this symbol is first used for a given mouse after its death, the invasive malignancy of the tumor was determinable only by histopathology.
- $\textcircled{i}$ Gross diagnosis of malignancy of tumor not confirmed by histopathology.
- $\overset{NS}{\boxed{i}}$ or $\overset{NS}{\textcircled{i}}$ No tissue section available for histopathology because of extensive post-mortem decomposition or cannibalism.
- * Tumors not recorded during this week.

Cumulative dose-response curves (summation of data from all cages unless otherwise specified):

Add definition of Tumor Index

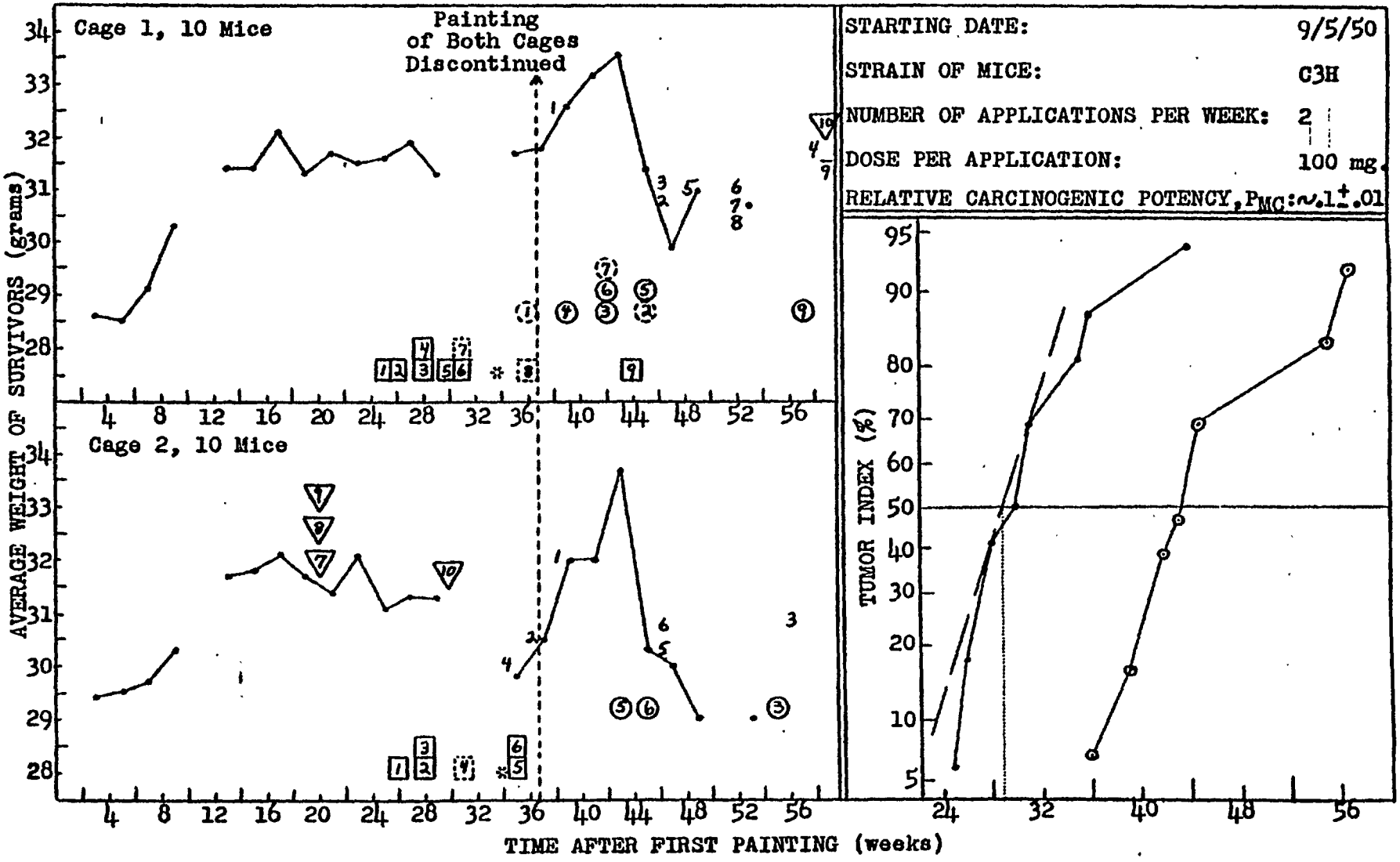
- ——— Experimental curve for benign papillomas.
- — — — — Hypothetical curve for papillomas. This curve furnishes average latent period (time for 50 percent tumor index) from which relative potency, P_{MC}, is determined).
- ⊙———⊙ Experimental curve for grossly malignant tumors.

Note slopes of 205, 206, and 227 All C3H, 1x/wK

Please note scales and do not attempt to compare slopes visually

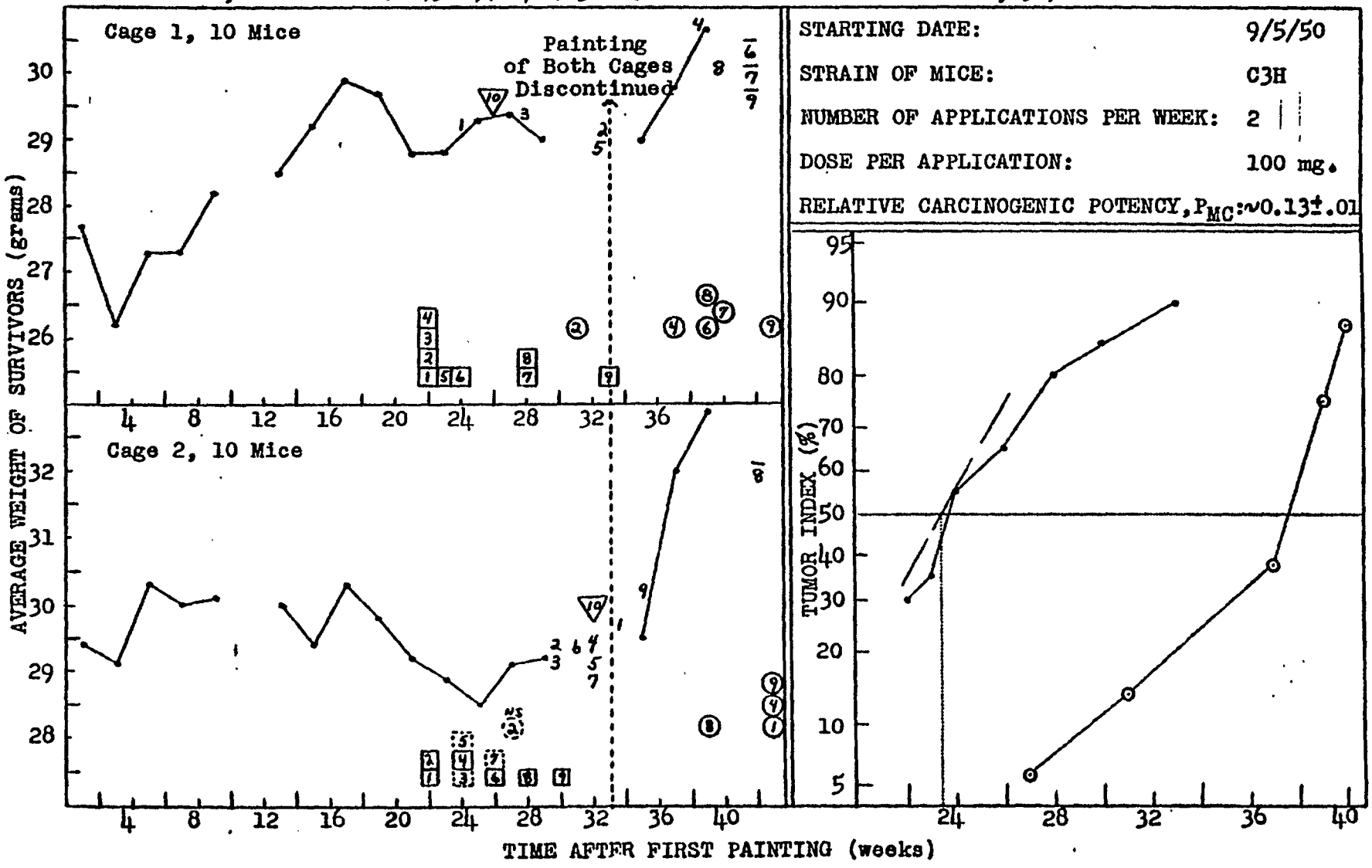
SKIN PAINTING EXPERIMENT

API-8-10, Fraction b. 142-175°C/0.03 mm. from Distillation of API-8, 50% Solution in Benzene



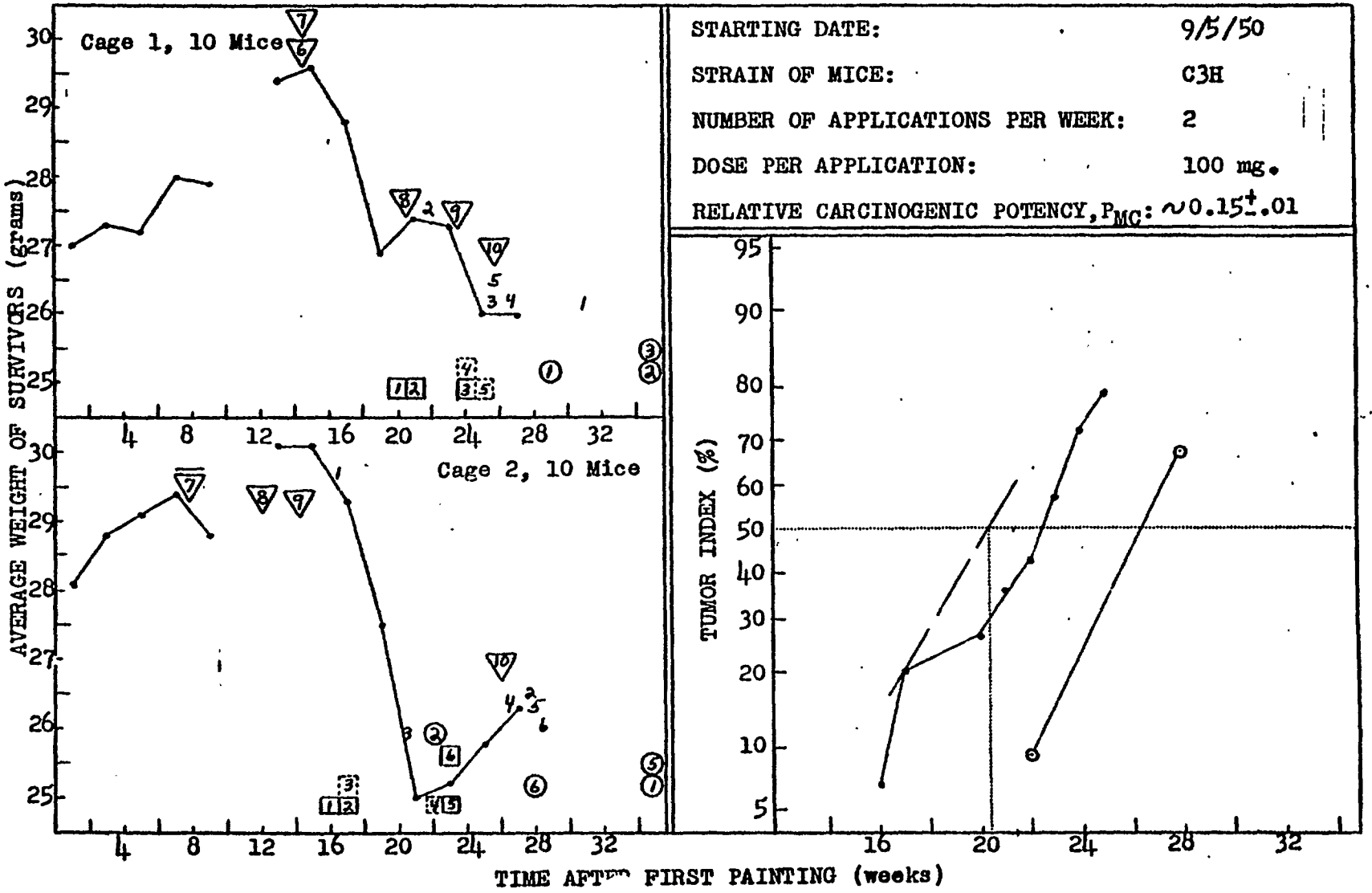
SKIN PAINTING EXPERIMENT

API-8-11, Fraction b. 175-197°C/0.03 mm. from Distillation of API-8, 50% Solution in Benzene



