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API HISTORY OF THE SUBCOMMITTEE ON CARCINOGENICITY

1945-1950

API

HISTORY

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Research and Development
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ATTENTION

Mr. P. V. Keyser, Jr.
Dr. A. A. O'Kelly
Dr. W. P. Hawthorne

Carcinogenic Hydrocarbons, Literature Survey

A brief literature survey of the cancer-producing hydrocarbons has been made as requested by Dr. L. C. Beard in his letter (W. M. Holaday/ P. V. Keyser, Jr.) of April 12, 1945.

Carcinogenic activity has been noted in various types of compounds including hydrocarbons, amino, azo and nitro compounds, hormones, and inorganic compounds. This report will be confined to the hydrocarbons and hydrocarbon fractions identified as carcinogenic.

Most of the carcinogenic hydrocarbons were originally identified in the pyrolysis products of coal, wood, petroleum and shale. In some cases these hydrocarbons exist, as such, in the original materials. The active hydrocarbons are almost without exception polynuclear aromatic hydrocarbons and are conveniently classified under the parent hydrocarbons from which they might be derived. Thus, the three main types are classified as benzopyrenes, cholanthrenes, and benzanthracenes.

Identified Carcinogenic Hydrocarbons

(7),(22),(45),(24),
(12),(10),(5),(28),
(29),(38),(47)

I. Benzopyrenes

1,2-benzopyrene
3,4-benzopyrene
1,2,3,4, dibenzopyrene

II. Cholanthrenes

cholanthrene
20-methyl cholanthrene
16,20-dimethyl cholanthrene
20-ethyl cholanthrene
15,16-benzdehydrocholanthrene

20-isopropyl cholanthrene
3-methyl cholanthrene
meso-dihydro cholanthrene
4-methyl cholanthrene
5-methyl cholanthrene
meso-dihydro 3-methyl cholanthrene
1-ketocholanthrene

III. Benzanthracenes

1,2-benzanthracene
10-methyl-1,2-benzanthracene
9-methyl-1,2-benzanthracene
5,10-dimethyl-1,2-benzanthracene
5,9-dimethyl 1,2-benzanthracene
8,9-dimethyl 1,2-benzanthracene
4,10-ace 1,2-benzanthracene
9,10-dimethyl 1,2-benzanthracene
8,10-ace 1,2-benzanthracene
10 ethyl 1,2-benzanthracene
5 methyl 1,2-benzanthracene
5 n-propyl 1,2-benzanthracene
6 methyl 1,2-benzanthracene
5,6 dimethyl 1,2-benzanthracene
6 isopropyl 1,2-benzanthracene
6,7 cyclopenteno-1,2 benzanthracene
3 hydroxy-1,2-benzanthracene
3 methoxy-1,2-benzanthracene
5 propyl-9,10 dimethyl-1,2 benzanthracene
5 ethyl-9,10 dimethyl 1,2 benzanthracene
5 methyl-7,8 dihydro-1,2 benzanthracene
1,2,5,6 dibenzanthracene
1',9 methylene-1,2,5,6 dibenzanthracene
1',2',3',4' tetrahydro-1,2 benzanthracene
5,6 cyclopenteno-1,2 benzanthracene

IV. Miscellaneous

sym. triphenyl benzene
tetra-phenyl methane
o-amino-azotoluene
9,10 dimethyl anthracene
1,2 cyclopenteno-510-aceanthrene

The Nature of Petroleum Carcinogens

The probability that the carcinogenic hydrocarbons in petroleum are of the same nature as those listed above has been indicated by various workers. Roffo (43) found that the fractions of fuel oil boiling between 270-300°C, and 300-330°C, produced tumors in eighty percent of the rabbits to whose skin these fractions were applied, and the absorption spectra of these fractions were similar to those of known cancer-producing compounds. Spectrographic analysis of distillates of all fuel oils tested showed the presence of the same class of hydrocarbons. Twort and Fulton (59) state that oils with a preponderance of paraffins have relatively little

carcinogenic activity, but that carcinogenesis is high in oils with a preponderance of isocyclic compounds.

Pessano (41) found that some of the products of combustion in gasoline engines are in the group considered carcinogenic. Rats respiring the products of combustion of fuel oil at high concentration developed carcinoma of the lungs. The liquid products formed by combustion of petroleum, when applied to the skin of rabbits, produced malignant tumors.

A substance containing the benzo (α) pyrene nucleus, with decidedly cancerogenic properties, has been isolated (32) from tar such as is used in paving roads.

The prevalence of cancer among paraffin workers has been shown (63) to be due to irritating impurities present in the crude paraffin wax. The pure paraffin ($C_{24}H_{50}$) has been tested and found to be non-carcinogenic.

The Most Carcinogenic Petroleum Fractions

Carcinogenic hydrocarbons have been shown to be more or less concentrated in certain fractions of petroleum. In general, the higher boiling fractions (fuel oil, lubricating oil, tar, etc.) contain more carcinogenic hydrocarbons than the lower fractions. Two petroleum oils used in cotton spinning mills yielded high boiling fractions 31 times as carcinogenic as the low boiling fractions (58). The heavier grade lubricating oils are said to be less potent than the spindle oils (54). Shale oil was found (58) to be about 12 times as carcinogenic as petroleum-well oils; the most potent shale oil fraction being the unfinished lubricating oil from which most of the paraffin wax has been removed but which has not been treated with sulfuric acid or filtered (54). Wood (62) found that while mineral oil of the type used therapeutically was not carcinogenic, heavy lubricating oils did show some carcinogenicity, and tar showed the same property to a larger degree.

Twort and Lyth (60) investigated a range of commercial distillates of a topped Borneo crude oil. They found that the peak carcinogenic activity was associated with the fraction having a viscosity of 200-225 centipoises at 25°C, and that the whole range of oils showed biological activity. This activity had been predicted from an examination of the physical properties of the oils which were alone sufficient to condemn their use as lubricants when likely to come into contact with the user.

Evidence of the presence of carcinogens in cracked mineral oil was noted (56) in an investigation of the oily, tarry material extracted from the soot of the expansion chamber of a high-compression, internal-combustion engine. This material was highly carcinogenic to the skin of mice. In general, the carcinogenic potency of crude shale oils decreased as the cracking temperature was lowered but was still present at 400°Centigrade. These investigators also found that a heavy grade of Diesel fuel oil was carcinogenic but that a light grade oil was not.

Effect of Treatment of Oils on Carcinogenicity

Woodhouse (64) found that the petroleum ether extract of pitch and the SO_2 extract of spindle oil distillate from a paraffin-base crude were carcinogenic. Lyth (36) noted, during careful fractionation of

Scottish shale oil and a Persian oil, that all samples of petroleum oil which were treated with ethanol provided residues of lower carcinogenicity and higher refractive index and density than the original oil. Twort and Fulton (59) found that saturation by oxidation and reduction or treatment by silica gels or clay reduced the cancerogenic activity of their mineral oils probably through adsorption and polymerization. Alcohol extraction and sulfuric acid treatment reduced the carcinogenicity of the oils by extracting the carcinogens. The same authors also found that the active agents could be concentrated by extraction with methyl sulfite or methyl sulfate and picric acid. They suggested the process for treating oil for industrial use.

Relation of Carcinogenicity to Fluorescence and Chemical and Physical Properties

Twort and Twort (54) found that the cancer-producing properties of mineral oils appeared to be related to their fluorescence; oils having a blue fluorescence seemed more active than those having a green fluorescence. Weiss (61) noted that strong fluorescence was almost confined to conjugated ring systems which possessed highly mobile electrons. Only the more symmetrically conjugated systems or those which do not give rise to strongly ionic structures show fluorescence. The author compared the mobile electrons with metallic electrons and stated that carcinogenic hydrocarbons belong to this group of hydrocarbons. Hieger (26) found that the fluorescence spectra of many carcinogenic substances show bands at wave lengths of 4000, 4180, and 4400A^{c}. These bands are similar to those of the spectra of 1,2-benzanthracene, a known carcinogen of high potency.

A relationship between physical properties and carcinogenicity was observed by Lyth (35) who stated that oils with a refractive index less than 1.5500 were non-toxic while oils with an index exceeding 1.5600 were highly toxic; Pennsylvania oils and certain mildly treated oils were an exception. The same author noted a relationship between the iodine value of untreated oils and carcinogenicity. Toxicity increased in the same order as the iodine value, Pennsylvania oils again excepted.

