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Medical Advisory Committee

For Information Only - Not For Publication

AMERICAN PETROLEUM INSTITUTE
MEDICAL ADVISORY COMMITTEE

Minutes of Meeting
November 16, 1945
Stevens Hotel
Chicago, Illinois

MEMBERS PRESENT:

McIver Woody - Chairman
D. V. Stroop - Secretary

W. O. Armstrong
V. C. Baird
F. F. Boys

T. M. Frank
A. E. Hoag
J. P. Holt

M. N. Newquist
B. B. Reeve
O. S. Somerville
(Rep. by W.W. Brooks)

MEMBERS ABSENT:

D. M. English
R. A. Jewett

W. R. Levis
W. A. Morrison

J. F. Peattie
H. S. Thomson

ASSOCIATES PRESENT:

E. W. Adams
L. C. Beard, Jr.
R. S. Bonsib

R. C. Cole
Nelson J. Gothard
H. P. Lankelma

H. R. Warrick
F. M. Watkins

GUEST:

Robert A. Mehoe, M.D. - Kettering Laboratory, University of Cincinnati.

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I

MINUTES OF PREVIOUS MEETING

Action: The minutes of the meeting held May 7-8, 1945 at St. Louis were approved as circularized.

II

REPORTS OF SUBCOMMITTEE CHAIRMEN

A - Subcommittee on Carcinogenicity - M. N. Newquist, Chairman.

Dr. Newquist presented a formal report with outline of proposed research project and copy of the form of agreement required by the University of Cincinnati in its toxicity investigations. (See Appendix A to these minutes.)

Dr. Vehoe and the members discussed in detail the report, the outline of work, and the form of agreement.

- Action:
1. The report of the chairman was accepted
 2. It was agreed unanimously that the type of agreement required by the University of Cincinnati should be signed, if necessary, in order that the Medical Advisory Committee may promptly progress the selection of a suitable investigator.
 3. It was agreed unanimously that the Kettering Laboratory of Applied Physiology should be selected to initiate the investigation on carcinogenicity as outlined by the subcommittee.
 4. It was agreed unanimously that the matter of selecting samples for the investigation should be referred back to the Subcommittee on Carcinogenicity with power.

B - Subcommittee on Chlorinated Compounds - F. F. Boys, Chairman.

Dr. Boys presented a formal report which was discussed at length by those present. (See Appendix B to these minutes.)

- Action:
1. With slight amendments, the report was accepted.
 2. The secretary was requested to transmit copies of the report to directors of the American Petroleum Institute with the suggestion that the report may be of interest to medical, legal, and cutting oil sales departments.

C - Subcommittee on Permissible Concentrations - V. C. Baird, Chairman.

Dr. Baird presented a formal report, a copy of which is attached as Appendix C to these minutes.

- Action:
1. With a few additions to the lists of industrial toxic materials, the report was accepted.
 2. The secretary was requested to send duplicate copies of the list of industrial toxic materials to all members and associates and to ask them to return one copy upon which the listed materials, and any additional materials, are classified into three groups so as to indicate three degrees of need for prompt publication of data.

D - Subcommittee on Medical Policies and Practices - R. A. Jewett, Chairman.

In the absence of Dr. Jewett, the subcommittee report was presented by Dr. Frank. (See Appendix D to these minutes.)

- Action: 1. The report of the Subcommittee on Medical Policies and Practices was accepted with expressions of appreciation for the splendid service contributed by Dr. Jewett.
2. The chairman was asked to make additional appointments to the membership of the subcommittee to replace those who have indicated their inability to serve.

III

BUDGETS FOR 1946 COMMITTEE ACTIVITIES

- Action: During the meeting, 1946 budgets were established and funds were allocated for activities as follows:
- (A) A budget was established and \$2,500 of the Medical Research Fund were allocated to initiate the library research on permissible concentrations, as recommended by the Subcommittee on Permissible Concentrations.
 - (B) A budget was established and \$6,000 of the Medical Research Fund were allocated to initiate the investigation to be conducted by the Kettering Laboratory.
 - (C) An unspecified amount of the Medical Research Fund was authorized for expenditure in the purchase of a library of 10 authoritative books on toxicology and a suitable shipping case so that arrangements could be made to have such books available at future meetings of the Medical Advisory Committee.