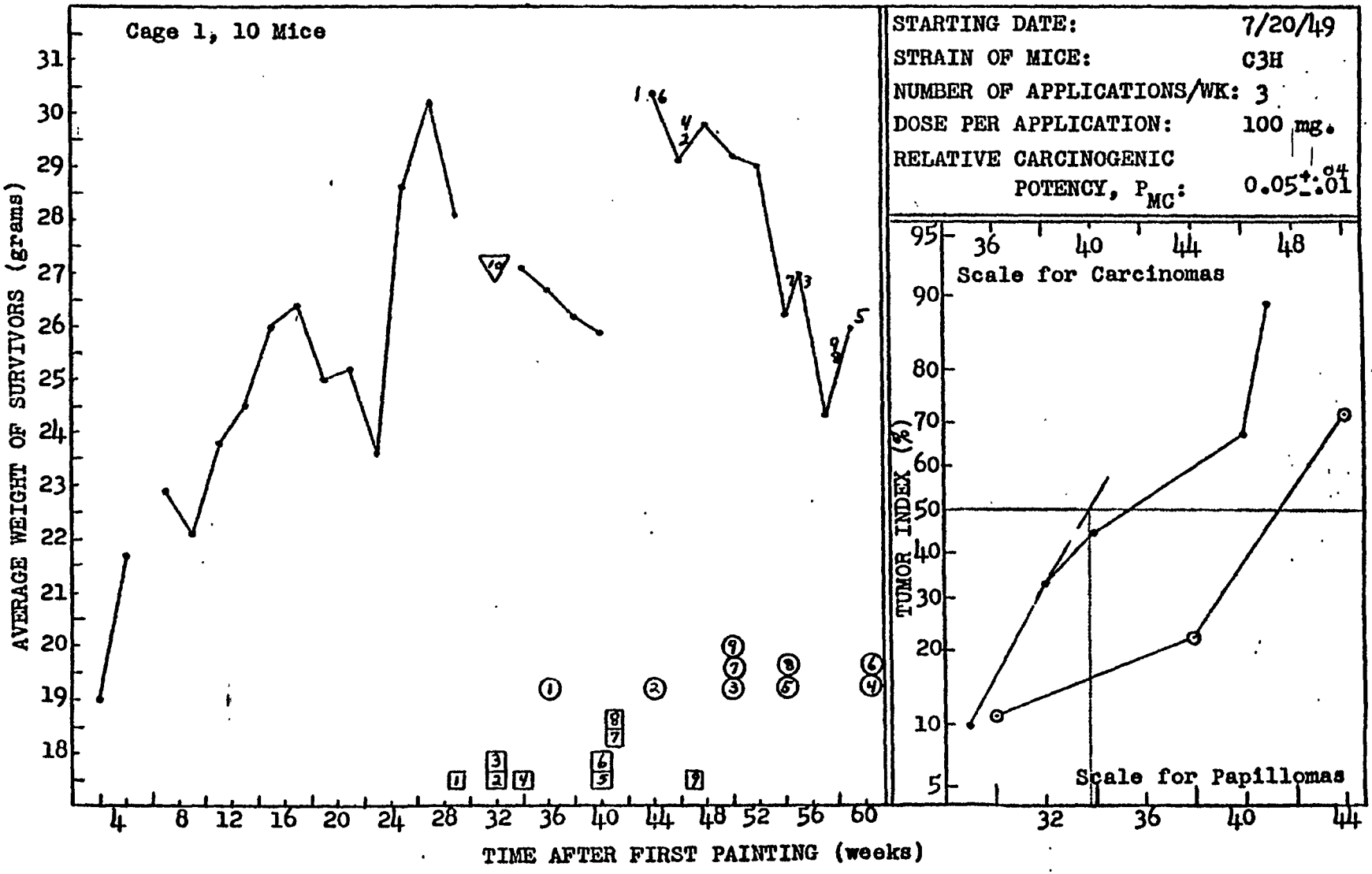
SKIN PAINTING EXPERIMENT

API-8-13, Fraction b. 215-238°C./0.045 mm. from Distillation of API-8, 50% Solution in Benzene