Fieser and Hershberg (21) found that the behavior of polynuclear hydrocarbons in lead acetate oxidation, aldehyde reaction, and diazo-coupling indicated that the most carcinogenic hydrocarbons of the series tested possessed special susceptibility to substitution.

Schmidt (48) discussed the theory of the box model of aromatic compounds and stated that the theory is especially successful in characterizing the cancer-producing hydrocarbons as compounds with abnormally high electrogen density and low excitation energy.

Other references relating structure and physical and chemical properties to carcinogenicity include Bradley (8); Clar (12); Dunlap and Warren (18); Fieser (19) and (20); Fieser and Campbell (22); Iball (28); Kennaway et al., (29); Lundgren (34); Shear et al., (51); and Truhaut (53).

More general references to known carcinogens, including reviews of the literature up to the date of the reference, are Addinall (1); Andervont (2); Barry (3); Blanc (4); Boyland (5) and (6); Brady (9); Bruce and Kahn (10); Butenandt (11); Cook (13) and (14); Cook et al., (16); Cook and Kennaway (15) and (17); Hartwell (24); Hewett (25); Kermack (30);

Kirby (31); Morton et al., (39); Roffo (42); Rondoni (44); Sampey (45); Sannié and Truhaut (46); Sasaki and Yoshida (47); Schürch (49); Shabad (50); and Siboni (52).

The greater part of the original references were unavailable and so were quoted directly from chemical abstracts. For these references the chemical abstract reference is listed in parentheses after the original reference in the bibliography.

/s/ L. J. Hillenbrand
L. J. Hillenbrand

LJH:RMW

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THE CARCINOGENICITY
OF
BITUMINOUS COMPOUNDS

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Literature Review

April 30, 1945

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N O T E

In view of the immense amount of published information on various phases of the cancer problem it should be emphasized that this literature review gives only a rapid survey of developments in the field of cancer research as applied directly to the petroleum, coal tar, oil shale and allied industries. While it is far from being complete, yet it is believed that most of the important work in this particular field has been covered, either in the report itself or in one of the bibliographical references given in the appendix and referred to at the bottom of page 1.

M. P. Doss

THE CARCINOGENICITY OF BITUMINOUS COMPOUNDS

It has long been recognized that the incidence of skin cancer is greater among workers in certain industries and occupations than among the population as a whole. Attention was first directed in 1787 to the very high death rate resulting from scrotal cancer of chimney sweeps; it is eight times more common in these workers than in the general public in England, and in the United States the ratio of cancer cases in chimney sweeps is double that of the general population[78]. In practically all cases it is the scrotum that is attacked; this is also the site in mule spinners cancer discussed later. Workers in other industries coming into direct contact with tars, pitches, shale oils, etc., likewise show a high incidence of skin cancer, for example, laborers in plants making briquettes, tar roofing, wood preservatives, artificial gas, insulating compounds, shale products, etc.

However, in spite of the recognition of the fact that bituminous compounds were apparently the cause of skin cancer, it was not until relatively recently that skin cancer was produced in laboratory animals by direct application of tar. This was accomplished by the Japanese investigators Yamigawa and Ichikawa[122] in 1915. Since then a great deal of very careful work has been done in synthesizing and testing various organic compounds, particularly polycyclic hydrocarbons and derivatives. For lengthy reviews of this work, see References 8-12, 14, 17, 20, 22, 23, 26-29, 32-34, 74, and 87; particularly the review by J. L. Hartwell of the National Cancer Institute covering 696 chemical substances, of which 169 are reported to be carcinogenic[41]. L. F. Fieser summarizes our knowledge in this field as follows[34]:

> "As judged by all available data for the production of skin and subcutaneous tumors in rats and mice, methylcholanthrene probably is the most potent of the known chemical carcinogens. Systematic studies of synthetic model compounds have shown that the methyl group is of no importance to the functioning of the compound; that much, if not all of the efficacy of cholanthrene is retained in the analogous hydrocarbon 5,10-dimethyl-1,2-benzanthracene; and that the most significant structural feature of cholanthrene or methylcholanthrene is the 1,2-benzanthracene ring system with a

carbon substituent at the meso position 10. 10-Methyl-1, 2-benzanthracene evokes sarcomas in mice nearly as rapidly as methylcholanthrene, and, though it is distinctly less effective in the production of skin cancer, the substance constitutes the nearest approach in a simple model compound to a simulation of the biological properties of the hydrocarbon of more complicated structure.

"All twelve possible monomethyl derivatives of the inactive 1, 2-benzanthracene have been synthesized and tested for carcinogenic activity, and of these the 10-isomer is the most potent. The meso-substituted 9-methyl compound stands next in order of potency, followed closely by the 5-methyl derivative, which produced sarcomas in mice with a latent period about twice as long as that observed with 10-methyl-1,2-benzanthracene. Methylcholanthrene and benzpyrene can be regarded as 1, 2-benzanthracenes substituted at the meso positions 10 and 9, respectively, and in model compounds the combination of the two types of substitution is particularly favorable. 9,10-Dimethyl-1,2-benzanthracene produced skin tumors in mice with remarkable rapidity and in this test surpasses methylcholanthrene in speed of action, though it is less effective when administered by subcutaneous injection. The thiophene isologue of the hydrocarbon has comparable properties."

Numerous attempts have been made to isolate the definite carcinogenic compounds in coal tar by means of distillation, solvent extraction, etc.[73], but while very potent fractions have been obtained, the individual compounds have been difficult to separate. Kennaway and Hieger [16] proved the carcinogenicity of 1,2,5,6-dibenzanthracene, the first pure carcinogenic hydrocarbon known. Cook, Hieger and Hewitt [24] in 1933 isolated 1,2-benzpyrene, 4,5-benzpyrene and 1,2-benzanthracene and estimated that the original coal tar pitch contained not less than 0.003% of the potent 1,2-benzpyrene.

Several investigators [22, 24, 25] have attempted to correlate carcinogenesis with <u>fluorescence</u>. For example, the cancer-producing material formed by the action of $AlCl_3$ on tetrahydronaphthalene shows a blue-violet fluorescence, showing three bands, 4000, 4180 and 4400 A.U., which are similar to the fluorescence spectrum of 1,2-benzanthracene [44]. Kennaway and Hieger [62] suggest the possibility of the use of the fluorescence spectrum for the preliminary examination of materials suspected of being carcinogenic.

An important fact brought out by several investigators is that the temperature to which a tar, shale oil or petroleum oil has been subjected determines its carcinogenic activity. In general, it would seem that temperatures up to 500°C. are without effect [52] but above that temperature carcinogens are formed, the maximum yield lying between 800 and 900°C. [53, 59]. Tar and pitch from gas works are far more active than that from coke ovens [58], accounting for 70% of all cases of tar cancer in the United States while the coke oven product causes only 5% [113].

While petroleum residues resulting from moderate heat treatment are inactive [120], yet by passing an inactive California petroleum through a tube at 880°C. Kennaway and Leitch obtained a very active carcinogen [59, 60]. Even an inactive medicinal paraffin oil heated to 380°C. under 50 atms. pressure acquired some carcinogenic activity [101].

Kennaway [56] likewise obtained an active material by passing isoprene through a tube filled with H_2 and heated to 820°C. Watson [115] achieved similar results with turpentine at 850°C.

Acetylene yields an active product on being passed through a red hot tube [59] but it must be pointed out that treatment with $AlCl_3$ at room temperature also produces an active compound [61].

On the other hand, synthetic lubricating oils produced by $AlCl_3$ polymerization at temperatures up to 150°C. were entirely inactive [121]. It is suggested that the condensation products of acetylene are of a more complicated nature and probably more unsaturated than those obtained from ethylene.

The carcinogenic activity of tars depends apparently not only on the temperatures of their formation but also on the chemical compound used as the base stock [100]. For example, a tar made from pinene at 850°C. was far more active than one from turpentine made similarly, the relative potencies being 100:19. Pinene tars made at 500, 600, 750, 850 and 950°C. had relative potencies

of 0, 12, 24, 100 and 64. Oxidation of a synthetic tar at 100°C. reduced its potency from 100 to 63, and at 150-160°C. its potency fell to 0. Oxidation with an acetone solution of $KMnO_4$ reduced the potency to 24; with pyridine as a solvent, almost to 0. The active constituents of synthetic tars form crystalline picrates, the remaining filtrate being almost inactive, and the picrate extremely potent.

Shale oil is carcinogenic, probably as a result of the high temperatures to which oil shale is subjected [104]. However, temperatures below 400°C. give a relatively inactive product, 500°C. and above being required [101].