IV

CHANGES IN COMMITTEE ORGANIZATION AND PROCEDURE

- Action: 1. The committee regretfully accepted the resignation of Doctor I. E. Percy.
2. The members agreed unanimously that Dr. Woody should continue as chairman during 1946.
3. The chairman was requested to consider and to make several changes in subcommittee memberships. (These will be announced in the near future.)
4. Chairmen of subcommittees were requested to prepare their reports at the earliest practicable date so that copies may be circularized in advance of each meeting.

Note by Secretary: Such prior circularization will be done by API Headquarters for reports received not later than 30 days prior to a meeting.

5. The secretary was requested to circularize copies of a revised list of members and associates complete with P.O. addresses.

NEW BUSINESS

Bacteria in Cutting Oils

Dr. Hong read memorandum dated November 2, 1945 from James T. Beard, Jr. as follows:

"The report of the Subcommittee on Chlorinated Compounds of the API Medical Advisory Committee, dated October 16, should be of interest to all marketers of cutting fluids. We feel that it is an important step in calling attention to the possible effects of various types of chlorinated materials. We are quite in agreement with the conclusions that have been reached.

"We are now suggesting that other phases of this problem are worthy of investigation -- namely, those phases that deal with bacteria, the effects of bacteria on operators, and the control of bacteria in all types of cutting fluids. We suggest the following line of investigation:

- (a) An investigation of the various types of bacteria found in used cutting fluids, both non-soluble and soluble -- the pathogenic groups, and the facultative anaerobic groups;
- (b) The rate of growth of the various bacteria in various types of fluids --
 - 1. Mineral oil
 - 2. Mineral oil and fat
 - 3. Mineral oil and sulphurized fat
 - 4. Sulphurized mineral oil
 - 5. Sulphurized mineral oil and fat
 - 6. Sulphurized mineral oil and sulphurized fat
 - 7. Mineral oil and chlorine
 - 8. Sulphurized mineral oils and chlorine
 - 9. Soluble oils and soft water
 - 10. Soluble oils and hard water
- (c) The effectiveness of various germicides on the various groups of bacteria, and the percentages required to keep cutting fluids sterile.

"This is an extensive program, and it may not be practical, or even possible, to carry out in its entirety. However, any steps that can be taken to enlighten us and the general public along these lines will be very beneficial."

Action: The subject was referred to the Subcommittee on Chlorinated Compounds for study.

The secretary requested the committee to nominate a member and an alternate to serve as API representatives on Committee 237.

Action: The committee nominated Dr. Woody and Mr. Bonsib as the member and alternate, respectively.

VII

NEXT MEETING

Action: It was agreed that the next meeting should be held in Chicago on Monday, April 8, 1946, which is the first day of the 1946 meeting of the American Association of Industrial Physicians and Surgeons.

VIII

ADJOURNMENT

As there was no further business to come before the meeting, it was adjourned.

Approved
McIver Woody
Chairman

D. V. Stroop
Secretary

December 3, 1945

APPENDIX A

For Information Only - Not For Publication

REPORT OF SUBCOMMITTEE ON CARCINOGENICITY

TO: DR. McIVER WOODY
CHAIRMAN, MEDICAL ADVISORY COMMITTEE - API

On August 13, 1945, a meeting of the Subcommittee on Carcinogenicity was called in New York. Those who attended were:

Dr. M. N. Newquist
Dr. A. E. Hoag
Dr. I. E. Percy
Dr. McIver Woody
R. S. Bonsib
L. C. Beard
H. R. Warrick
D. V. Stroop
Dr. R. A. Kehoe (guest)

At this meeting, the objectives and procedure for study of Carcinogenic properties of hydrocarbons were presented in outline form to Dr. R. A. Kehoe to see if he and the Kettering Laboratory would undertake to make the study. Dr. Kehoe seemed to be interested in making the study, but he wished to consider it further before coming to a conclusion.

In a letter to Mr. Stroop dated August 28, 1945, Dr. Kehoe stated that he wished to have two matters clarified before proceeding further, namely, (1) A formal agreement under which the work of the Kettering Laboratory was to be carried out (copy of agreement form attached), and (2) He wished to have a clearer understanding of the particular problem in question.