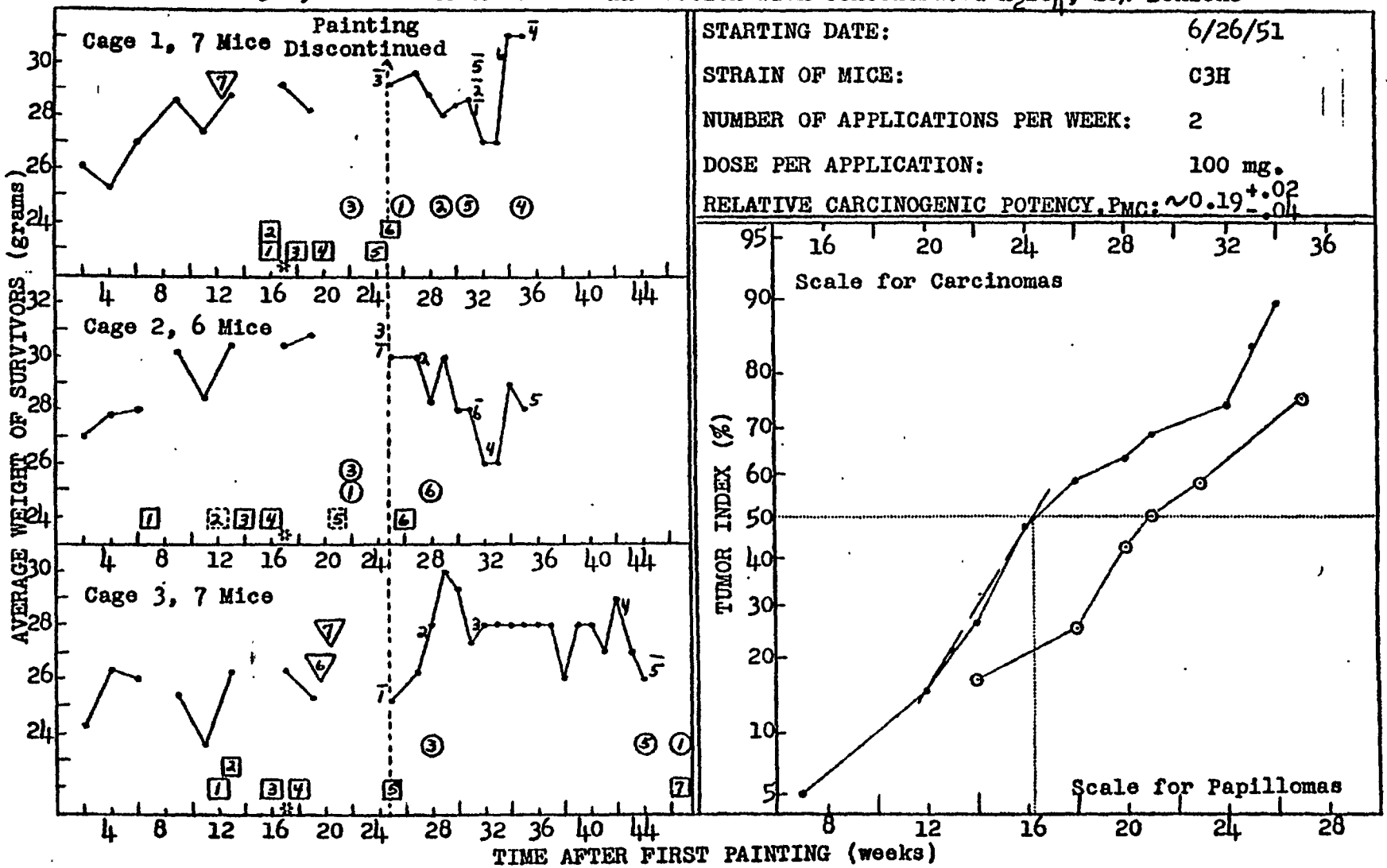
SKIN PAINTING EXPERIMENT

API-9, T.C.C. Cracked Residuum



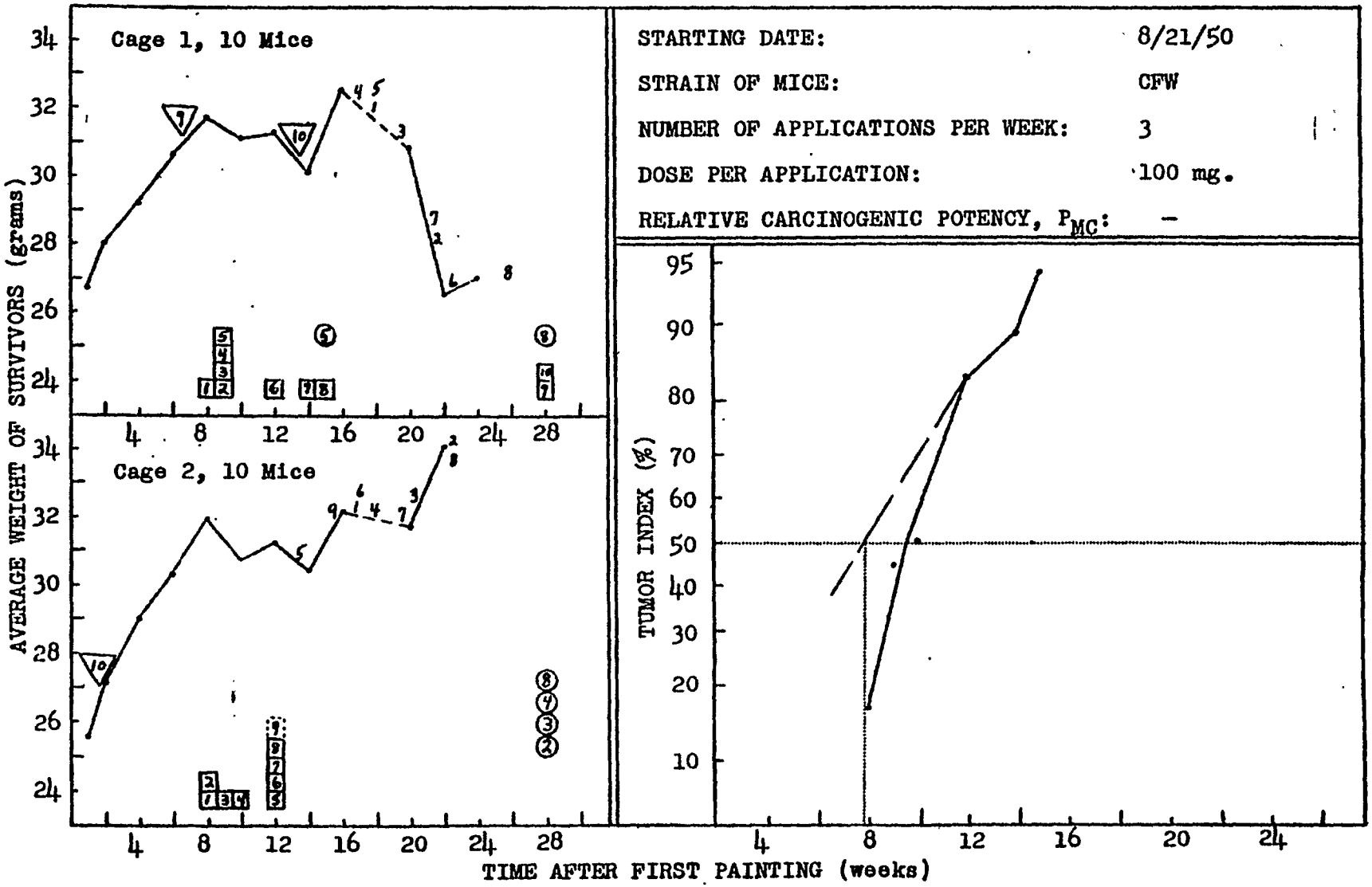
SKIN PAINTING EXPERIMENT

API-23-1, Extract from Solvent Extraction with Concentrated H_2SO_4, 20% Benzene



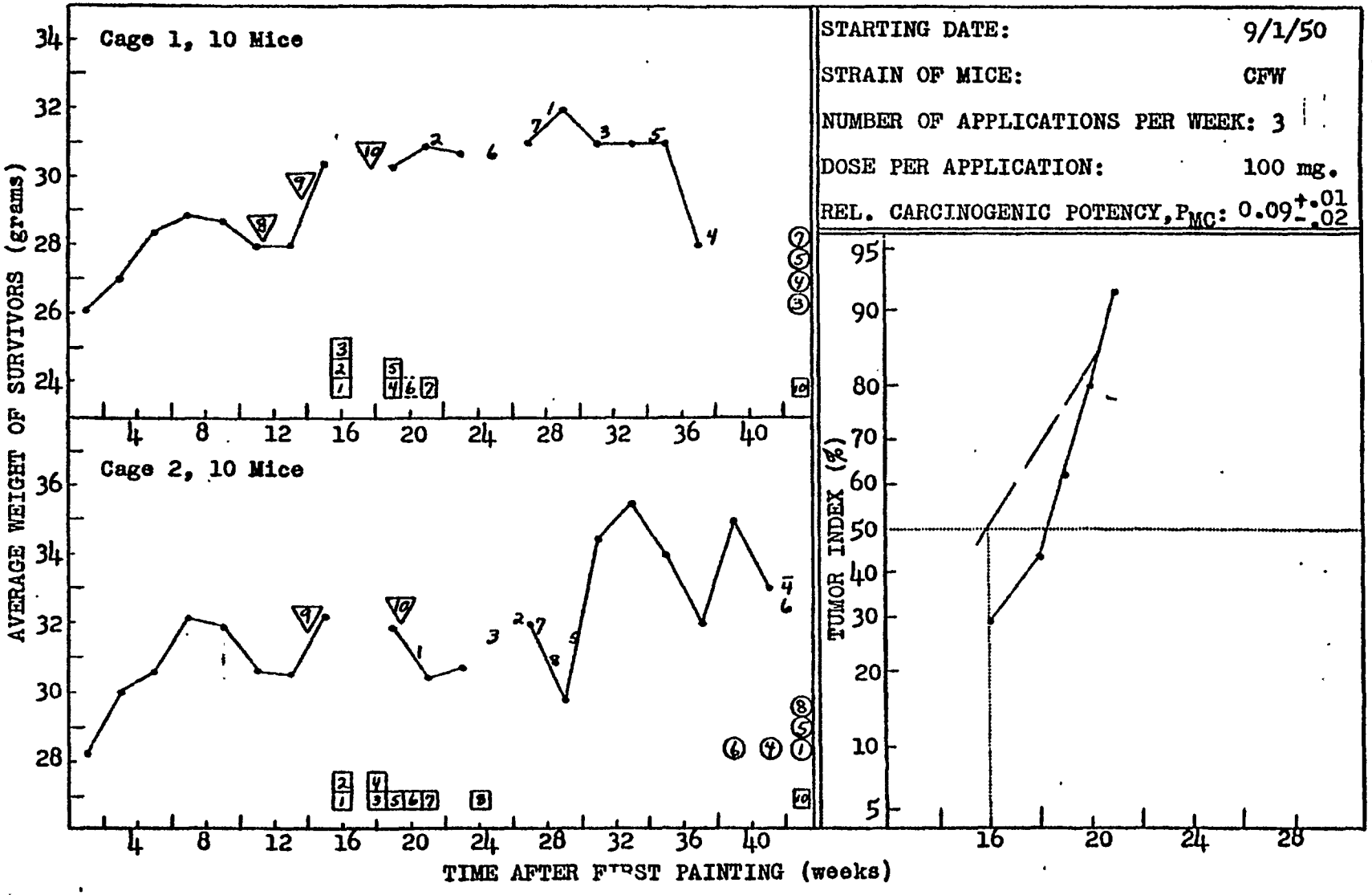
SKIN PAINTING EXPERIMENT

API-33, Cracked Sidestream from Delayed Coking



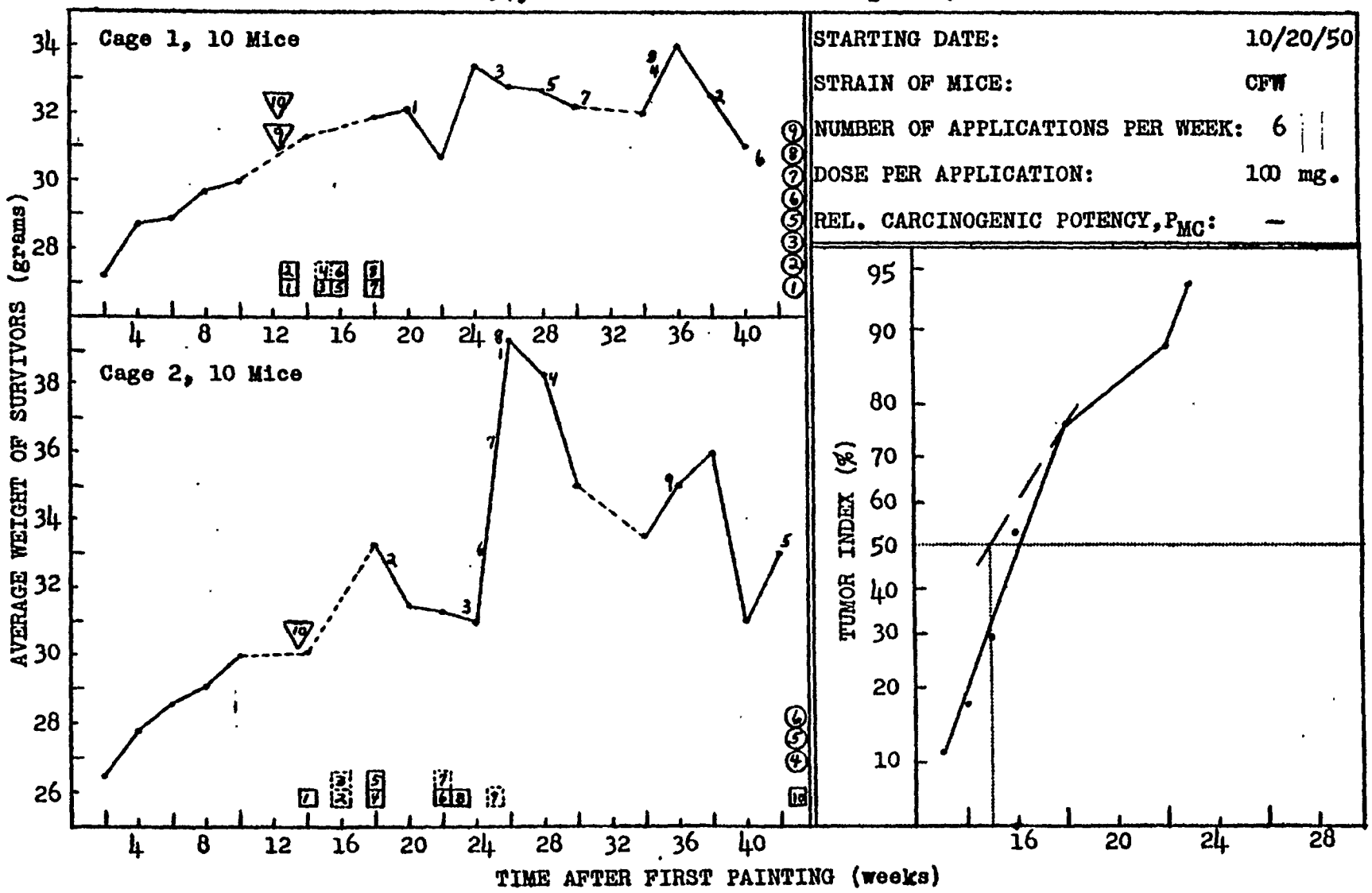
SKIN PAINTING EXPERIMENT

API-46, F.C.C. Cracked Sidestream



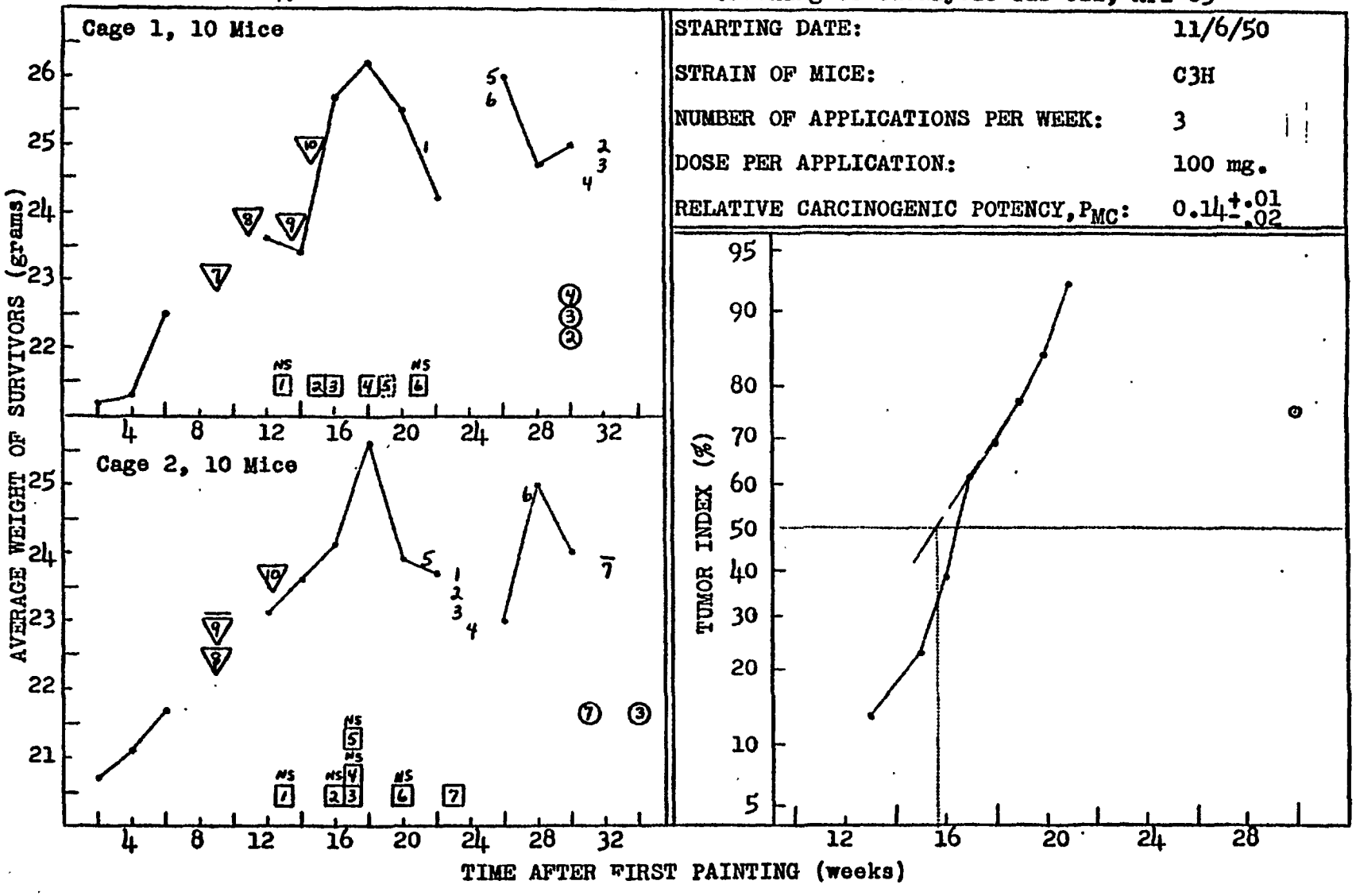
SKIN PAINTING EXPERIMENT

API-57, Dewaxed Oil from Pressing API-56



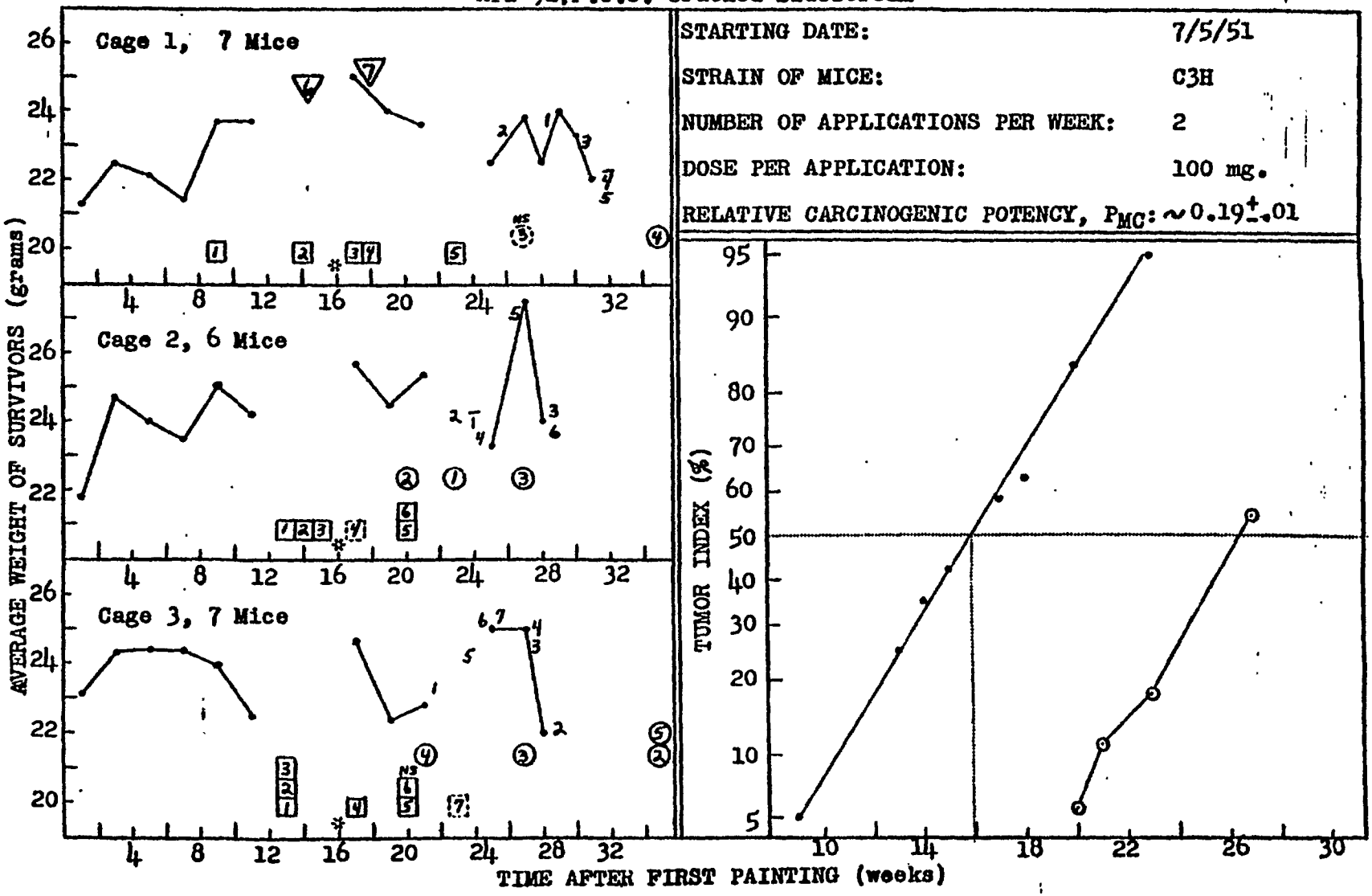