In England where high temperature tar is used in briquette manufacture, there are many cases of skin cancer among the workmen, which is not the case in France where the low temperature product is used.

The greatest amount of investigation of any type of occupational cancer has been carried out on mule spinners cancer in the cotton mills of Lancashire, England. Southam and Wilson [88] in 1922 first called attention the excessive occurrence of cancer in mule spinners. Women workers are not affected and about 70% of all cancer among mule spinners is of the scrotum [84], apparently due to the fact that a mule spinner at work walks to and fro in front of his machine, leaning over the moving frame from time to time to join up broken ends of the yarn. The base of the frame is on a level with the groin and the spindles on the frame as they rapidly revolve throw off oil from their bearings onto the clothes. In the hot mills the men perspire freely and so wash off the natural grease of the skin, thus allowing the oil closer contact [15]. Irritation by the trousers and overalls also helps the process. It is interesting to note that no trouble of this sort was noticed in England until mineral oil replaced animal and vegetable oils as a lubricant [16]. Henry [43] estimates that 0.25% of all cotton mule spinners in England suffer from scrotal cancer. On the other hand in the United States during 1926, for example, there were only 33 deaths from cancer of the

scrotum, of which only three of the victims were textile workers and three were mule spinners; four of the six were born in England and the other two in Canada [45], which tends to show that mule spinner cancer is rarely contracted in the United States. In a woolen mill in the United States employing about 200 mule spinners no cases of scrotal cancer were found [84]. Since the method of operating this equipment is the same in both countries this striking contrast is attributed by Hamilton [40] to the fact that Scottish shale oil is used in the Lancashire mills. However, the literature is not entirely clear as to the origin and type of the oil used in Lancashire in mule spinning [53].

Leitch [70] brings out a fact of possible significance, to the effect that cancer is not known in woolen spinning mills, even though the same machines are used as in the cotton factories, but points out that the room temperatures in the cotton mills are much higher, possibly resulting in more relaxation of the tissues of the scrotum and permitting entry of oil into the sebaceous follicles. Breckbank [16], however, states that in the woolen industry piecing of broken ends of yarn is done with both hands with a forward level bending movement of the body and thus there is not the same friction of the clothes on the scrotum as in the cotton mills. He admits, however, that the same oil is used in both types of mills.

As a result of the preliminary investigation of Southam and Wilson mentioned above, the Manchester Cancer Commission, consisting of more than fifty members, was organized in 1925 under the direction of Dr. C. C. Twort to investigate the mineral oils used in Manchester cotton mills. Lubricating oils from the various fields throughout the world were found to have widely varying degrees of activity. A sample of Venezuela oil was very potent while Russian and Pennsylvanian samples were on an average less than one-tenth as active. Purified medicinal oil had no carcinogenic properties and several saponifiable oils, such as sperm, olive, rape, cottonseed and neatsfoot oil, failed to produce

tumors when applied to mice, even under the most severe experimental conditions. In general terms, the more saturated were the constituent hydrocarbons of the lubricating oil, the less capable were they of inducing cancer in experimental animals, the physical characteristics being the same [101].

This preliminary report was criticised severely in an editorial in the "Petroleum Times" of London [4], in that while various oil companies (Anglo-American, Anglo-Persian and Shell-Mex) had contributed £1,000 for two years for the support of this investigation, yet the Manchester Cancer Commission had not availed itself of the services and advice of experts from the oil industry relative to the characteristics and methods of treatment of petroleum oils. The Institute of Petroleum Technologists, while making no definite criticisms at this time of the work of the commission, formed a committee of its own to follow closely the work in progress [63]. In 1934 Dr. A. E. Dunstan, Dr. F. H. Garner and Mr. James Kewley of the Institute of Petroleum Technologists are shown as members of the Manchester Commission [21].

In 1933, Twort and Lyth [104] of the Manchester Cancer Committee reported that by means of solvents, extracts were obtained of high refractivity and correspondingly high carcinogenicity. Their recommendations for the selection of an oil of low carcinogenicity were as follows:

When selecting from several mineral oils with similar gravity, specify that with the lowest refractive index; when selecting from those with similar refractive index, specify that with the highest gravity; when selecting from those with similar refractivity, specify that with the highest viscosity; and when selecting from origin alone, choose in the following order: Russian, Pennsylvanian, Texas, Mid-continent, Mexican, Californian, Persian, Rumania, Borneo, Venezuelan, shale.

However, it should be emphasized at this point that these authors state definitely that "adequate refining of any of the oils handled, of no matter what origin, results in a product ..... possessing only a very low

carcinogenicity" [104]. Also, that a single extraction of an unrefined distillate with SO_2 may profoundly lower the activity of a previously very dangerous oil, while a second extraction may render it almost inert. They state that "it is probably commercially feasible to treat oils of any origin, or oils of any degree of carcinogenic activity, so that they may be less dangerous than even the very best of the straight oils used today". They evidently assume that untreated textile oils are used in the Lancashire mills.

Lyth of the Commission further stated [71] that when the refractivity* of an oil was less than 0.5500 it was found to be non-toxic, while when the value was greater than 0.5600, the oil was highly toxic. Pennsylvanian oils and certain mildly treated oils were an exception. The iodine value of an oil seems to afford an indication of its toxicity, providing the oil has not been treated and again the higher the value, the more potent the oil. The toxicity increases in the same order as iodine value, except for Pennsylvanian oils which again occupy too high a position. The permanganate values are not regarded as of any value in connection with estimating the toxicity of oils.

Lyth adds that extraction with alcohols, acetone, etc., clay and acid treatment, leads to a reduction in the potency, especially in the case of the more potent oils but a corresponding reduction in the refractivity does not always occur. Where a marked reduction in the refractivity does occur, there is, without exception, a marked decrease in carcinogenicity; with a marked increase in refractivity, a corresponding increase in potency. Where the refractivity is not much altered, the potency may or may not be affected and further tests are necessary.

In spite of the apparent definite findings and recommendations of the Manchester Cancer Commission, the Cancer Research Committee of the Institute of Petroleum Technologists [51] was not convinced that "the so-called incidence of

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* (Refractivity = $\frac{\text{Refractive Index} - 1}{\text{DENSITY}}$)

cancer is in any shape or form connected with the use of spindle oils". No elaboration of this statement was given, but was possibly based on refined oils only being used as textile lubricants.

An editorial in the "Petroleum Times" of London in 1937 once again attacked the conclusions of the Manchester Committee, pointing out that only one oil from each of a number of countries was examined [5].

In 1937 the Federation of Master Cotton Spinners Association sent out a letter to its members recommending that when purchasing spindle oils a guarantee should be obtained that the oil conforms to the specifications of the Manchester Cancer Commission, and that tests had shown that many of the oils in use at that time conformed to the specification.

While throughout the reported work of the Manchester Cancer Commission it is stated repeatedly that acid or solvent treatment of a potent oil greatly reduces or eliminates its activity [97, 102, 104, 71], yet in 1939 Twort and Lyth [107] investigated acid and clay treated distillates from a Borneo oil and found them to be active, the maximum potency being at a viscosity of 200-250 cp at 25°C. Molecular distillation gave a greater concentration of the carcinogenic material than was obtained by ordinary distillation at from 3 - 10 mm. In confirmation of previous findings the middle fractions of this Borneo oil were mostly responsible for pathological changes in the organs.

A carcinogenic shale oil was separated by molecular distillation into fractions which were subjected to chromatographic adsorption. Two apparently pure hydrocarbons have been isolated and are being investigated [2,109].

A recent report (1941) by C. C. Twort of the Manchester Cancer Commission [109] states that animal tests are variable, lengthy and costly and that a more reliable estimate of the carcinogenicity of oils can be obtained from the refractive index and viscosity. (Yet the data on which selection of these two properties was based were obtained by means of this variable skin test.)

Woodhouse of the Birmingham Cancer Research Laboratory also states that mouse tests to determine carcinogenicity are difficult to correlate with human tendencies to cancer unless these animal tests are strongly positive or negative [121]. For example, two oils were tested (a) from a spinning mill where no cases of mule spinners cancer had been recorded, and (b) from a mill where six cancers had recently been reported. Mouse tests indicated slight carcinogenic properties in the case of the two oils but a greater action on mice of (a) than (b).