Since there was a difference of opinion among members of the Subcommittee as to whether the contract should be signed in the form submitted by Dr. Kehoe, a meeting of the Subcommittee members in New York (Newquist, Woody, Hoag, Adams, Beard, Warrick attended) was called on September 20th in New York for further discussion, and for a tentative selection of petroleum products to be studied. The difference of opinion with respect to the contract still existed at the close of this meeting, so Mr. Stroop was requested to write Dr. Kehoe for further clarification of certain phases of the proposed contract. This was done by Mr. Stroop on September 25, 1945 - which included an invitation to Dr. Kehoe to attend the meeting of the Medical Advisory Committee in Chicago on November 16, 1945.

In a letter to Mr. Stroop dated October 13, 1945, Dr. Kehoe advises to the effect that the Kettering Laboratory could not undertake to make our proposed study unless the contract submitted by the University of Cincinnati was signed by the American Petroleum Institute. Dr. Kehoe may wish to amplify his position personally at the meeting on November 16th.

Since the signing of the proposed contract involves a matter of policy of the API, it is suggested that the recommendation of the Medical Advisory Committee of the API be obtained in this connection before proceeding further.

API 06778

Respectfully submitted,

Dr. H. N. Newquist, Chairman .

November 16, 1945

Members:

Dr. H. N. Newquist
Dr. A. E. Hoag
Dr. Joseph P. Holt
Dr. I. E. Percy
Dr. Wm. h. Lewis

Mr. H. R. Warrick
Mr. L. C. Beard
Mr. Roy S. Bonsib
Mr. H. E. Kemmerer

PROPOSED RESEARCH PROJECT

Outline of Study of Carcinogenic Properties of Hydrocarbons

Objectives

- A - Immediate -- To study carcinogenic properties of those petroleum products which, on the basis of present knowledge, are most likely to embody such qualities, (diesel oil, furnace oil, heavy fuel oil, road oils, asphalt and coke) and with which refinery employees and the public are most likely to come into contact, so that any indicated precautionary measures may be instituted
- B - Future -- To study pure hydrocarbons contained in petroleum products in an effort to determine the presence or absence of specific carcinogenic factors.

Procedure

- A - It is proposed that a centralized laboratory adequately staffed and equipped (portions of the study may be assigned to other acceptable research institutions) conduct appropriate studies in line with the objectives stated above, which would include:
 - 1. Literature survey of the carcinogenicity of bituminous compounds to date.
 - 2. Examination of samples of petroleum products* which will be submitted at the direction of the Medical Advisory Committee, these samples to be subjected to both analytical and animal testing in order to determine their possible carcinogenic properties. It is proposed that these samples be drawn from representative thermal and catalytic cracking operations, using a wide range of crudes and operating conditions. Control tests will also be run using known similar carcinogens.
 - 3. The development, concurrently and based upon the above testing of samples, of a chemical and/or physical test which will determine the carcinogenicity of a given material without the necessity of conducting animal tests.
 - 4. The development of a means or a method by which the carcinogenic properties of the petroleum product concerned may be neutralized.
- B - Although the incidence of cancer among petroleum workers is not unfavorable as compared to that of the general population, it is proposed, nevertheless, to request information from the medical departments of those companies having adequate records, as to the incidence of cancer among their respective employees which was ascribed to their occupation (1) in the past, and (2) in the future.

* 1. Domestic No. 2 Fuel Oils

- a. Straight run
- b. Thermal Recycle
- c. Houdry or TCC Recycle
- d. Fluid Recycle

2. Heavy Fuel Oils

- a. Straight Residual
- b. Thermal Tars
- c. Houdry or TCC Tars
- d. Fluid Tars

~~C O P Y~~

THIS AGREEMENT

Made this 19th day of 1946, between ~~the American Petroleum Institute~~ (hereinafter called: "the Donor"), and the UNIVERSITY OF CINCINNATI, (hereinafter called: "the University")

W I T N E S S E T H

WHEREAS, the ~~AMERICAN PETROLEUM INSTITUTE~~ wishes the Kettering Laboratory of Applied Physiology (hereinafter called: "the Laboratory") to investigate the toxicity and mode of action of certain ~~chemical~~ petroleum products to be mutually agreed upon hereafter from time to time; and

WHEREAS, the University has approved such investigative work by said Laboratory,

In consideration of the mutual promises hereinafter specified,
IT IS AGREED:

1. The Laboratory shall carry out such investigations within the limits of its available facilities and scientific interests.
2. The Donor shall pay the University therefor the sum of SIX THOUSAND (6000) DOLLARS on or before FEBRUARY 1 1946 and additional sums in advance from time to time as may mutually be agreed upon as necessary to prosecute projected experimental work for a definite period of time. At the end of each fiscal year or other period agreed upon for the completion of a specific project, the University shall refund to the Donor any unexpended balance of any payment remaining after the investigative work has been completed, or shall apply the balance to the continuance of such similar work as may be agreed upon as desirable.
3. The name of the University or of the Laboratory or of any member, officer or employee of the University or the Laboratory,

~~C O P Y~~
~~(continued)~~

- 2 -

shall not be used in any advertising matter at any time during the progress of the work or thereafter. A written report shall be made of the findings and such a report or a photostatic copy thereof may be used by the Donor as evidence of the facts established. If the findings are published in a scientific journal, the Donor shall be free to quote such findings subsequent to publication.

4. The investigative work shall be planned and carried out by the University, and the University shall have the right to disseminate for the public good, any information obtained: However, before the issuance of public reports or scientific publications, the manuscripts thereof will be submitted to the Donor for criticism and suggestion.

5. No person shall be required to make an application for patent based on any invention, discovery or development resulting from any investigative work under this Agreement.

IN WITNESS WHEREOF the parties hereto have executed this Agreement by their proper officer, respectively, who are hereby certified to have been duly authorized to execute the same.

AMERICAN PETROLEUM INSTITUTE

By _____ *President*
By _____ *Secretary*

UNIVERSITY OF CINCINNATI
through its BOARD OF DIRECTORS

By _____ Chairman

By _____ Clerk

APPENDIX B

For Information Only - Not For Publication

REPORT OF SUBCOMMITTEE ON CHLORINATED COMPOUNDS API MEDICAL ADVISORY COMMITTEE

THE PROBLEM

Cutting oils containing several percent of Chlorinated Compounds have been used in industry. The compounds used have been Chlorinated Paraffin, Chlorinated Naphthalene, Chlorinated Diphenyl and Chlorinated Diphenyl Oxide. These compounds have been employed to improve the finish of the work and to increase tool life. There have been certain objections both real and theoretical to the use of such compounds from the standpoint of the health of the workers. This has been particularly true in the case of the Chlorinated Aromatics.

A. Systematic Effects - There have been fatal accidents from the use of Chlorinated Aromatics in the coating of electrical cables when drawn through Chlorinated Aromatics such as the Chlorinated Naphthalenes. In these cases, large quantities of the Chlorinated Aromatics were held at elevated temperatures and as a consequence material percentages of the product vaporized and established toxic concentrations in the atmosphere. Frequently ventilation was poor. As a result, inhalation of the product occurred and was in a few cases followed by systemic effects, notably acute yellow atrophy of the liver. This history naturally has made the use of Chlorinated Aromatics suspect.

B. Dermatological Effects - Dermatitis from cutting oils, containing only petroleum hydrocarbons, is not unusual when conditions of uncleanness obtain and when the workers are allergic to petroleum hydrocarbons. More recently recognition has been given, especially by Dr. Louis Schwartz of the U. S. Public Health Service, to a specific type of dermatitis which he has named Chloracne. Dr. Schwartz has published several papers on this subject. The investigations were said to deal with the Chlorinated Aromatics.

The problem of the Subcommittee was to evaluate the importance of both the systemic and dermatological effects of Chlorinated Compounds as related to the health of the workers using cutting oils containing them.

REVIEW OF LITERATURE AND ACCUMULATION OF DATA FROM INDUSTRY

As the quickest approach to obtaining such information as was available either in the literature or in the files of industrial companies, a questionnaire was sent to two manufacturers of Chlorinated Paraffins, to a manufacturer of Chlorinated Naphthalenes, to a manufacturer of Chlorinated Diphenyls and to a manufacturer of Diphenyl Oxides. These companies were the outstanding manufacturers and marketers of such products. They were requested to supply any data or the results of any physiological investigations they had on:

1. Dermatological effects of the compounds made by them.
2. Systemic effects of the compounds made by them.
3. Recommended precautions in use from the standpoint of inhalation and contact.

4. Brief statement as to any serious cases of dermatosis or systemic poisoning.
5. What laboratories or institutes they considered most skilled in conducting investigations of the toxicity of such compounds as related to their industrial uses.