SKIN PAINTING EXPERIMENT

API-64, Cracked Residuum from Thermal Cracking of Catalytic Gas Oil, API-63



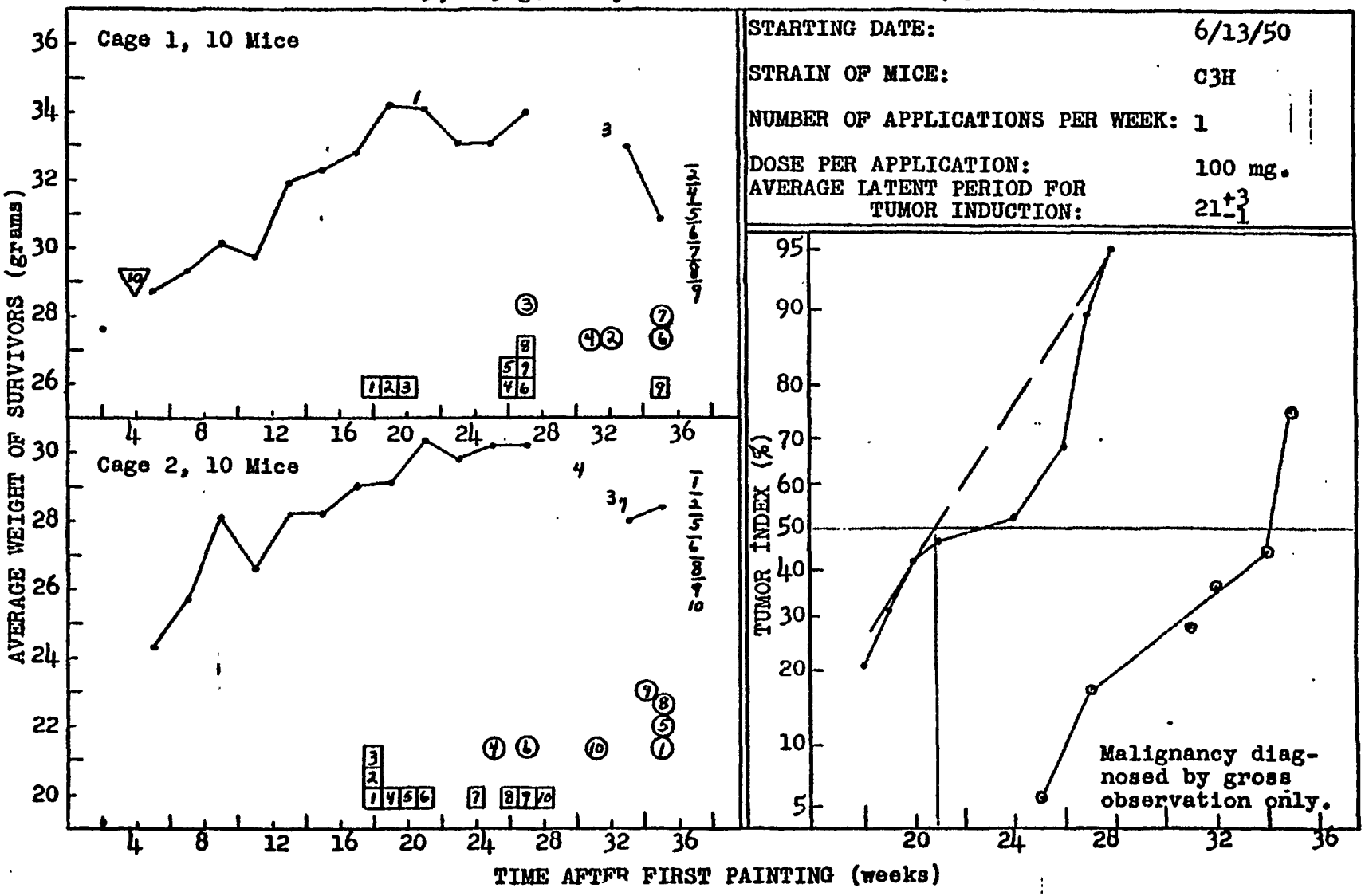
SKIN PAINTING EXPERIMENT

API-91, F.C.C. Cracked Sidestream



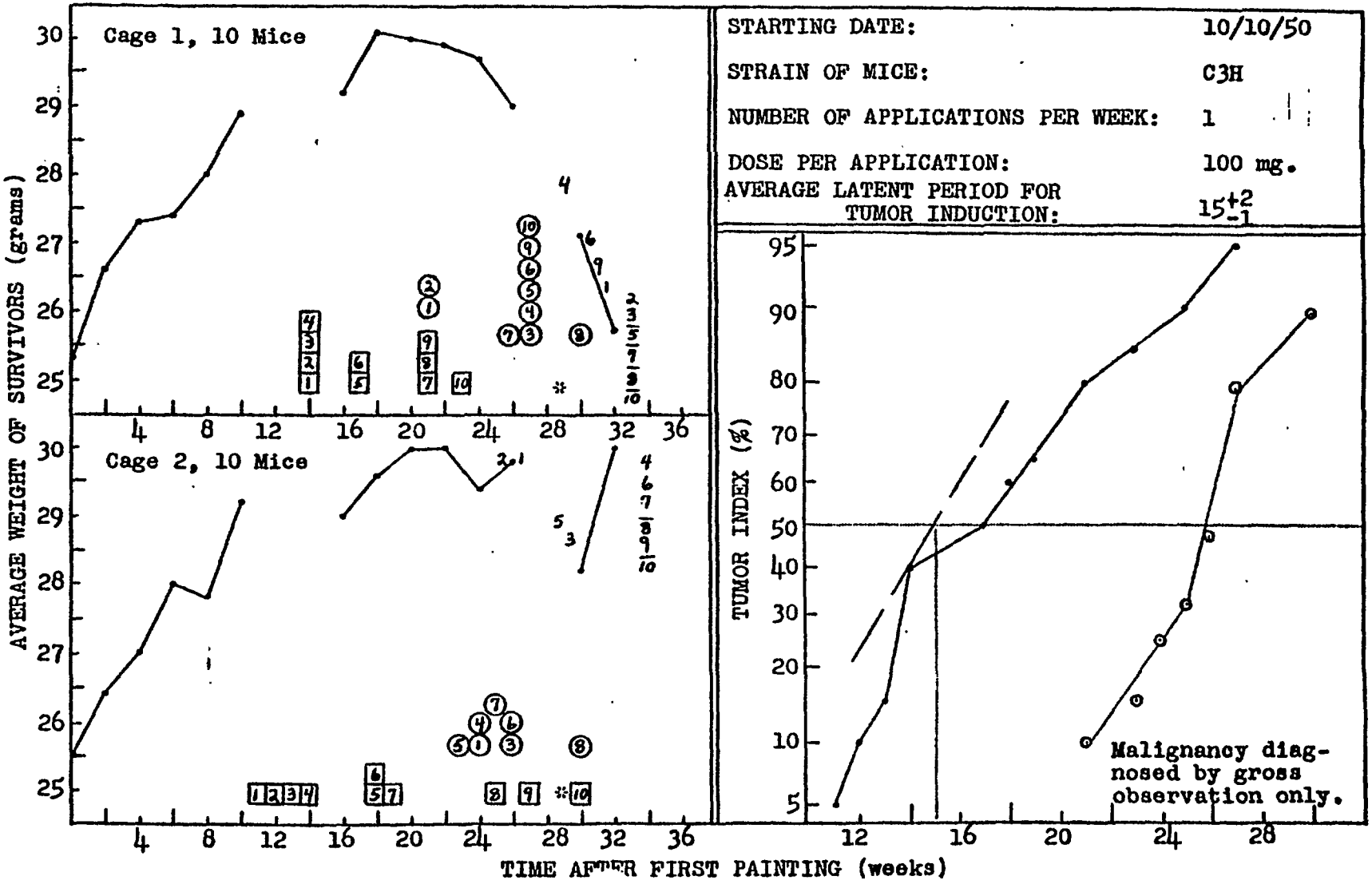
SKIN PAINTING EXPERIMENT

API-205, 0.3 g. Methylcholanthrene in 100 ml. Benzene



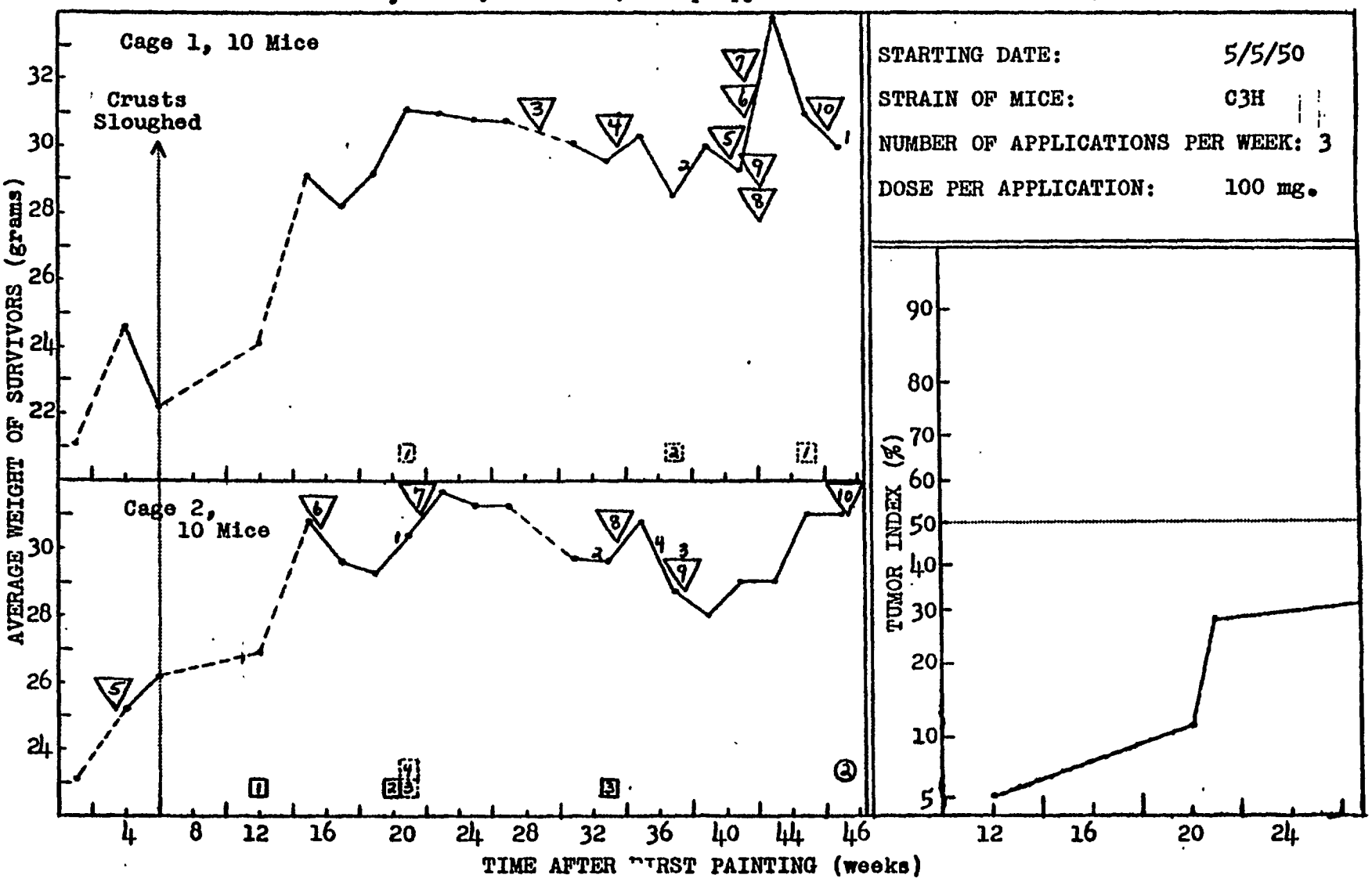
SKIN PAINTING EXPERIMENT

API-206, 0.6 gm. Methylcholanthrene in 100 ml. Benzene



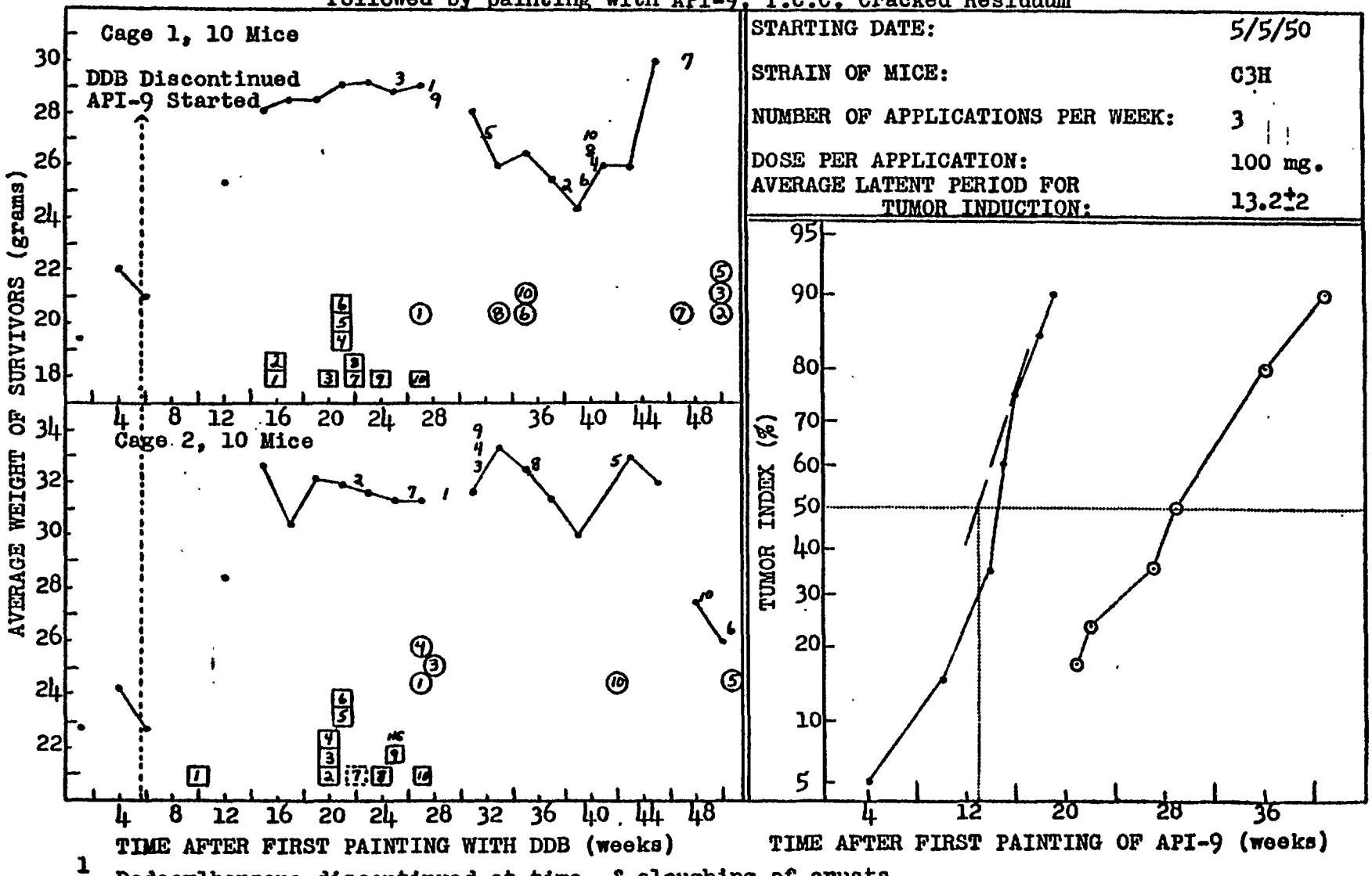
SKIN PAINTING EXPERIMENT

API-221, Dodecylbenzene (from propylene tetramer and benzene)