Dr. E. M. Brockbank, chairman of the Manchester Cancer Commission, has briefly summarized the investigations of the Commission in a recent publication [16]. He lists the hygienic precautions to be exercised in mule spinning and urges the adoption of the oil specification given previously by Twort. He also makes this interesting generalization: "As a general rule an oil that is strongly dermatitic will not be strongly carcinogenic and vice versa". This is also mentioned by Kennaway [61] who states that cyclohexene (which is non-carcinogenic) is extremely irritating to the skin and should produce cancer if chronic irritation were an essential factor in carcinogenesis.

As mentioned previously, shale oils are very carcinogenic and in the Scottish shale industry the case incidence of skin cancer is about 0.1% per annum among the oil workers but 0.5% among the paraffin workers 53 (this is based on a 28 year record). This activity of paraffin is restricted by Schwarz and Tulipan [84] to the crude product, the refined wax being inactive, which view is supported by Wood [119] who states that the active components are present only in the crude paraffin oils.

With regard to the refining of petroleum oils, Wood [120] made an investigation of refineries in Pennsylvania and found no scrotal cancer, which was confirmed by Heller [42]. However, Heller found evidence of carcinogenic compounds in Mid-Continent oils as refined in plants in Ohio and Indiana. Here oil boils are fairly common and in some cases lead to skin cancer. In one case

a paraffin pressman in the Middle West was treated for "wax boils" for three years when a cancerous growth developed on the right forearm and was removed, but eight years later a second similar growth in the same place had to be removed. Heller also found records of cases of skin cancer in another refinery, using crude from the Lima field; eight cases had occurred in this refinery and one was fatal. All of these cancers were preceded by warts. The length of exposure before malignancy appeared varied from four to thirty four years. The part most often affected was the scrotum and all but one man worked in the paraffin department. These cases were caused by unrefined oils and Hamilton 40 states that so far there is no proof of the occurrence of skin cancer in the U.S. from the use of refined lubricating and spindle oils which have been acid-treated.

Heller 42 believes that the relative freedom from occupational cancer in the U.S. is due to the mechanization of industrial processes, preventing direct contact with the pitch and tar; the extensive employment of negroes, who are apparently less subject to skin irritants than whites; the use of refined lubricants from crudes which are poor in carcinogenic properties, and the use of tar from coke-ovens instead of from gas works.

Phillips 77 reports the particulars of a study carried out by the U.S. Public Health Service as to the incidence of occupational cancer in Texas. The records of 1190 individuals having microscopically verified skin cancers were analyzed, covering the period 1920 to 1940. The occupation of the largest group of these patients was outdoor work (farming and ranching); the work of housewives comes next in order, followed by various activities requiring moderate outdoor life. The professions were next, followed by laborers and carpenters. The railroad and petroleum industries furnished few cutaneous cancers.

Gafafer and Sitgreaves in a U.S. Public Health report issued in 1940 37 analyze 70 cases of cancer recorded for the male members of the sick benefit plan of an oil refining company during the period 1933-38; there were 46 deaths. The death rate was 0.78 per 1000 and a frequency of 1.2 per 1000 (all U.S. death rate

0.96 per 1000). Almost 70% of the deaths were related to the digestive system and the rate for this site was higher than in the total population. Deaths from cancer of the genito-urinary system was 6.5% of the total, compared to 15.0% in the case of the total population.

In 1934 Campbell [20, 21] made laboratory tests on mice with dust obtained from tarred roads. This dust caused warts and cancer of the skin and in six months 24 out of 59 mice showed typical tar warts, half of which developed malignancy. This finding was confirmed by Kling, Samsonow and Heros, [64, 65] who also separated a substance containing the benzopyrene nucleus from the tar. However, Hogouneg [47] is doubtful of the danger from road tar since it usually takes years of direct contact of coal tar to the skin to produce skin cancer. (Teutschlaender [91] calls attention to the fact that almost all industrial cancers require an exposure of about ten years before growth appears, although a few cases may arise much later.) Valade [111] likewise is of the opinion that while primary lung tumors can be induced in mice painted with tar or exposed to inhalation of dust from tar roads, yet these results cannot be transferred to humans. Animals other than mice should be employed in experiments and an inquiry should be carried out on workers exposed daily to such dusts.

While the manufacture of briquettes in England is attended by a high cancer rate, [58] since high-temperature tar is used, yet in the few plants in the U.S. making briquettes cancer is entirely absent, partly due to the lack of contact with the binder since the process here is entirely mechanized and partly due to the use of petroleum asphalt as a binder, [42]. This finding was confirmed by Wood [120] in his investigation of briquette manufacture in Pennsylvania.

The addition of glycerides [89] reduces the carcinogenic potency of mineral oils but not to as great an extent as lanolin. Speakman and Chamberlain [89] state that while alcohols have not been used for this purpose there can be little doubt that such polar compounds will reduce the risk of cancer formation by promoting emulsification, since an oil which is easily and completely removed from the skin

must carry less risk than one which is difficult to emulsify. These investigators also believe that polar compounds in a mixture with mineral oil may, however, function in yet another way. It is known that the carcinogenic agents of mineral oil when associated with unsaturated compounds are free to concentrate at any surface to which the oil is applied, the non-polar paraffin molecules offering little or no resistance. However, when oil-soluble polar compounds, such as oleyl alcohol or wool-fat ether, are mixed with mineral oil they concentrate at the surface, excluding the less polar carcinogenic hydrocarbons.

Sequeira [86] stresses the necessity of absolute cleanliness of body and clothing, the application of castor oil [85] to exposed surfaces and medical inspection every three months. Brockbank [15] suggests a mixture of lanolin and olive oil be applied to the skin.

Duckham advocates the use of an oil-solvent cleanser similar to the ether soap used in hospitals in order to remove all of the lubricant from the pores [3].

In view of the suggested use of lanolin the following should be of particular interest: Dr. E. V. Cowdry, of the Washington University School of Medicine, St. Louis, has just announced (N.Y. Herald Tribune April 29, 1945) that cells can be sensitized to become cancer cells by treating them with a substance which does not cause cancer and which will even prevent powerful cancer-producing chemicals from exhibiting that property.

For example, when the powerful carcinogen methylcholanthrene is mixed with lanolin it is without action when applied to the skin of mice, although alone it always results in cancer. However, when these mice were then treated with methylcholanthrene in benzene they developed cancers more quickly and tumors of greater virility than mice which had not received the cancer-preventing treatment.

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REFERENCES

1. Anon., Cancer from Spindle Oil. Oil and Color Trades J., July 2, 1937, 38.
A letter sent out by the General Committee of the Federation of Master Cotton Spinners' Association recommends that when purchasing spindle oil members should obtain a guarantee that the oil conforms to a specification of the Manchester Cancer Committee which recently issued a formula claimed to minimize the so-called cancer-producing elements of mineral oil. Tests showed that many of the oils in use at present conform to this specification and are obtained at regular prices.

2. Anon., Cancer and Mineral Oils. Oil and Color Trades J., 102, 695 (1942)
The report of the Manchester Committee on Cancer, issued for the year ended October, 1941, states that in efforts to isolate and characterize individual carcinogenic hydrocarbons from shale oil, recently appreciable quantities of crystalline material have been obtained, but it is too early to discuss results in detail. As far as can be judged, all fractions obtained from Venezuelan Oil by chromatographic adsorption are active. Proprietary colloids have varying effects, depending on the conditions of the experiment. A colloid containing a chlor-compound was found less efficacious than an olive oil-lanoline mixture as protection against the carcinogenic action of shale oil, while the reverse appeared to be the case when the carcinogenic agent used was benzpyrene.

3. Anon., The Problem of Cancer. Petroleum Times, 23, 59, 300 (1930)
(a) The following appeared in a recent issue of the British Medical Journal in connection with the use of mineral lubricating oils in the Lancashire cotton mills: "The Manchester Cancer Committee, while studying the part played in the production of malignant growths by the lubricating oils used in cotton mills, has obtained information about the carcinogenetic power of various oils and the concentration within them of a cancer-producing principle. In the course of this research, two pure compounds of known chemical composition have been proved capable of producing tumors, and a study has been made of the factors which change a non-carcinogenic into an active carcinogenic substance. Already some of the methods for destroying the cancer-producing power of certain oils have proved to be effective, at least in part, and one method led to the preparation of a purified oil which, when subjected to vigorous test, has failed altogether to produce cancerous growths. Representatives of the cotton industry, after comparing this oil with the crude untreated oil have said that its lubricating power is unimpaired, and the Manchester Committee is therefore able to hold out the hope that before long it may be possible to put on the market an oil which fulfills the needs of industry without being a source of danger to the workers."