The response to this questionnaire was unanimous, cooperative, and unbiased. The consensus was that the Chlorinated Aromatics could and did cause serious systemic poisoning, as well as dermatosis, especially under conditions of poor ventilation and poor hygiene. The Chlorinated Paraffins on the other hand seem to be relatively free of these objections.

One company reported, "In all our experience we have been unable to learn of any evidence that Chlorinated Paraffin Wax has either dermatological or systemic toxic effects." The other company, quoting the results of a physiological laboratory, said, "These results show that the Chlorinated Paraffins made by our processes were not toxic under the condition of test and did not cause dermatitis." They stated that they had confidence in the laboratory making the tests for them, but they could not guarantee their findings and that it would be necessary for each user to make their own toxicity and dermatosis studies on the particular combinations that they might use.

A literature reference on Page 420 of the "Rubber Age" August 1943, states, "A. G. Cranch in a recent personal communication to one of the authors, stated that the effect of these waxes on the skin resulting in the appearance of acne is not determined by the presence of chlorine alone, but is due rather to the compound effect of chlorine and a tar derivative. No such marked tendency to acne formation results from exposure to chlorinated petroleum derivatives, such as Chlorinated Paraffin."

EXPERIMENTAL

The information given above showed that in relatively high concentrations the Chlorinated Aromatics can be harmful. It was felt desirable, therefore, to determine the order of concentrations which might occur in the atmosphere in the locality of metal grinding and cutting work. To this end three experimental cutting oils were compounded containing Chlorinated Paraffin, Chlorinated Naphthalene, and Chlorinated Diphenyl. The total chlorine content of each of these oils was 3%, equivalent to approximately 6% of the Chlorinated Compounds.

Use was made of a Warner and Swasey turret lathe and a Cincinnati Cylindrical Grinder. These tools were first operated under normal conditions of feeds and speeds and secondly, with heavier cuts and reduced oil flow in order to induce smcking. Analyses were made of the chlorine content of the air at distances of from 16 to 60 inches from the cutting edge. The concentrations of chlorine found ranged from none to 0.55 milligrams per cubic meter of air. The concentration of Chlorinated Compounds were approximately double this amount since the Chlorinated Compounds used contained roughly 50% of chlorine.

The above tests were conducted in the Technical Service Laboratories of the Soccony-Vacuum Oil Co., Inc. and the Carbide and Carbon Chemicals Company assisted in obtaining the analyses. A member of the API Medical Committee was present during the tests.

- 2 -

Comparison of the concentrations obtained with the permissible limits reported by Dr. C. K. Drinker (J. of Ind. Hyg. and Tox., Vol. 21, 1939, p. 157) shows that in general the concentrations obtained were well below his permissible limits, which ranged from 0.5 to 10.0 milligrams per cubic meter. In some cases Drinker's permissible limit was exceeded. In a private communication, however, to the members of the committee, Drinker stated that his limits are predicated on eight hours per day continuous inhalation. Drinker further stated that he felt it unlikely that in cutting operations a sufficiently high concentration would occur to cause systemic effects.

PERSONAL CONTACTS

Several of the companies replying recommended Dr. C. K. Drinker of Harvard School of Public Health as an outstanding authority on this subject. On September 26, 1945 Dr. Drinker met with the New York members of the Subcommittee on Chlorinated Compounds. As stated above, Dr. Drinker expressed no concern regarding systemic effects when Chlorinated Compounds were used in cutting oils because he felt the concentrations were not sufficiently high. He did, however, sound a warning to the effect that since Chlorinated Aromatics had under more rigorous conditions of use caused yellow atrophy of the liver, any case of yellow atrophy of the liver, whether rightly attributable to the cutting oil or not, would be so construed. This points to the need for careful medical examination of employees or prospective employees using chlorinated cutting oils for liver damage. Additionally, for much the same reasons, workers with adolescent acne or a predisposition to acne as well as those with skin allergies should be excluded from such work. He further mentioned that workers subject to treatment with arsphenamine and the like should be barred.

Commenting on the Chlorinated Paraffins, Dr. Drinker said that in animal experiments he had administered enormous amounts of Chlorinated Paraffin without the occurrence of yellow atrophy of the liver.

