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# CONDENSED SUMMARY OF THE OBJECTIVES AND FINDINGS OF AN EXPERIMENTAL PROGRAM FOR THE APPRAISAL OF THE POTENTIAL CARCINOGENIC CHARACTERISTICS OF CERTAIN PETROLEUM PRODUCTS

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## I. INTRODUCTION

Experiments were initiated in 1947 in order to develop more information concerning the carcinogenic characteristics of certain petroleum oils, some of which had been found by other investigators to be surprisingly active in this respect, when applied upon the skin of experimental animals. The initial work was exploratory in type, but it succeeded in heightening the interest of representatives of both the Laboratory and the Sponsors in an investigation of broader scope. Accordingly, in 1949, a program was designed and embarked upon which had as its ultimate purpose the determination of the degree of the potential hazard of cutaneous cancer which might be associated with contact of the human skin with a wide variety of petroleum oils. In the course of the investigation some attention was given to an examination of the potential usefulness of certain preventive procedures.

## II. OBJECTIVES

The attack upon the primary problem was directed toward three primary objectives:-

1. That of testing representative samples of intermediate and finished petroleum products for their ability to induce cancer of the skin of mice, by methods which would demonstrate their relative activities in this regard in as nearly quantitative and reproducible terms as might be possible.

2. That of comparing the "carcinogenic potencies" of the various test materials with the chemical or physical characteristics of their components, so as to develop, if possible, out of consistent correlationships, technical means for detecting the carcinogenic properties of petroleum products and determining their relative potencies.

3. That of surveying as large and as representative a segment of the population of the American petroleum industry as might be relevant and available in temporal, spacial, and occupational terms, in an effort to establish, by appropriate epidemiological and bio-statistical methods, the existence or non-existence of the occupational hazard of cancer, generally, in the recent past or at the present time.

## III. RESULTS

### 1. Biological Estimation of Carcinogenic Properties

More than one hundred representative samples of intermediates or products of refining operations were collected, and their relative carcinogenic potency for the skin of inbred mice were determined and so expressed as to denote both the rate of development of tumors and the proportion of experimental mice affected thereby.

(a) Tumors of the skin of mice, at the site of multiple applications, were induced most rapidly by the residual products of catalytic cracking or reforming, and by the cycle gas oils from delayed coking. They developed somewhat less rapidly at the site of contact with the residual products of thermal cracking or reforming. Almost all of the cracked residual oils selected for examination produced a high frequency of occurrence of tumors of the skin of the mice, when

applied thereon three times each week.

(b) The results of tests on uncracked oils covered a very broad spectrum of potency, from the high level of certain "lube" distillates and solvent extracts (which produced tumors about as rapidly as the catalytically cracked residue), to the completely negative behavior of certain other highly refined oils.

(c) Limited numbers of data indicate that extraction with phenol, as commonly applied to lubricating distillates, removes almost all of the polycyclic aromatic carcinogens. Similarly, treatment with fuming sulfuric acid, commonly employed in the manufacture of white oil, appears to render the raffinate free of carcinogenic compounds.

2. Chemical Characteristics of Carcinogenic Oils

Relationships were established between the chemical components of certain oils and the carcinogenic potency of the latter when applied upon the skin of mice:-

(a) Benzo(a)pyrene and its alkyl derivatives were found to be important contributors to the potency of cracked residua, and a fairly rapid method for their determination in the oils was developed.

(b) There being no benzopyrenes in the catalytically cracked fractions in the 700° to 750° range, the development and application of a method of liquid partition chromatography revealed the presence of alkyl derivatives of benzo(c)phenanthrene as important contributors to the carcinogenic potency of these fractions.

(c) There is no general physico-chemical method, as yet, whereby the carcinogenic potency of refinery streams generally

can be estimated. However, a fairly satisfactory classification of residua (fractionator bottoms) of catalytically cracked oils can be made through chemical measurements of their polycyclic aromatic components by means of the combined techniques of chromatography and spectrometry (mass and ultraviolet), in correlation with their potency for the skin of mice.