Assuming that the use of spindle oils be such a source of danger, it almost necessarily follows that other lubricating oils which come into closer physical contact with the worker must be sources of higher potential danger than any of the light lubricating oils used in the looms of the Lancashire cotton industry. It might be proved upon investigation that little difficulties would present themselves in the production of a spindle oil which is non-carcinogenic, and lest the present attack widens itself to include the whole range of mineral lubricating oils, it would be advisable to make an investigation of the most embracing character.

4. Anon., A Dangerous Report on Lubricants and Cancer. Pet. Times, 27, 319-320 (1932)

Criticizes the report of the Manchester Cancer Committee in that the Committee has accepted contributions of £1000 for two years from the Anglo-American, the Anglo-Persian and the Shell Mex but has not availed itself of the services and advice of experts from the oil industry relative to the character and methods of treatment of petroleum oils.

5. Anon., Manchester Committee on Cancer Report. Pet. Times, 38, 295 (1937)

The 1935-36 report of the Manchester Committee on Cancer claims that "with a knowledge of the refractive index of an oil, and of the viscosity, one can form a more reliable estimate of its cancer-producing powers than by the application of the sample to the skin."

It is pointed out, however, that similar conclusion in the 1933-34 report was based on insufficient evidence and that some discrepancies with animal tests were admitted, and that in the 1934-1935 report the animal tests were reverted to.

It is also pointed out that the above conclusion was based on the examination of only one oil from each of a number of countries.

6. Occupational Cancer of the Skin. Annual Report, Chief Inspector of Factories and Workshops, Year 1937.

A table showing distribution of epitheliomatous ulceration by industry for each of the years 1933-1937 is given in an abstract in American Journal of Cancer, 34, 610 (Dec. 1938). Tar distilling and cotton mule spinning take the greatest toll. The increased 1937 figures for tar distilling cases is attributable to voluntary periodical examination in some plants.

7. Alapy, H. Cancer Prophylaxis by Preliminary Treatment with Carcinogenic Polycyclic Hydrocarbons. Z. Krebsforsch. 48, 3209 (1938)

Mice and rats were treated with very small doses of 3 carcinogenic hydrocarbons (benzo-pyrene, methylcholanthrene and 1, 2, 5, 6-dibenzanthracene as a method of protection against the implantation later of highly virulent tumors. Usually a single subcutaneous injection was made of the carcinogenic agent dissolved in sesame oil. The most efficient dose in mice was 1.5-3y and the most favorable time 40-70 days before the implantation of the tumor emulsion. Ditenzanthracene was somewhat the most effective. The protection in mice was only slight. Development of the tumor was delayed 5-6 days and for 5-6 days was slow. Growth then became rapid and on the 17th or 18th day after implantation of the tumor the tumors were of the same size in the animals with treatment and the control animals. No hindrance to tumor growth was obtained in rats given 1-100y doses, occasionally 150-180y doses 3-4-80 days before implantation of the tumor. A definite active protection cannot be obtained by this method.

8. Bachmann, W. E. et al. Production of Cancer by Pure Hydrocarbons. Proc. Roy. Soc. B123, 343-68 (1937)

With respect to high carcinogenic potency, methylcholanthrene is not surpassed by any compound yet tested, although it is almost equaled by cholanthrene. Production of carcinoma is favored by introduction of substituents into the 5 position of the 1, 2-benzanthracene mol.;

2-Me-3, 4-benzophenanthrene is carcinogenic to a high degree as are certain hexacyclic hydrocarbons derived from the pentacyclic hydrocarbon 3, 4-benzopyrene.

9. Badger, G. M. et al. Production of Cancer by Pure Hydrocarbons. Proc. Roy. Soc. B129, 439-67 (1940)
Information as to the most effectual method for the production of any particular tumor (painting, subcutaneous injection, feeding) is not decisive; in the two latter the fur is always contaminated, and inhalation and swallowing cannot be excluded by any of the methods. The 3, 4-benzophenanthrene compounds possess carcinogenic properties, and apparently are more active than the benzanthracenes in the production of multiple tumors, cholangioma, and tumors of the lung; the 1, 2-substituted compounds are more active with respect to gastric tumors. Compounds substituted on the 1, 2-side are usually more carcinogenic than those substituted on the 6, 7, 8-side. Among the 1, 2-benzanthracenes, the 5-n-Bu, 5-n-Am, and 5-n-hexyl resemble the 3, 4-benzophenanthrenes in their association with a higher incidence of lung adenomas and multiple tumors, and a deficiency in sarcoma production.

10. Badger, G. M. et al. Production of Cancer by Pure Hydrocarbons. Proc. Roy. Soc. B131, 170-82 (1942)
In the series of 5-alkyl derivatives of 1, 2-benzanthracene (Me, Et, Pr, iso-Pr, Bu, C_5H_{11}, C_6H_{13}, C_7H_{15}) the higher members showed progressive diminution of carcinogenic power on the skin; member with more than 3 C atoms in the side chain did not produce sarcoma. With derivatives of 3, 4-benzophenanthrene, substitution in position 2 and, to a lesser extent, in position 1, promoted carcinogenic action; most of these compounds were deficient in power to produce sarcoma. 1, 2, 3, 4-Tetramethylphenanthrene had a slight but distinct ability to produce skin tumors. 3, 4, 5, 6-Dibenzofluorene had no action on the skin and thereby differed from the 1, 2, 3, 4-, 1, 2, 5, 6-, and 1,2, 7, 8-compounds. 1, 2, 5, 6-Dibenzocarbazole exhibited a slight tendency to produce tumors of the liver. While multiple tumors could not be ascribed with certainty to the action of the administered compounds, the most striking cases of multiplicity occurred under the influence of 2, 3, 4-substituted phenanthrenes, 1, 2, 5, 6-dibenzocarbazole and 1, 2-5, 6-dibenzacridine.

11. Barry, G. et al. Production of Cancer by Pure Hydrocarbons. Proc. Roy. Soc. B117, 318-51 (1935)
A large number of compounds, chiefly tetracyclic and pentacyclic aromatic hydrocarbons, were tested for cancer-producing action, with mice as experimental animals. Considerable cancer-producing power was possessed by 1, 2-benzopyrene (from coal-tar pitch), methylcholanthrene (a deriv. of deoxycholic acid of bile) and 3, 4-benzophenanthrene. In order to be carcinogenic, derivs. of 1, 2-benzanthracene must contain substituents in positions 5 and 6.

12. Bergmann, F. Mechanism of Tumor Production by Chemical Agents. Cancer Research, 2, 660. (1942)
The following principles for tumor production by chemical agents are hypothetically established: 1. The form and size of a carcinogenic hydrocarbon and of its related heterocyclic compounds determine its activity. Every substance which imitates more or less closely a given parent structure resembles it also in its blastomatogenic action.

2. In the living cell, the carcinogens are adsorbed by an acceptor possessing a definite adsorption area. This sets an upper limit for the dimensions of the active compounds. A lower limit is given by a decrease in adsorbability with decreasing size of the molecule. 3. All carcinogens are conceived as parts of an "ideal carcinogenic structure." 4. A carcinogen can be inactivated by additions which prevent its proper adsorption. The mechanism of this hindering effect is discussed.

13. Bonser, G. M. Tumors of the Skin Producte by Blast-Furnace Tar. Lancet 1, 775-6 (1932)

The results obtained with four samples were remarkably similar to Berenblum's and blast furnace tar is therefore carcinogenic, though not so potent as the gas tar employed. The reason that it has been innocuous for man is that the yield is small, and it is regarded as a waste product and is disposed of without further handling.

14. Boyland, E. and Brues, A. M. Carcinogenic Action of Dibenzcarbazoles. Proc. Roy. Soc. 122B, 429-41 (1937)

Cancer of the bladder is unduly frequent among chemical workers, and those dealing with naphthylamines and benzidine seem most liable to the disease. It has not been demonstrated satisfactorily that naphthylamines are carcinogenic, and it is possible that it is not they which are responsible for cancer of the bladder, but impurities formed during their manufacture, such as dinaphthylamines and dibenzcarbazoles. Substances of this nature were therefore tested for carcinogenic activity by painting on the skin of mice and one (which proved most active on mouse skin) also by subcutaneous injection into rats.