Commenting on the dermatological aspects, Dr. Drinker felt that it would be a waste of money to investigate this phase further. For a competent investigation, there would be a need for human volunteers, who are unlikely to be forthcoming. In the absence of these, clinical observations of workers in industry using cutting oils containing chlorinated compounds might supply useful information. It was suggested that consultations be had with the heads of the Departments of Industrial Hygiene of some of the states. Dr. Leonard Greenburg of the New York State Department of Industrial Hygiene was suggested in this respect; such consultation was had and a letter from him is attached.

CONCLUSIONS

All the above leads to the following conclusions:

1. Chlorinated Paraffins appear to be relatively free from condemnation due to either systemic or dermatological effects.
2. The likelihood of systemic effects by the use of chlorinated aromatics in cutting oils is remote. There are claims in the literature of adverse dermatological effects.
3. Suitable precautions should be taken in the selection of workers, the working conditions and hygiene.
4. The toxicity of carbon tetrachloride is well recognized and therefore should not be used as a cutting oil additive.

This report should be viewed as preliminary and work is continuing.

November 10, 1945

API 06785

STATE OF NEW YORK

NEW YORK
100 Nassau St.

ALBANY
State Office Bldg.

ROCHESTER
70 Exchange St.

UTICA
106 Foster Bldg.



DEPARTMENT OF LABOR

SYRACUSE
214 So. Warren St.

BUFFALO
State Office Bldg.

BINGHAMTON
502 Press Bldg.

DIVISION OF INDUSTRIAL HYGIENE AND SAFETY STANDARDS

New York City, 15
November 7, 1945

Mr. A. E. Hoag
Medical Department
Socony-Vacuum Oil Co.
26 Broadway
New York City, N. Y.

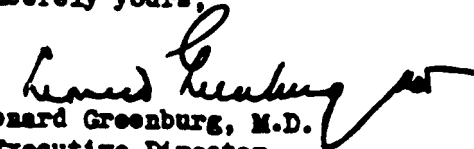
Dear Dr. Hoag:

We have read over the draft of the report of your sub-committee on chlorinated compounds of the A.P.I. Medical Advisory Committee, prepared by you and Dr. Beard and dated October 16, 1945.

With reference to this report, I would like to say that we believe the use of chlorinated paraffins to be relatively free of hazard and essentially we agree with your first conclusion. With reference to the use of chlorinated aromatic compounds in cutting oils, we believe there is a very real possibility and even likelihood of producing dermatitis and that the incidence of this may be quite high, particularly with long, continued exposures. With reference to systemic poisoning, we believe the possibility to be far more remote but, nevertheless, we feel that industry should be fully warned as to such a possibility and instructed just how to utilize precautionary measures.

I trust this answers your purpose but should any further questions arise, please do not hesitate to call on me.

Sincerely yours,


Leonard Greenburg, M.D.
Executive Director

APPENDIX C

For Information Only - Not For Publication

REPORT OF SUBCOMMITTEE FOR PERMISSIBLE CONCENTRATIONS OF TOXIC SUBSTANCES IN THE PETROLEUM INDUSTRY

We have outlined the scope of our assignment as follows:

1. To prepare a list of the toxic substances used and produced in the petroleum industry.
2. To collect and publish information on those substances in the above list whose toxicology has already been established.
3. To select those of the subjects remaining on the above list which are of sufficient and general importance and on which satisfactory toxicological information has not been determined, and to develop a research program for their study.

We have prepared a tentative list of the toxic substances used in the petroleum industry. Many of the compounds are listed by type only, thus eliminating in this list an enormous number of possible homologs, for example, "naphthas," "mercaptans," and "phenolic homologs." A copy of this tentative list is attached.

We propose to develop the following information in connection with the second objective listed above:

- I. Name of substance
- II. Properties and Characteristics - Physical and Chemical
- III. Uses in Petroleum Industry
- IV. Toxicology
 - a. Acute effects, including symptoms
 - b. Chronic effects
 - c. Safe limits
- V. Treatment
- VI. Examinations -
 - a. Preplacement Examination
 - b. Periodic reexamination
 1. Frequency
 2. Extent
- VII. Safety Precautions -
 - a. Working Rules
 - b. Equipment
- VIII. Bibliography

API 06787

To prepare this information, we have entered into negotiations with Dr. Cecil K. Drinker, Professor of Physiology and head of the School of Public Health of Harvard University. Dr. Drinker has agreed to undertake this assignment. Much of the library and research work will be done by a graduate student,