SKIN PAINTING EXPERIMENT

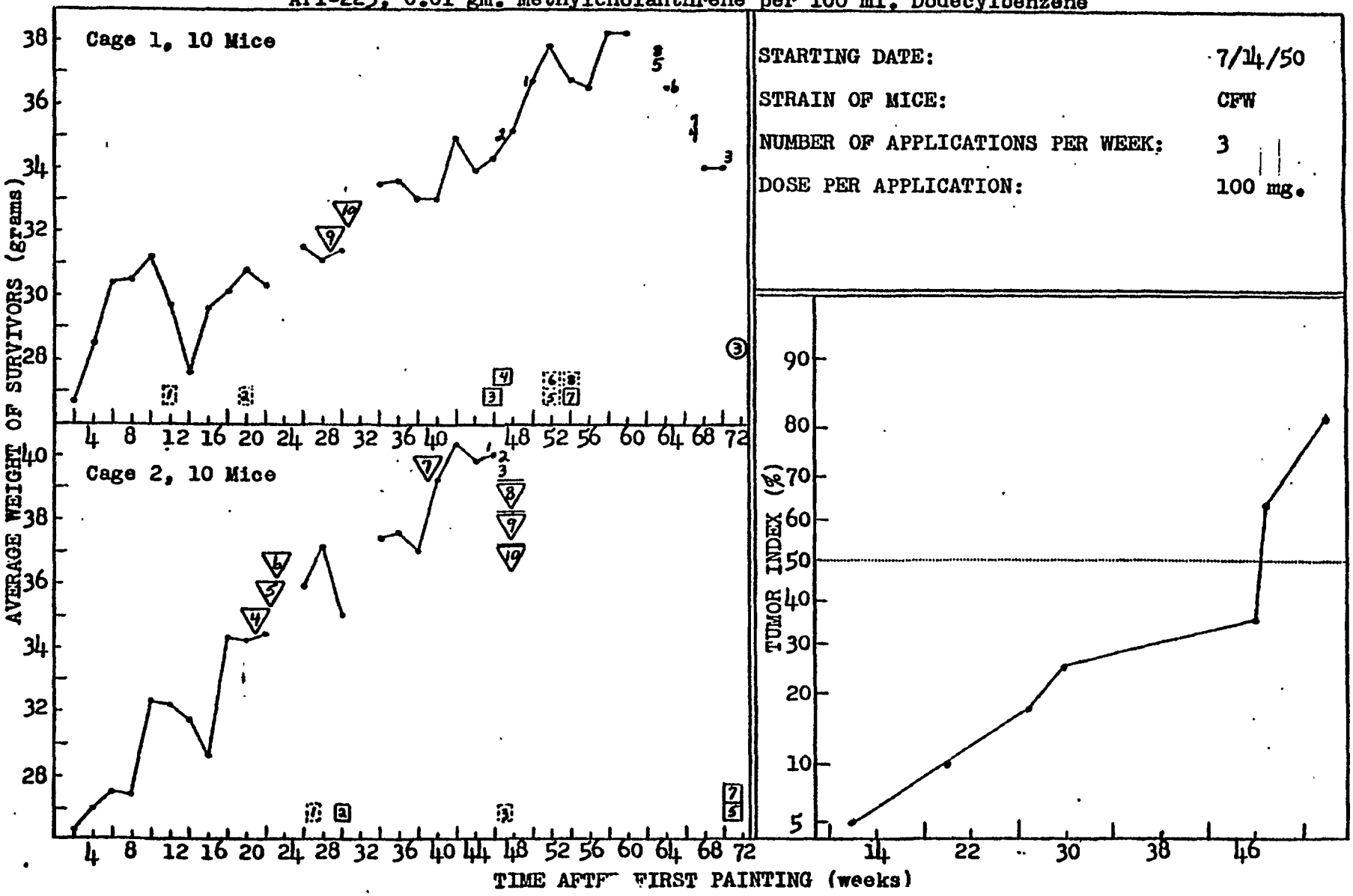
API-221-9, Dodecylbenzene (DDB) painted for first six weeks[1], followed by painting with API-9, T.C.C. Cracked Residuum



[1] Dodecylbenzene discontinued at time of sloughing of crusts.

SKIN PAINTING EXPERIMENT

API-225, 0.01 gm. Methylcholanthrene per 100 ml. Dodecylbenzene



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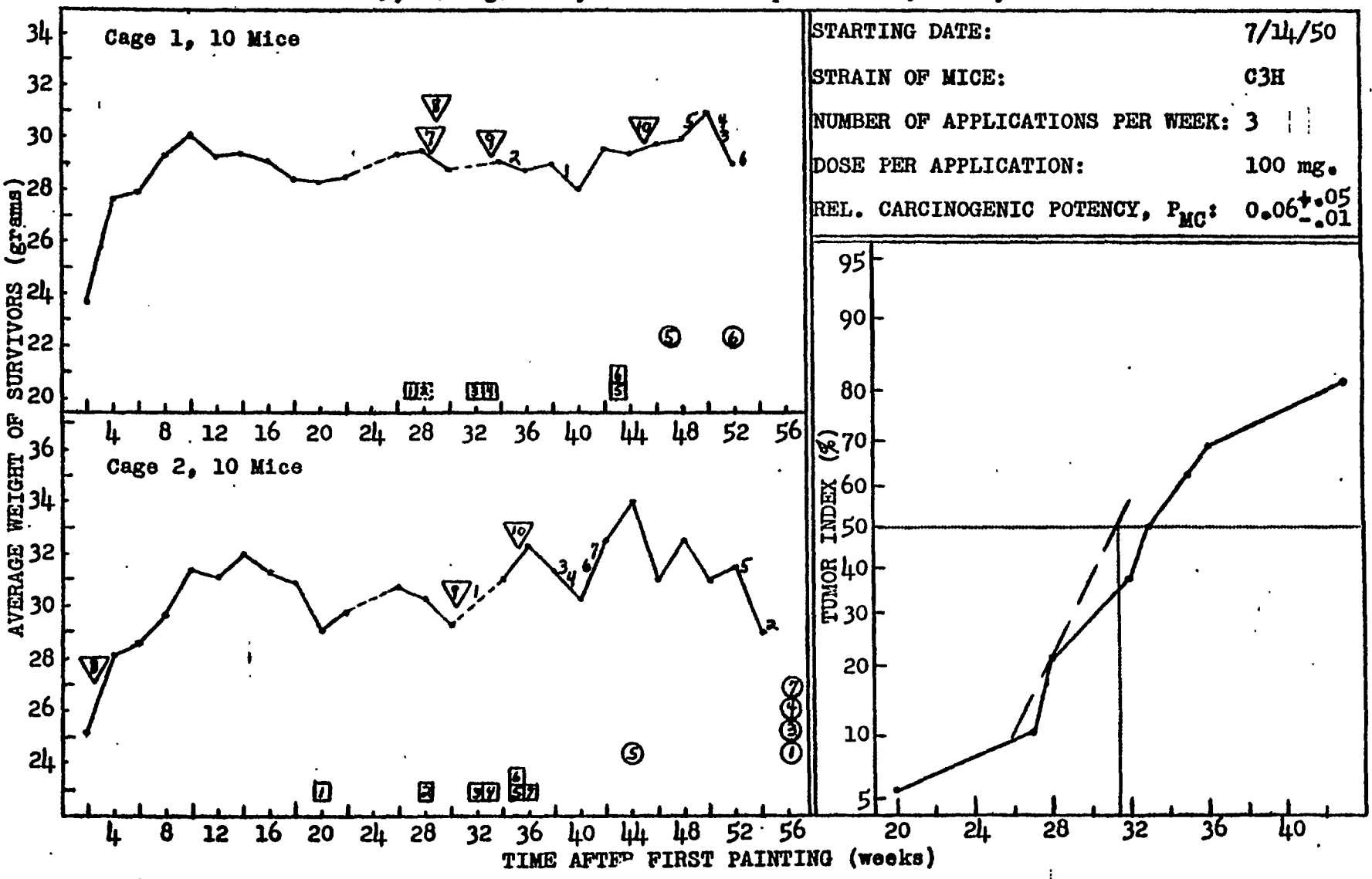
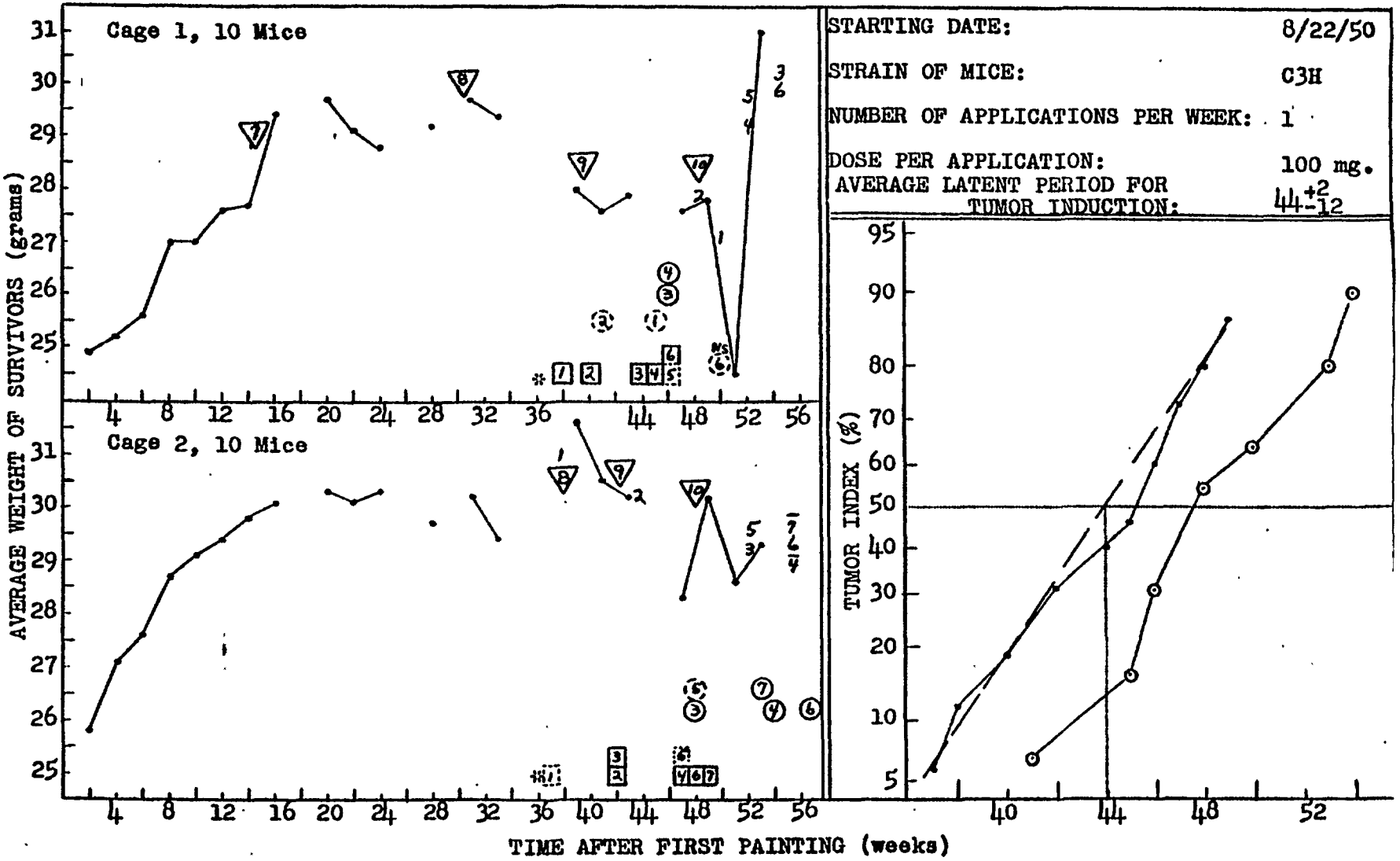
API-225, 0.01 g. Methylcholanthrene per 100 ml. Dodecylbenzene



SKIN PAINTING EXPERIMENT

API-227, 0.10 gram Methylcholanthrene per 100 ml. Benzene



Meeting 2-26-52

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

March 20, 1952

To Members and Associates
Subcommittee on Carcinogenicity

Gentlemen:

I am enclosing a copy of the minutes of the meeting of the Research Project Advisory Committee which was held at Kettering Laboratory, Cincinnati, Ohio, February 26, 1952.