The most active was 3:4:5:6-dibenzcarbazole but this was toxic. It produced malignant skin tumors in mice in 180 days. Of the other substances tested, 1:2:5:6-dibenzcarbazole was carcinogenic and 1:2:7:8-dinbenzcarbazole feebly so. The dinaphthylamines, O-aminoazotoluene, known to produce hepatoma, and diamino-azobenzene (chrysoidine) all failed to produce tumors on the skin of mice. Spindle-cell sarcomata, one of which was proved transplantable, were produced in rats by subcuraneous injections of a colloidal suspension of 3:4:5:6-dibencarbazole.

15. Brockbank, E.M. Mule-Spinner's Cancer. Brit. Med. J., 622-3 (4.26.41)

16. Brockbank, E. M. Mule Spinners Cancer. Epithelioma of the Skin in Cotton Spinners. H. K. Lewis and Co., Ltd., London. 36 pp. (1941)

The first known case of scrotal cancer in a mule spinner was reported in Manchester in 1887, 37 years after the introduction of mineral lubricating oil; before that time sperm oil and neatsfoot oil had been the principal lubricants. It is now known that cancer of the skin, whether of the scrotum or elsewhere, in mule spinners is caused by carcinogenic compounds which are present in mineral lubricating oils though not in lubricants derived from animal or vegetable sources. Some mineral oils are more carcinogenic than others, that derived from shale being particularly dangerous, and it has been learned by experience that cancer is more likely to be caused if the same lubricant is used continuously, than if the kind of oil employed is occasionally changed. It has been found also that by mixing animal or vegetable oil with mineral oil the carcinogenic potency of the lubricant may be abated.

17. Burrows, H., Hieger, I., and Kennaway, E. L. Experiments in Carcinogenesis: the Effect of the Subcutaneous and Intraperitoneal Injection of Lard, Olive Oil and Other Fatty Material in Rats and Mice. J. Path. Bact. 43, 419-26 (1936)

18. Campbell, J. A. Experimental Production of Cancer by Dust Obtained from Tarred Roads. Brit. Med. J., 2.3.34, 233-4
This dust caused warts and cancer of the skin of mice with metastases sometimes in the lungs; in 6 months 24 out of 59 mice showed typical tar warts, half of which developed malignancy.

19. Campbell, J. A. The Effects of Road Dust "Freed" from Tar Products Upon the Incidence of Primary Lung Tumors of Mice. Brit. J. Exptl. Path. 18, 215-24 (1937).
It has been shown that dust from tarred roads causes cancer of the skin of mice. Road dust minus tar, as removed by benzene, does not cause cancer of the skin of mice; it stimulates the production of lung tumors in mice, but not to so great extent as when the tar is also present.

20. Campbell, J. A. Carcinogenic Agents Present in the Atmosphere and Incidence of Primary Tumors in Mice. Brit. J. Exp. Path., 20, 122-32 (April, 1939)
The author has continued his research on substances that might induce lung tumors. He employed chimney soot and soot scraped from exhaust pipes of engines burning heavy oils. Rats were exposed to these dusts for 10 min. an hour for 6 hrs., 5 days a week for 1 yr. The death rate of both groups was well within the limits of that for the controls but the number of lung tumors was somewhat higher. Of those exposed to exhaust pipe soot, 33% living 10 mos. or more developed tumors. The most active substances tested was dust from tarred roads. Data are also given on mice whose skin was painted with "tar" from these substances.

21. Clark, R. V. Cancer from Lubricating Oils. Oil-Color Trades J., 11.9.34, 1278-9

22. Cook, J. W., Hewett, C. and Hieger, I. Coal-Tar Constituents and Cancer. Nature, 130, 926 (1932)
Several hydrocarbons were isolated from coal tar which were active in producing cancers and which had the typical fluorescence spectrum of carcinogenic fractions. The most active hydrocarbon isolated was 1, 2-benzopyrene which produced cancer in half the time required by 1, 2, 5, 6-dibenzanthracene. Perylene and 4, 5-benzopyrene were also isolated.

23. Cook, J. W. et al. Production of Cancer by Pure Hydrocarbons.
(a) Proc. Roy. Soc. (London), B111, 455-84 (1932);
(b) Proc. Roy. Soc. (London), B111, 485-96 (1932)
(a) Mice were used as exptl. animals, and a study was made of the action of 22 different polycyclic aromatic hydrocarbons, contg. 3-8 rings in their resp. mols. and applied in soln. to the interscapular region, usually twice weekly. Of these pure compds. only 1, 2, 5, 6-dibenzanthracene and certain closely related compds. produced cancer; it was active in 9 different solvents, and was effective when applied in 0.003% soln. in C_6H_6. Of 273 mice treated with this compd., 107 developed tumors, including 77 epitheliomas and 21 papillomas.

(b) The investigation has been extended to include 52 addnl. polycyclic aromatic compds. Tumors were produced by 6-isopropyl-1, 2-benzanthracene, 5, 6-cyclopentene-1,2-benzanthracene, phenanthreacenaphthene, and 5 derivs. of 1,2,5,6-dibenzanthracene: 2'-Me, 3'-Me, 9-NH_2, 9-MeO, 9,10 $(C_6H_5CH_2)_2$.

24. Cook, J. W., Hewett, C. L. and Hieger, I. The Isolation of Cancer-Producing Hydrocarbons from Coal Tar. J. Chem. Soc., 395-405 (1933)

The preparations derived from coal tar pitch by a variety of solvent extraction methods, the fractions separated by formation of picrates, distillation and crystallization, and the hydrocarbons, 1:2-benzpyrene, and 4:5-benzpyrene, perylene and 1,2-benzanthracene, have proved carcinogenic and have given the same fluorescence spectrum (bands at 4000, 4180 and 4400A°). The original coal tar pitch contained not less than 0.003% of 1, 2-benzpyrene.

25. Cook, J. W. Synthesis and Biological Effects of Carcinogenic Hydrocarbons. Chem. and Ind., 54, 1022-3 (1935)

Certain forms of skin cancer due to occupation causes in industries where shale oil, coal tar and lubricating oil are employed, have been shown to be due to the benzanthracene group of hydrocarbons which also impart fluorescence to the oils. The exact nature of cancer formation in the human body has not been explained although a similar benzanthracene hydrocarbon has been found to be produced by body changes from substances normally present in the human body.

26. Cook, J. W. Carcinogenic Hydrocarbons and Their Relationship to the Sterols. Chem. Weekblad, 32, 563-6 (1935)

Review of historical development of recognition of the cancer-producing constituents of coal tar and earlier investigations; the development of fluorescence spectroscopy and the systematic study of synthetic carcinogenic hydrocarbons including a summary of the results obtained from the examination of a complete series of tetra- and penta-cyclic hydrocarbons and a moderately wide range of benzanthracene derivatives. The speculation is advanced that a meso H atom in a completely aromatic structure plays some role in the carcinogenic process. The isolation of 1,2-benzopyrene from coal tar and its synthesis are recounted and an account is given of the cyclization of bile acid derivatives, and the eventual synthesis of methylcholanthrene, a carcinogenic hydrocarbon related to the sterols. It is inferred that there is some enzymic factor present in the animal body which is capable of effecting dehydrogenation of the sterol ring system and that excessive activity of this factor may conceivably contribute to the production in vivo of carcinogenic compounds.

27. Cook, J. W., et al. Chemical compounds as Carcinogenic Agents. Am. J. Cancer, 29, 219-59 (1937)

A full survey is given of the carcinogenic chemicals, dealing both with their chemical relationships and their biologic effects, bringing together, under well chosen headings, all the material published up to the end of 1936. They include not only the hydrocarbons of the benzanthracene type, but also the azo compounds, estrin, the styryl quinoline derivative discovered by Browning et al., and the inorganic compounds zinc chloride and arsenic. A bibliography of 194 references is appended.

28. Cook, J. W. and Kennaway, E. L. Chemical Compounds as Carcinogenic Agents. First Supplementary Report: Literature of 1937. Am. J. Cancer, 33, 50-97 (1938)

Authors present an exhaustive review of this subject which should be of interest to all industrial physicians. It continues the earlier review and the two reports together have bibliographies totaling 374 references.

29. Davis, E. Chemical Carcinogenesis, Drugs, Dyes, Remedies and Cosmetics with Particular Reference to Bladder Tumors. J. Urol. 49, 14 (1943)

Author discusses at considerable length the large number and variety of proved chemical carcinogenic agents which may be introduced into the body by ingestion, inhalation, injection or cutaneous application. He strongly inclines to the theory of some chemical carcinogenic agent. Many are cited such as derivatives of coal tar, crude mineral oils, an anilin dye "intermediate", azo dyes and estrogenic substances. The aniline bladder tumor of dye factory works develops after years of exposure to what are probably extremely small daily doses.