(d) The potency of an oil containing a minute proportion of aromatic components in the molecular range of 220 to 320, depends greatly upon the extent to which other constituents of the oil exert an indirect influence upon the carcinogenic process (see below in (d1) a brief account of "acceleration"). The available data are insufficient for the estimation of such activity by physico-chemical methods. Therefore, while a limited number of uncracked oils and cracked distillates may be classified as carcinogenic on the sole basis of their content of polycyclic aromatic hydrocarbons, the majority of such oils can now be so classified only in terms of the responses elicited by their application upon the skin of suitable test animals.

(d1) The carcinogenic potency of certain oils for the skin of mice was found to vary with the nature of their non-carcinogenic components. Some completely saturated fractions containing no polycyclic aromatic compounds were found to be capable of accelerating, three- or four-fold, the rate at which a given carcinogenic agent, introduced therein in a known concentration, induced tumors of the skin of mice. The investigation of the "accelerating activity" of various pure compounds indicated that this property was shared by a wide variety of hydrocarbons containing 10 to 50 carbon atoms, including such examples

as n-dodecane, dodecylbenzene, amylnaphthalene, and triisopropylbenzene. Experiments with various distilled fractions of petroleum oils indicated that the accelerating compounds occurred mainly in the fraction distilling between 450 and 700°F., whereas the compounds that were truly carcinogenic for the skin of mice occurred predominately in the higher boiling fractions.

(d2) A limited group of results indicated that certain sulfur compounds in catalytic cycle gas oils were also contributing to the carcinogenic potency of these oils. Further experiments with a pure sulfur compound, benzyldisulfide, indicated that this contribution was probably that of a special type of accelerator rather than that of a carcinogenic agent. The nature of this activity is being investigated further.

(d3) While oils employed as diluents have been found to be disproportionately effective in reducing the accelerating activity of n-dodecane and dodecylbenzene, as compared with the similar effect (apparently simple dilution) of more common solvents such as benzene and decahydronaphthalene.

3. Experimental Reduction of Carcinogenic Action by Washing Skin.

Removal of an oil from the skin of mice shortly after its application, by washing with a typical aqueous detergent, lengthened the time required for the production of cutaneous tumors. Such washing also reduced the frequency of the occurrence of tumors on the skin of the mice within groups subjected to multiple applications of the oils (with the exception of the more potent of those produced by catalytic cracking).

4. Epidemiological Information

The results of the epidemiological survey have been reported in detail and are not dealt with in this summary, except to indicate that, while they were unsatisfactory in several respects and therefore, inconclusive, they yielded no evidence of the occurrence of occupational cancer within the population surveyed. This summary has dealt with the potential hazard of occupational cancer, therefore, in relation to the products investigated, as revealed by the responses of mice to carcinogenic stimuli, rather than to a present and demonstrable danger within the industry. To the extent that this dubiously negative evidence is reassuring, it may well be accepted as a favorable condition for the further development and maintenance of a technologic surveillance of petroleum products, and an hygienic and medical supervision of occupational conditions and personnel.

## IV. PUBLICATIONS

In addition to the regular interim reports to the Subcommittee on Carcinogenicity of the Medical Advisory Committee of the American Petroleum Institute, certain of the results of these investigations have been published in scientific journals as follows:

1. Tye, R., Graf, M.J., and Horton, A.W.: Determination of Benzo(a)pyrene in complex mixtures; use of catalytic iodination on activated alumina. Anal. Chem. 27, 248-53 (1955).

2. Horton, A.W. and Denman, D.T.: Carcinogenesis of the skin. A re-examination of methods for the quantitative measurement of the potencies of complex materials. Cancer Research 15, 701-9 (1955).

3. Horton, A.W., Denman, D.T. and Trosset, R.P.: Carcinogenesis of the skin. II. The accelerating properties of aliphatic and related hydrocarbons. Cancer Research 17, 758-66 (1957).

An oral presentation of additional data was made as part of the Symposium on Polycyclic Aromatic Hydrocarbons at the meeting of the American Chemical Society, September 1956, under the title "Relationships Between the Composition and Carcinogenic Properties of Various Refinery Streams."

Other publications will follow in due course.

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