Will you kindly indicate your approval or disapproval of the actions and decisions of the R.P.A. Committee on the enclosed letter ballot and return it to me. Negative votes should be accompanied by an explanation.

I will also appreciate receiving any comments and suggestions you may have concerning the research project at Kettering Laboratory.

Very truly yours,

M. N. Newquist

M. N. NEWQUIST, M.D.
Chairman, Subcommittee
on Carcinogenicity

MNN:RMS
Enclosures
mc: Members and Associates
Medical Advisory Committee
(Without letter ballot)

For Information Only - Not For Publication

REPORT ON SECOND MEETING

Research Project MC-1 Advisory Committee
February 26, 1952
Kettering Laboratory
Cintinnati, Ohio

.....

MEMBERS PRESENT OR REPRESENTED

M. N. Newquist, M.D. - Chairman
E. W. Adams
L. C. Beard, Jr.
Kieffer Davis, M.D.
Robert E. Eckardt, M.D.
T. M. Frank, M.D.
R. M. Landon
E. K. Linder, M.D.
K. G. Mackenzie
R. C. Mithoff
R. M. Shepardson

MEMBERS ABSENT AND NOT REPRESENTED

C. H. Hine, M.D.

OTHERS PRESENT

Kenneth R. Fourcher, M.D.
F. F. Heyroth, M.D.
A. W. Horton
Robert A. Kehoe, M.D.
John J. Phair, M.D.
B. B. Reeve, M.D.

.....

I

PROPOSED OBJECTIVES AND STUDIES

The following memorandum was presented by Dr. W. A. Horton and Dr. John J. Phair, with full discussion by those present:

A. Experiments on Samples of High Potency to Improve Analytical Tools

1. Emphasis on cracked sidestreams from F.C.C. and Coking units, and some cracked residua from T.C.C. units, which have exhibited much higher potencies than predicted on the basis of absorption spectra in the 350-450 m μ range.

   a. Contribution of white oil fractions to effective potencies (initial work on API-8 and 71).

   b. Contribution of fractions, boiling below 675° F., to effective potencies.

   c. Catalytic influence on carcinogenesis of dodecylbenzene used previously not dependent on highly branched side chain; same effect observed with straight chain 2-phenyldodecane.

   d. Consideration of earlier work on limited application tests.

2. Relative contributions of various types of polycyclic compounds to effective potencies of oils.

   a. Pyrene type (including benzpyrenes) more important than non-pyrene type in API-23, F.C.C. cracked sidestream.

   b. Reverse true in fractions 8-10 and 8-11, in which 4-ringed polycyclics predominate, of API-8, F.C.C. cracked residuum.

   c. Further experimentation planned along this line with the aim of developing correction factors to extend the range of applicability of available analytical techniques for estimating potencies.

B. Experiments on Samples of Low to Moderate Potency

1. Untreated lube distillates.

   a. Spectra of fractions of Oklahoma, Kuwait, and Lagunillas crudes received from British Medical Research Council.

   b. Comparison of spectra of distillates from Gulf Coastal crudes with those above and with spectra of API-56, Mid-Continent paraffin distillate, and API-79, San Joaquin (California) naphthenic distillate.

   c. Prediction of potency of many of these distillates from physical properties still more an art than a science; more study needed.

2. Experiments on skin creams and cleansing agents.

   a. Time of appearance of tumors induced by API-8 retarded by barrier cream used (Experiments 312 and 306 described in report of September 25, 1951).

   b. Further experiments along this line, using cream made up of lanolin and olive oil.

C. Modification of Method of Presentation of Data on Individual Animal Experiments

1. Inclusion of average weight curves (see examples attached).

2. Correction of tumor index curves based on "normal" distribution of times of appearance of tumors.
   a. Deviation from "normal" distribution ascribed to variations in health of animals.

   b. Average latent periods for tumor induction (and correlated values of relative potency, P_{MC}) based on corrected tumor index curves.

D. Standardization of Testing Methods (see outline dated January 30, 1952)

1. Control of variations in health of animals.

   a. Efforts to prevent spread of intercurrent infections by sterilization of cages and equipment and isolation of sick animals.

   b. Proportional reduction of total dosage of oil per application and area of skin covered to alleviate systemic toxic effects without lengthening the average latent periods for tumor induction.

   c. Possible elimination of traces of highly toxic constituents of oils by percolation through a suitable adsorbent (probably not applicable to residual fuel oils).

2. The relative carcinogenic potency, P_{MC}, as a value dependent only upon the composition of the material tested, but independent of variations in strain of mice, frequency of application and dosage per application.

3. Reproducibility of determinations of relative potency, P_{MC}.

   a. Repeat experiments on selected oils for biological reproducibility.

   b. Application of statistical methods to analyze observed variance.

E. Procurement of Pure Hydrocarbons for Determination of Catalytic Effects (Alkylaromatics) and Identification of Polycyclics Isolated from Oils

1. API Research Project 6 at Ohio State University possible source of 1-phenyldecane; other alkylaromatics from API Research Project 45.

2. Generous contribution by Dr. M. S. Newman, Ohio State University, of methyl derivatives of chrysene, pyrene, phenanthrene, benzo-(c)-phenanthrene, and 1,2-benzanthracene.

3. Possible sources of dimethylpyrenes and benzacridines in Paris and Brussels being developed.

4. Thanks also due to Professor W. Bergmann, Yale, and Dr. R. N. Jones, National Research Council (Canada), for samples of perylene and various pyrenes.

F. Central Cancer Registry (to date)

1. Reporting

   a. 872 case reports
   b. 12 companies

2. Tabulation

   a. Coding 50 per cent complete
   b. Punching 25 per cent complete

LEGEND FOR DATA SHEETS ON INDIVIDUAL EXPERIMENTS

Symbols used in connection with average weight curves:

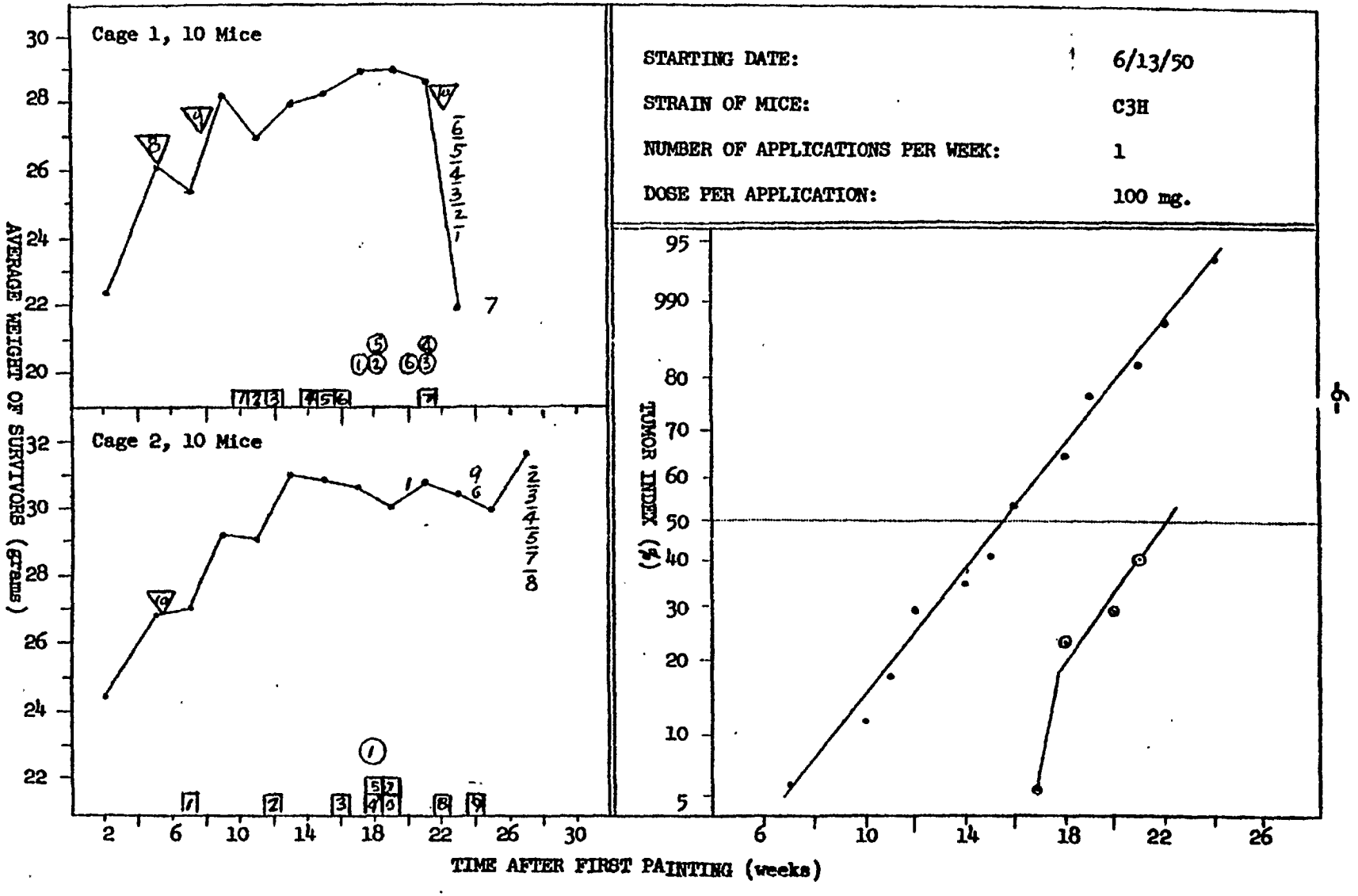
$\overset{i}{\triangledown}$	Time of death of i th tumor-free mouse by "natural" causes.
$\underline{i}$	Time of death of i th tumor-bearing mouse by "natural" causes.
$\overset{i}{\triangledown}$ or $\overline{i}$	Time mouse killed.
$\boxed{i}$	Time of appearance of 1st papilloma in i th mouse.
$\textcircled{i}$	Time of appearance of gross changes indicative of malignancy in tumor of i th mouse (when this symbol is used for a given mouse after its death, the malignancy of the tumor was determinable only by histopathology).

Cumulative dose-response curves:

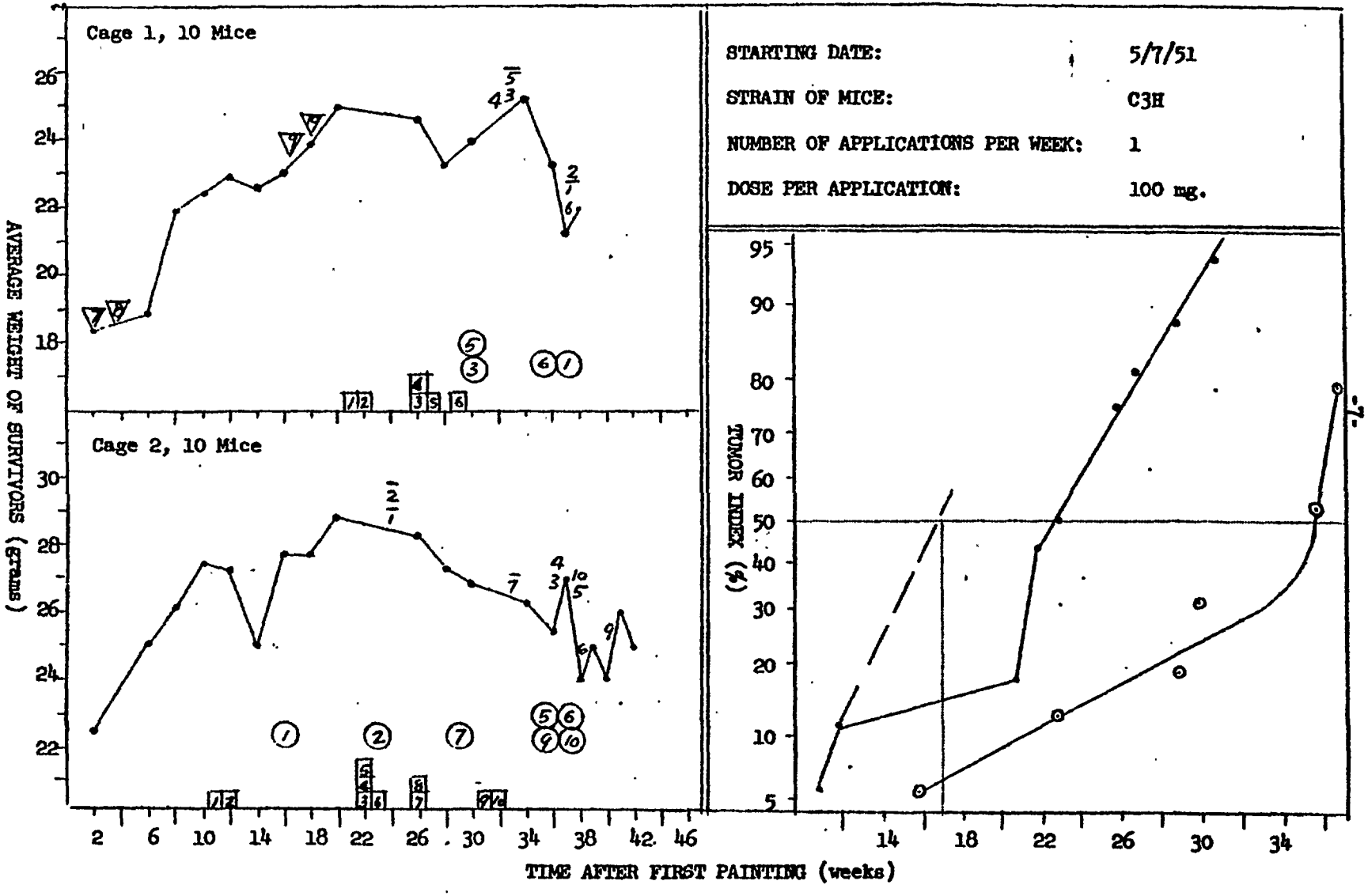
	Experimental curve for benign papillomas.
	Hypothetical curve for papillomas.
	Experimental curve for malignant tumors.