The theory is advanced that there may be many other carcinogenic agents as yet unknown which are unknowingly encountered in the routine of daily life, and perhaps through the use of many drugs, patent medicines and cosmetics, vitamins, sex hormones, and the tremendous list of anilin dyes used in the coloring of food stuffs and fabrics.

30. Downing, J. G. Industrial Dermatoses. J. Ind. Hyg., 17, 138-165 (1935)

A review with 208 references. A section on chemical agents including inorganic compounds, hydrocarbons and crude coal tar products and other organic compounds; treatment and legal aspects.

31. Feil, A. Oil Button (Elaiokoniosis). Presse Med., 40, 1541-2 (1932)

Description of a dermatitis in industrial workers caused by heavy mineral oils, including treatment and prophylaxis.

32. Fieser, L. F. Carcinogenic Activity, Structure, and Chemical Reactivity of Polynuclear Aromatic Hydrocarbons. Am. J. Cancer, 34, 37-124 (1938)

A long review which includes: I, a critical evaluation and comparison of the methods for determining carcinogenic activity; II, information concerning the preparation and purification and the commercial sources of the carcinogenic hydrocarbons; III, a summary of the work on correlation of chemical structure and carcinogenic activity, and IV, a summary of investigations on the metabolic fate of various active hydrocarbons. There is a very extensive bibliography.

33. Fieser, L. F. Production of Cancer by Polynuclear Hydrocarbons. Univ. Penna. Bicentennial Conf. Cause and Growth of Cancer, 1-27 (1941)

A review devoted to N-containing carcinogens, relation of carcinogenic hydrocarbons to the steroids, carcinoganic activity, chem. structure and chem. reactivity, nature of a possible reaction leading to carcinogenesis and of the metabolism reaction. If carcinogenic hydrocarbons can be produced at times in the body by steroid metabolism, their most likely precursors are among the steroids of the adrenal cortex. The initiating action of a hydrocarbon in carcinogenesis probably involves substitution in the hydrocarbon at its most reactive center, probably a direct interaction of the hydrocarbon with an S-S linkage of the cell

protoplasm. Metabolic elimination of a carcinogen probably is a detoxication produced by a mechanism different from that leading to carcinogenesis, and involving a different point of attack in the mol. The reaction of detoxication and that of carcinogenesis are competitive. Detoxication may involve biol. hydroxylation to a phenolic deriv., or conversion into derivs, of mercapturic acid.

34. Fieser, L. F. and Fieser, M. Carcinogenic Hydrocarbons. "Organic Chemistry", 1944, 814-26.
Carcinogenic activity and structure; correlation with chemical reactivity; methods of synthesizing carcinogenic hydrocarbons.

35. Firquet, J. and Malter, M. A. Pitch Cancer as an Occupational Disease. Archive de Medecine Sociale et d'Hygiene et Revue de Pathologie et de Physiologie du Travail, II, 797-807 (1939-40)
The authors report their experiences made in medical supervision of 126 workers in the province of Liege, working with pitch or tar. There were found two epitheliomata only, and no lung cancers. V. Henry made a chemical examination of various pitches as to their content in 1.2 benzeneanthracene and 3.4 benzopyrene, (the two most effective cancerogenic substances in animals) and he found in the pitch 1-8% of the first, traces up to 0.4% in the second. The examination of the pitch dust in the two briquette factories revealed mostly large particles: in the workshop 80% of a diameter of 50-100u, in the storage rooms 90% of 20-50u.

Therefore it seems--according to the authors--that substances which are cancerogenic to animals are not for men, but more research is necessary. (The material is much too slight for any conclusions in the opinion of the abstractor.)

37. Gafafer, W. M. and Sitgreaves, R. Disabling Morbidity and Mortality from Cancer among Male Employees of Oil Refining Company, with Reference to Age, Site and Duration, 1933-38,inclusive, U.S. Pub. Health Repts. 55, 1517-1526 8.23.40)

38. Guglielminetti, M. Do Macadam Roads Produce Cancer. Bull. Acad. Med., 122, 89-94 (1939)
The author first reviews the literature. He questioned various hospitals in some of Germany's large cities regarding the number of observed cases of cancer and sent these reports to the managers of the road building system in these cities. Increase of cancer was affirmed but without relation to macadam roads.

39. Hamilton, Alice. Cancer from Tar and Petroleum, "Industrial Poisons of U.S.", 410-7 (1925)

40. Hamilton, Alice. "Industrial Toxicology", 134, 253-4
Occupational cancer is rare in France. In the U.S. the only published case up to 1930 was the case of a man who had worked for 20 yrs. at the paraffin process in a petroleum refinery.

In 1928 the Health Committee of the League of Nations requested its members to aid in a world-wide inquiry into the occurrence of occupational cancer by undertaking a study of the question in their own countries. The Rockefeller Foundation then made it possible for Imre

Heller to make an intensive investigation in this country, and his report was published in 1930. Heller confirmed the impression held by American authorities on cancer, that those of occupational origin are very very rare in the United States. He found in the records of the two New York hospitals specializing in cancer only 37 cases of skin cancer that could possibly be traced to tar and tar products, 26 of these occurring among men handling gas-house tar or pitch, only two in coke-oven tar or pitch workers. In a Cleveland plant making carbon and dry batteries, imported English gas-house pitch was used up to 1906, when it was supplanted by American coke-oven pitch. There were 21 cases of cancer among the workers in this plant, only 4 of which were in men handling coke-oven pitch, and these were not considered by the physician in charge to be indubitable cases.

41. Hartwell, J. L. Survey of Compounds which have been Tested for Carcinogenic Activity. U. S. Public Health Service, 371 pp. (1941)

This bulletin represents a survey of the field of chemical carcinogenesis in the higher animals: the action of carcinogens on isolated tissues, tissue cultures, plants, protozoa, and bacteria is not considered. The literature is covered to 1939, and the compilation also includes experiments with 153 compounds from the unpublished work of Dr. M. J. Shear and Dr. H. L. Stewart of the National Cancer Institute. The results of the testing of 61 of these compounds are newly reported, while 45 are new to the whole cancer literature. Altogether the work comprises data referring to 696 chemical substances: of these, 169 are reported to be carcinogenic, apart from 23 observed as causing papillomas only. After an introductory discussion, the bulletin takes the form of a tabular review on the following classification (figures in parentheses show the number of entries for each category): A. Inorganic substances (35). B. Organic compounds: I, Aliphatic (36); II, Polycyclic [dicyclic (26), tricyclic (37), tetracyclic (152), pentacyclic (114), hexacyclic and higher (25)]; III, Azo-compounds (39); IV, Steroids (86); V. Heterocyclic (59); VI, Unclassified (77).

Within this arrangement, compounds are individually numbered and then grouped according to prototypes and alphabetically. The tables give structural formulae, literature references, particulars of species, strain, sex, and number of animals used, preparation, dosage, and route of administration of compounds, nature of sites of tumors induced, with details of duration of experiment and survival rates and other remarks. The above conditions show the wide range of information necessary in order to assess the carcinogenic activity of a given compound. The author draws attention to the incompleteness of the data for many of the compounds listed, and urges the more systematic investigation of compounds already studied in a preliminary fashion, and for the filling of large gaps among substances which it would seem desirable to test. The review is completed by a bibliography (over 1200 references) and separate indexes to compounds, routes of application, vehicles, animal species, and tumor-sites.

42. Heller, I. Occupational Cancers (in U.S.). J. Ind. Hyg., 12, 169-197 (1930)

The chemical properties of gas-works, coke-oven, producer-furnace and blast-furnace tars and pitch are briefly outlined with a view to correlating these properties to cancer incidence among workmen in the industries involved. As a result of extensive surveys and health record

examns., gas-works tar and pitch were responsible for 70.2% of the cases while coke-oven tar and pitch were held responsible for only 5.4%. Coke-oven tar is much the less injurious especially when cognizance is taken of the fact that coke-oven tar is used much more extensively. The presence of olefins in gas-works tar seems to be of particular importance and may be a cause of oil cancer. Occupational cancer does not occur in the briquet mfg. industry. Mineral oils vary in carcinogenic activity according to their olefin or unsatd. hydrocarbon content. There is no method for the detn. of the amt. of olefins in the various crude oils; if such a method existed, it would be possible to measure the cancer-producing power of mineral oils. Cancer is not attributable to the occupagion of mule spinner in the U.S., possibly because of the carefully refined lubricating oils used on the machines, thus ensuring relative freedom from olefins or unsatd. hydrocarbons.