SKIN PAINTING EXPERIMENT

API-8, F.C.C. Cracked Residuum



SKIN PAINTING EXPERIMENT
API-8, F.C.C. Cracked Residuum



McBEE KEY-SORT CODE

API CASE STUDY

Banks		Banks	
T 1-2-3	Case Number	B 1-2-3	Type of Tumor - American Cancer Society Code
T 4-5	Company Number	B 4-5	Primary Site - Maryland State Code
T 6-7-8-9	For Future Use	B 6	Stage of Disease
T 10	Geographic Location	B 7-8	For Future Use
		B 9	Age at Onset
		B 10	Sex and Race
L 1-2	Primary Petroleum Occupation	R 1-2	Principal Other Occupation - National Code
L 3-4	Secondary Petroleum Occupation	R 3	Approximate No. of Years Employed at Principal Other Occupation
L 5	Principal Petroleum Product to Which Exposed	R 4	Principal Irritant Other Than Petroleum
L 6	Secondary Petroleum Product to Which Exposed	R 5	Approximate No. of Years Exposed to Principal Irritant
L 7	Approximate No. of Years in the Petroleum Industry Prior to Onset	R 6	Secondary Irritant Other Than Petroleum
		R 7	Approximate No. of Years Exposed to Secondary Irritant

ACTION ON THE ABOVE MEMORANDUM:

1. It was the consensus that more rapid progress would be made in developing an analytical tool if known carcinogens in pure solvents were also used in order to establish reliable base lines.

2. It was agreed to conduct a series of tests on a limited number of rabbits and mice using known carcinogens to establish comparative data and to coordinate, if possible, our findings with those of the British research workers.

3. It was agreed that we modify our previous action limiting studies on crude to include a heavy distillate of heavy gulf coastal crude and that such a sample should be referred to in subsequent reports by its spectroscopic character or other appropriate identifying data rather than by its source. This principle of labeling to be observed if other studies are made of domestic crudes even though no further studies are contemplated at this time.

4. It was agreed to study the effects of viscosity by altering the physical rather than the chemical properties of a sample, which could be accomplished by use of additives such as vistanex, methyl stearates, acryloids, etc. Mr. R. M. Shepardson offered to supply vistanex in suitable quantities.

5. It was agreed that study of any possible accelerating or inhibiting effects of trace metals on carcinogenicity be referred in view of the press of other work.

6. Dr. Phair made a progress report calling attention to the need for adequate records in various medical departments throughout the industry and to the need for obtaining both historical and current epidemiological data. Practically all reports submitted have been historical. In view of the importance and urgency of collecting reliable biostatistics, it was voted to request the Subcommittee on Carcinogenicity to initiate prompt action aimed at adequate records and filing practices and the gathering of the indicated reports for the central cancer registry.

II

PROGRESS OF WORK SINCE LAST RPA COMMITTEE MEETING 11/26/51

A review of the minutes of the above meeting revealed that the items were either covered by the memorandum presented on 2/26/52 by Drs. Horton and Phair or they were either under study or about to be studied.

With respect to the study of Scottish shale oil and fractions thereof, Dr. Horton commented that the studies may be run outside of the API project.

Work on an analytical tool is progressing, using a spectrophotometric approach. Eventual success is hoped for, but considerable work remains to be done. Accomplishments, future objectives and budgetary requirements can only be determined as the work progresses.

With respect to accomplishment, it was the consensus that sufficient work has now been done at Kettering Laboratory on the subject of carcinogenicity to warrant publishing an article or report in an appropriate scientific journal. Dr. Kehoe agreed to do this in the reasonably near future.

III

BUDGET

Dr. Kehoe presented his estimated budget of $104,760 for one year beginning July 1, 1952, covering research project MC-1 API as submitted to Mr. D. V. Stroop on February 11, 1952.

ACTION It was voted that the budget submitted by Dr. Kehoe, totaling $104,760 be recommended to the Subcommittee on Carcinogenicity for acceptance and that the budget so submitted show amounts assigned to the different types of work such as chemical, biological and epidemiological studies.

IV

TIME AND PLACE OF NEXT MEETING

It was agreed that the RPA Committee would meet again at the call of the chairman.

V

ADJOURNMENT

There being no further business, the meeting was adjourned.

Approved:
M. N. Newquist, M.D.
Chairman

T. M. Frank, M.D.
Acting Secretary

MEMORANDUM FROM THE KETTERING LABORATORY

SECOND MEETING OF THE ADVISORY COMMITTEE

API RESEARCH PROJECT MC-1

February 26, 1952

A. Experiments on Samples of High Potency to Improve Analytical Tools

1. Emphasis on cracked sidestreams from F.C.C. and Coking units, and some cracked residua from T.C.C. units, which have exhibited much higher potencies than predicted on the basis of absorption spectra in the 350-450 mμ range

   a. Contribution of white oil fractions to effective potencies (initial work on API-8 and 71)

   b. Contribution of fractions, boiling below 675°F., to effective potencies

   c. Catalytic influence on carcinogenesis of dodecylbenzene used previously not dependent on highly branched side chain; same effect observed with straight chain 2-phenyldodecane

   d. Consideration of earlier work on limited application tests

2. Relative contributions of various types of polycyclic compounds to effective potencies of oils

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   b. Reverse true in fractions 8-10 and 8-11, in which 4-ringed polycyclics predominate, of API-8, F.C.C. cracked residuum

c. Further experimentation planned along this line with the aim of developing correction factors to extend the range of applicability of available analytical techniques for estimating potencies.

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a. Spectra of fractions of Oklahoma, Kuwait, and Lagunillas crudes received from British Medical Research Council (also Manchester white oil)

Kuwait like API-Okla very low" Lagun. higher than but [illegible] (highest boiling have greatest effect in long run

b. Comparison of spectra of distillates from Gulf Coastal crudes with those above and with spectra of API-56, Midcontinent paraffin distillate, and API-79, San Joaquin (California) naphthenic distillate

Code Spectra

Use Code letters in report tables

Shall we test 2 samples from Gulf Coast? 250 for heavy cor. Mid C ac g.o. for sweet [illegible]

c. Prediction of potency of many of these distillates from physical properties still more an art than a science; more study needed

Yes

2. Experiments on skin creams and cleansing agents

a. Time of appearance of tumors induced by API-8 retarded by barrier cream used (Experiments 312 and 306 described in report of September 25, 1951)

Report ingredients in Verex in April interim report

b. Further experiments along this line, using cream made up of lanolin and olive oil

500 Vistanex (iso C4-polymer

Viscosity effects (increase visc. of an oil by Rohm & Haas acryloids or similar)

C. Modification of Method of Presentation of Data on Individual Animal Experiments

1. Inclusion of average weight curves (see examples attached)

2. Correction of tumor index curves based on "normal" distribution of times of appearance of tumors
   a. Deviation from "normal" distribution ascribed to variations in health of animals
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      c. Possible elimination of traces of highly toxic constituents of oils by percolation through a suitable adsorbent (probably not applicable to residual fuel oils)
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$\overline{\triangledown}$ or $\overline{i}$ Time mouse killed

$\boxed{i}$ Time of appearance of 1st papilloma in i th mouse

Ⓘ Time of appearance of gross changes indicative of malignancy in tumor of i th mouse (when this symbol is used for a given mouse after its death, the malignancy of the tumor was determinable only by histopathology).

Cumulative dose-response curves:

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o———•——— Experimental curve for malignant tumors

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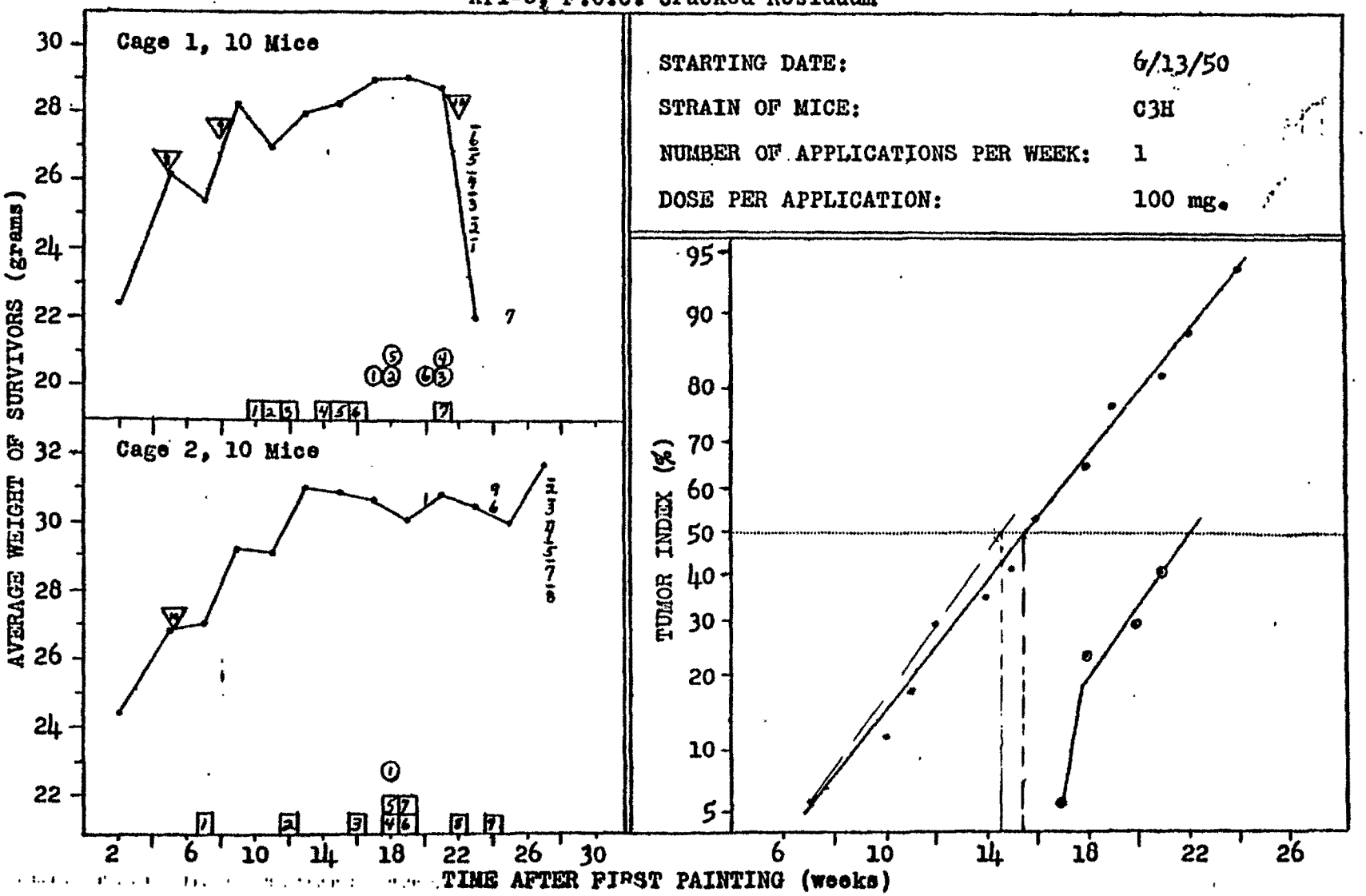

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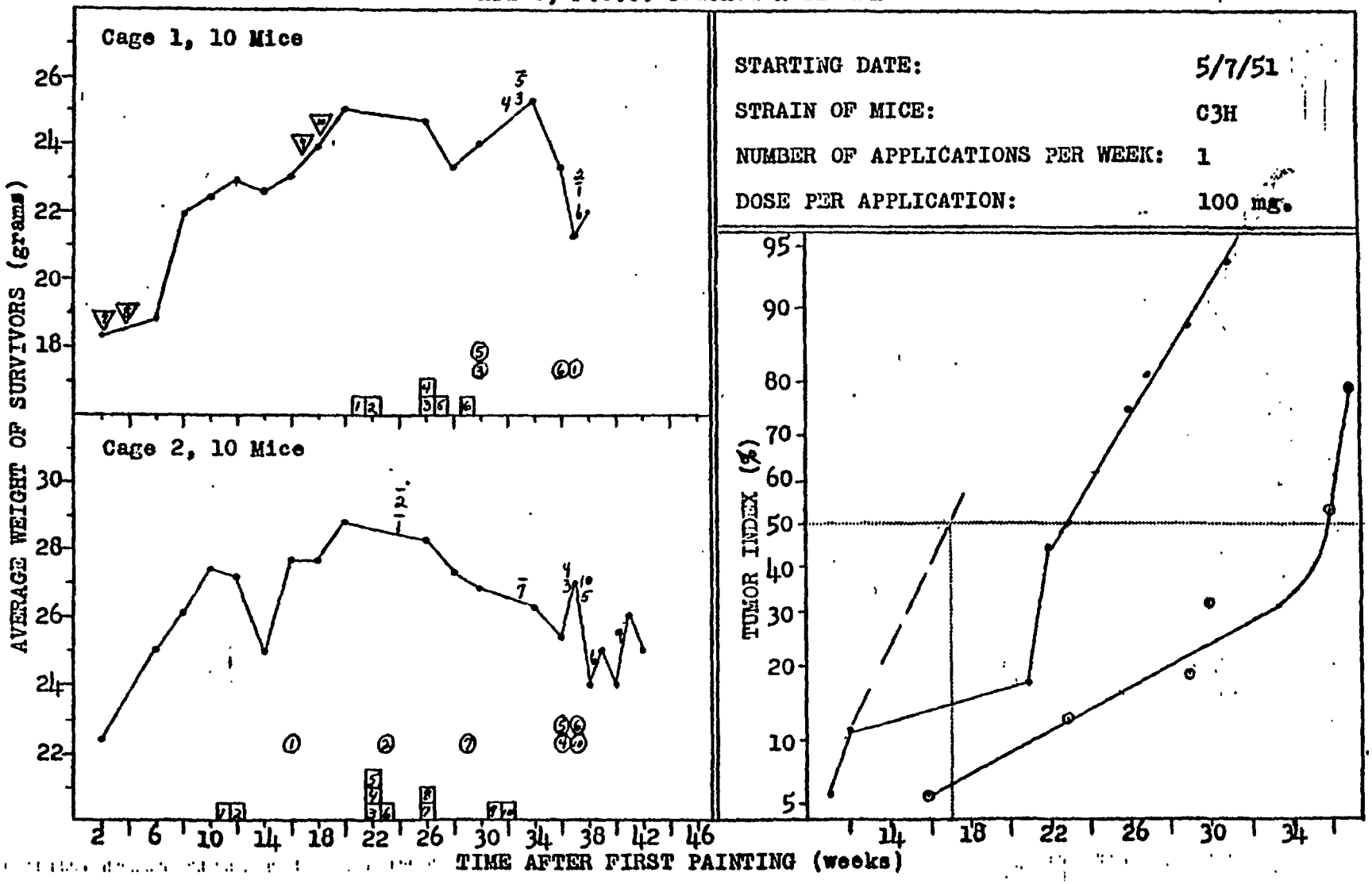

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API CASE STUDY

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T	4-5	Company Number	B	4-5	Primary Site - Maryland State Code
T	6-7-8-9	For Future Use	B	6	Stage of Disease
T	10	Geographic Location	B	7-8	For Future Use
			B	9	Age at Onset
			B	10	Sex and Race
L	1-2	Primary Petroleum Occupation	R	1-2	Principal Other Occupation - National Code
L	3-4	Secondary Petroleum Occupation	R	3	Approximate No. of Years Employed at Principal Other Occupation
L	5	Principal Petroleum Product to Which Exposed	R	4	Principal Irritant Other Than Petroleum
L	6	Secondary Petroleum Product to Which Exposed	R	5	Approximate No. of Years Exposed to Principal Irritant
L	7	Approximate No. of Years in the Petroleum Industry Prior to Onset	R	6	Secondary Irritant Other Than Petroleum
			R	7	Approximate No. of Years Exposed to Secondary Irritant

meeting 11-26-51

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

December 10, 1951

Members and Associates
Subcommittee on Carcinogenicity

Gentlemen:

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Will you kindly indicate your approval or disapproval of the actions and decisions of the R.P.A. Committee on the enclosed letter ballot and return it to me. Negative votes should be accompanied by an explanation.

I will also appreciate receiving any comments and suggestions you may have concerning the research project at Kettering Laboratory.

Very truly yours,

M. N. Newquist

M. N. Newquist, M.D.
Chairman, Subcommittee
on Carcinogenicity

MNN:GH
Enclosure

mc: Members and Associates
Medical Advisory Committee
(WITHOUT LETTER BALLOT)

REPORT ON FIRST MEETING

RESEARCH PROJECT MC-1 ADVISORY COMMITTEE

November 26, 1951
Kettering Laboratory
Cincinnati, Ohio

MEMBERS PRESENT OR REPRESENTED

M. N. Newquist - Chairman

E. W. Adams
L. C. Beard, Jr.
Kieffer Davis
R. E. Eckardt
T. M. Frank
R. M. Landon
E. K. Linder
(Rep. by R. D. Bent)
K. G. Mackenzie
R. M. Shepardson

MEMBERS ABSENT AND NOT REPRESENTED

C. H. Hine
R. C. Mithoff

OTHERS PRESENT

F. F. Heyroth - Kettering Laboratory
A. W. Horton - Kettering Laboratory
Robert A. Kehoe - Kettering Laboratory
John J. Phair - Kettering Laboratory
David V. Stroop - American Petroleum Institute

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I

PROGRAM OF PROJECT MC-1

In opening the meeting the chairman outlined the aims of the Medical Advisory Committee, and stated that the Research Project Advisory Committee had been appointed to afford a closer bond of understanding between committee members and research workers.

Those present were handed copies of a "Memorandum from Kettering Laboratory on Further Prosecution of API Research Project MC-1," dated November 26, 1951, which was discussed and acted upon item by item as follows:

"A. Process Samples for Animal Tests

"1. Cracked residua from thermal cracking of virgin gas oils (samples to be collected)."

Two samples of residua from thermal cracking operations at Everett and Aruba refineries were offered by R. M. Shepardson as products of thermal cracking operations which have been used without significant change for many years.

ACTION The advisory committee voted to accept the offer of the two samples.

"2. Sidestreams and residua from other cracking processes to be tested on a limited basis to improve analytical methods of estimating potency and further to test the validity of these methods (these samples already collected, analyzed spectrophotometrically, and held in reserve in the laboratories of twenty-one of the participating companies)." A

In response to a question, it was explained that these samples were not fuel oil; they comprised a limited number of existing samples requiring biological tests to round out data needed in the development of the analytical tool.

ACTION The recommendation was accepted.

"3. Untreated lube stocks from straight run distillation now being screened by analytical methods. Samples to be selected for animal testing on the basis of a comparison of their physical properties (including absorption spectra) with those of virgin distillates already tested." B 1

ACTION In the understanding that these samples comprised those received from the British Medical Research Council, the committee voted for a prompt initiation of animal and analytical tests on the Oklahoma Bright Stock and Kuwait and Venezuela crude oils.

"4. Scottish shale oil and fractions thereof. To gain further analogies between potencies to mice and potential hazards to exposed humans, two or three fractions of shale oil comparable to those employed as spindle lubricants in the British cotton industry to be tested. (Samples already collected and held at Kettering Laboratory.)"

ACTION Because of its value as a historical tie-in, the committee accepted this recommendation.

"B. Reference Standards

"For control purposes and improvement of biological methods it is contemplated that tests on known concentrations of standard carcinogens in standard solvents will be carried out with about 9 per cent of the animals received." D

Discussion of this phase of work pointed up its growing importance as a fundamental tool needed by independent investigators in seeking comparable and reproducible results.

This shift in relative importance towards fundamental factors, such as solvents, dosage, and "co-carcinogens" was emphasized by a number of members.

ACTION The committee accepted Doctor Kehoe's offer to submit, within 60 days, a revision of this item to include all known factors and corrections of significant importance to the establishment of standardized procedures.

"C. Analytical Techniques for Estimating Carcinogenic Potencies of Petroleum Products

"Chemical research will continue on the two main approaches to this goal, the empirical and the fundamental. Animal testing of fractions which can furnish useful information for this purpose will, as in the past, be given priority over tests on process samples. At the same time, it is recognized that an analytical tool has very limited significance when based on an inadequate number of biological tests of samples of materials to which it is to be applied.

A + B

"Tests on non-carcinogenic fractions of various oils will be conducted to determine the effects of variations in the composition of these fractions upon the total effective potency of the oils. It is obvious that if fractions which do not contain polycyclic carcinogens are markedly affecting the rate of induction of tumors in the test animals, then any tool based purely on the concentration of polycyclics will be seriously limited in general applicability."

Members discussed the differing criteria used by investigators at New York University and Kettering Laboratory and pointed out the desirability for a full exchange of data in order to expedite the completion of the best possible analytical tool.

ACTION The committee voted to request these investigators to exchange all data of value incidental to the prompt development of the best possible analytical tool or tools.

"D. Epidemiological Studies

"Efforts to expedite the collection of case records and other pertinent information on an industry-wide basis will be continued. At the present rate of reporting, there should be sufficient accumulation of information by the time of the spring meeting in 1952 to permit a preliminary tabulation of the data."

Doctor Phair made a brief but complete outline of the program of epidemiological studies.

ACTION The committee accepted Doctor Phair's report and program (see Kettering interim reports for past 18 months for program details).

"E. Experimental Study of Efficacy of Various Cleansing Agents and Skin Creams

"As soon as the current tests which employ rinsing with white oil and washing with detergent solution have been completed, new experiments will be started to compare hydrocarbon solvents, such as technical white oil, with the viscous medicinal white oil currently employed as a rinsing material.

"Further tests with other skin creams will be designed on the basis of the results of the current tests with Verex."

ACTION The committee offered no objections to the proposal except to suggest that proprietary cleansing agents and skin creams should not be included in tests unless complete formula information is available, and that in no case should trade names be used in reporting results.

"F. Dilution of Carcinogenic Oils

"Sixteen of the participating companies have already started or completed collection of representative production blends containing carcinogenic streams from catalytic cracking or recycle coking, together with data on the composition of these blends. The majority of the members of the committee have evidenced their desire for an analytical tool applicable to these complex mixtures. Since it is obvious that no such tool could be developed without knowing the biological potency of at least a few of the blends, a selected group of these materials, on which detailed information is available, should be subjected to animal testing."

Members of the committee pointed out the endless complexities of mixtures occurring in refinery operations and the futility of testing two or six or twelve of the hundreds and even thousands of mixtures which would be produced in refineries during the progress of such tests.

ACTION The committee voted against the collection of these production blends in favor of blending samples now at hand for which analytical and biological data are already available.

II

SYNTHESIS OF CARCINOGENS AND SOLVENTS

ACTION At the suggestion of L. C. Beard, Jr., it was agreed that synthesis of each carcinogen or solvent should be considered jointly by directors of Projects MC-1 and 42, but that the initial step in each case should be taken by Doctor A. Wesley Horton by letter addressed to Doctor Harry Sutherland, Chairman,

Project 42 Advisory Committee, c/o Shell Oil Company, P.O Box 1531, Modesto, California, with carbon copies to Doctor L. C. Beard, Jr., and Doctor Robert W. Schiessler, Director, API Project 42, The Pennsylvania State College, State College, Pennsylvania.

III

LIMITED APPLICATION TESTS ON "HIGH-POTENCY" OILS

Discussion of this subject developed information of work already done independently by two investigators.

ACTION It was a consensus that the results of work done should be correlated and that additional work should be done if needed to supplement the correlation.

A1d

IV

PAPILLOMAS VS. MALIGNANCIES IN REPORTING POTENCIES

ACTION There was a consensus that the supplying of complete data sheets was the only factual answer to this difficulty; also it was agreed that microscopy should be used to prove malignancies.

C

V

NEXT MEETING

Consideration was given to the time and place of the second meeting of the advisory committee.

ACTION The committee agreed that the second meeting should be held at Kettering Laboratory sometime in February or early March, but left the exact date to be selected by the chairman at a time when there would be no conflict with the Washington meeting of ASTM Committee D-2, or other important industry meetings.

VI

ADJOURNMENT

There being no further business the meeting was adjourned.

Approved:

M. N. Newquist, M.D.
Chairman

D. V. Stroop
Acting Secretary

12-10-51

Notes - Research Project Advisory Committee Meeting November 26, 1951

A. 1. Two fuel oils from Jersey

2. Lowest priority

3. British

4. Check

B. More Reference standard experiments

E. Part of B.

F. Use synthetic blends of samples already tested.

Dr. Sutherland - Shell Agricultural

N_2 blanket for all samples

Keep this copy where we can find it

MEMORANDUM FROM THE KETTERING LABORATORY ON FURTHER PROSECUTION OF API RESEARCH PROJECT MC-1

Scope of Project

In February, 1949, the Medical Advisory Committee recommended that materials from the following processes be studied:

NON-CATALYTIC CRACKING

Cracking of catalytic gas oil
Cracking of virgin gas oil
Viscosity breaking of residues or extracts
Naphtha reforming
Coking
Gas reversion and polyforming
Steam cracking

CATALYTIC CRACKING

Houdry
T. C. C.
F. C. C.
Houdryflow
Cycloversion
Hydroforming
Desulfurization (marginal case)

PRODUCTION AND LUBE REFINING

Rod waxes
Slack waxes and press oils
Certain raw lube stocks (untreated)
Solvent extracts (furfural, phenol, sulfurdioxide)
Acid oils from acid sludge (marginal case)

PRODUCTS FROM OTHER INDUSTRIES

Coal tar
Water gas tar
Shale oil - domestic and British sources.

In line with the interests of this committee and further recommendations expressed at the regular meetings, the following related phases of the problem have been given careful attention by the investigative group:

June 19, 1956

Dr. L. C. Curtis
California Research Corporation
200 Bush Street
San Francisco, California

Dear Doctor Curtis:

Attached is a copy of a paper which we propose to present as part of a symposium on polycyclic hydrocarbons at the September meeting of the American Chemical Society. Copies have been distributed to each member of the Subcommittee on Carcinogenicity for their review and suggestions for improvement.

As you will note from the attached letter of transmittal, we are, with the chairman's agreement, running considerably beyond the formal deadline for receipt of manuscripts for this symposium. We have prepared thirty additional copies of this manuscript for distribution to the other members of the API Medical Advisory Committee. We shall, of course, hold them until we have your instructions as to the timing of the distribution desired. Or, if you prefere, we can of course send them on to you or to Mr. Stroop for further processing.

With best personal regards,

Sincerely yours,

A. Wesley Horton

AWH:mjg
Attachment
CC: Dr. R. C. Mitthof