43. Henry, S. A. Study of Fatal Cases of Cancer of the Scrotum. J. Am. Med. Assn., 109, 1667 (1937)

44. Hieger, I., Spectra of Cancer-producing Tars and Oils and of Related Substances. Biochem. J., 24, 505-11 (1930)

45. Hoffman, F. L. Mule Spinners Cancer. Monthly Labor Rev. of U.S., 27, 457-475 (1928)

46. Hoffman, W. J. Industrial Cancer. Prevent. Med., 6, 7-34 (1936)
One of the seven types of industrial cancer discussed is cancer of skin in workers exposed to coal, tar, pitch, soot, shale, petroleum and arsenic. They may cause an epitheliomatous form of cancer.

47. Hogouneng, L. The Cancerigenic Hydrocarbons from Tar and the Tarring of Roads. Ann. Hyg. Publ. Sociale, 27, 1-7 (1939)
The cancerigenic hydrocarbons found in coal tar produce skin cancer in exposed workers usually only after direct contact with the skin for long periods of time. It is believed that man is much more resistant to the action of these materials than lab. animals.

48. Hueper, W. C. Cancer in Relation to Occupation and Environment. Bull. Am. Soc. Control Cancer, 25, No. 6 (June, 1943)
Owing to industrial development, the general population and factory workers in particular, are exposed to many new environmental factors, many of which are disease producing. Occupational cancers are caused by numerous chemical and physical agents. Among them are the heavy metals, nitrates, aromatic amino compounds, benzol, asbestos, mineral oil, soot, radio-active substances, ultraviolet radiation and X-rays. The author cites statistics taken mainly from the records of industrial concerns, but points out their shortcomings.

Cancer of the urinary tract due to coal-tar is the most recent addition to the list of occupational cancers. It is most frequent in the aniline dye and related industries.

49. Home Office, Rept. of Departmental Comm. to Consider Evidence as to Occurrence of Epitheliomatous Ulceration Among Mule-Spinners. (London, 1926)
Contains a bibliography on cancer among petroleum refiners.

50. Hunt, E. S. An Investigation into the Incidence of Cancerous or Precancerous Skin Lesions Among Tar Workers in New South Wales. Med. J. Australia, 8.26.33, 281-3
The general conclusion is that tar used in New South Wales for local road-work is not a serious danger.

51. I.P.T. Cancer Research Committee. Carcinogenicity of Spindle Oils. J. Inst. Pet. Tech., 23, 205 (1937)
The I.P.T. Committee has not been convinced that the so-called incidence of cancer is in any shape or form connected with the use of spindle oils.

52. International Labour Office. Carcinogenicity of Oils. Ind. and Labour Information, 34, 279 (1930)
Tars at varying temperatures have been prepared to determine at what temperature carcinogenic compounds are formed, from which experiments it would appear that such compounds begin to be formed between 500° and 600°, the maximum yield lying between 800° and 900° C. Attempt is now being made to determine the constitution of a few apparently pure or almost pure compounds isolated from such tars. Applying their standard test for determination of carcinogenicity, the staff found that olive oil, neats-foot oil, sperm oil were non-cancer producing and they have reason to suppose that natural skin fat is an important factor in the prevention of cancer.

53. International LabourOffice. "Occupation and Health", I, 547 (1934); II, 837, 1156 (1934)
Before mineral oils came into vogue the practice in textile mills was to use sperm, lard and neat's-foot oils and to some extent castor oil and colza oil. Henry states that shale oil was introduced about 1850 and American petroleum oil about 1864, and that, towards 1872, these oils were being used as components of spindle oil; also that Russian oil was first imported about 1880, Rumanian oil about 1900 and Persian oil about 1909, and all these were used for this class of lubricating oil before the war. During the war Scottish shale oils naturally came more into use for lubricating purposes. Oil refiners have their own private formulae for mixings, but there is no doubt that the bulk of the oil sold for lubricating spindles during the past forty years has been principally made up of natural mineral oil.

According to the 1929 report of the Manchester Cancer Committee, in the distillation of tars, the carcinogenic products begin to form at a temperature ranging from 500 to 600 C. and reach a maximum at between 800 and 900 C. The addition of sulfuric acid at the time of use suffices to make the oils harmless without injuring or modifying their lubricating power.

54. International Labour Office, Occupational Tumors. Suppl. to Occupation and Health, I.L.O., Geneva, (Oct. 1939)
Carcinogenic substances are discussed under the headings of hydrocarbons, non-radioactive inorganic compounds, radioactive substances and radiation, and parasites and microbes. Attention is called to the absence of any common physical or chemical characteristics shared by these various cancer-producing agents.

It is suggested that the cancer problem is essentially biochemical and that its solution will come with the discovery of the nature and cause of the intra-cellular chemical changes which follow the application of a carcinogenic agent.

55. Jordan, H. Experimental studies on the Production of Cancer by Gas-works Tar. Z. Krebsforschung, 19, 39-55 (1922)

Author has corroborated the work of others; in white mice treated with tar for four months or less, 100% showed either cancer or precancerous changes. When the tar was distd. at 400° the volatile fraction did not produce these changes but the residue produced the typical proliferative changes in about ½ the time required with the whole tar. No proliferation could be produced with anthracene oil. Different mice showed a marked difference in the rapidity with which they developed proliferation with the same amt. of injury by the tar. Apparently the work was not followed to a point to det. just how many of the mice with precancerous changes would have developed actual carcinoma.

56. Kennaway, E. L. The formation of a Cancer-producing Substance from Isoprene. J. Path. Bact. 27, 233-8 (1924)

56A. Kawahata, K. Lung Cancer Among Generator-Gas Workers in the Steel Mills. Gann, 32, 367-88 (1938)

During the past 6 years, 21 cases of primary lung carcinoma were observed among the generator-gas workers at the Yawata Iron-Steel Mills. These workers have av. service periods of 16 years. In no other sections of the mills has such frequent appearance of lung cancer been noticed. The workers are exposed to the spraying of gas contg. heavy dust. The inhaled gas contained about 0.7% of gaseous or dust-like tar. Analyses showed creosote oil 24.56%, phenols 0.31%, cresols 0.07%, naphthol 4.65%, anthracene 2.00%, pitch oil 62.67% and water 5.74%. The metastases may appear very early in the brain, spinal cord and lymph nodes. The duration of lung cancer is very short, about 7 months.

57. Kennaway, E. L. Cancer-Producing Constituents of Coal Tar. Brit. Med.J., 564-7 (1924)

Cancer formation by tar products was investigated by author. Only higher fractions boiling at 250-500° C. were found active in inducing cancer (creosote, green oil, crude anthracene and pitch).

58. Kennaway, E. L. Cancer-Producing Tars and Tar Fractions. J. Ind. Hygiene 5, 462-88 (1924)

Experiments on several thousand mice and analysis of a great mass of clinical records indicate that tar cancer is caused by a very small quantity of an unstable compound that exists in the high-boiling fraction (250° to 500°) of a high-temp. coal tar, i.e., creosote oil and anthracene oil. Purified anthracene, like all other pure compounds tried, did not produce cancer. Splashing with hot, crude anthracene or creosote oils seems to be the usual method of contact. Shale oil produces cancer but is less active than gas works tar; crude petroleum is much less active; and blast-furnace tar (a low-temp. tar) does not produce cancer. The briquetting industry has reported more than half of the known cases of tar cancer. Tar made by distilling coal at a low temperature (below 550°) produces cancer very slowly or not at all.

59. Kennaway, E. L. Experiments on Cancer-Producing Substances. Brit. Med. J., II, 1-4 (1925)
Cancer has been produced in mice by substances obtained by heating C_2H_2, isoprene, yeast, human skin to temps. ranging from 700° to 920°. A petroleum which produced no tumors of any kind in mice in a prolonged experiment showed very active cancer-producing properties after exposure to 880°.

60. Kennaway, E. L. and Leitch, A. The Anatomical Distribution of the Occupational Cancer. J. Ind. Hygiene, 7, 69 (1925)

61. Kennaway, E. J. Further Experiments on Cancer-Producing Substances. Biochem. J., 24, 497-504 (1930)
Carcinogenic substances were obtained by the action at roomtemperature of $AlCl_3$ on acetylene, xylene, naphthalene, naphthalene and bromobenzene and tetrahydronaphthalene, the last two being the most active. Two cancers were also obtained in a series of 10 mice painted with a soln. of 1,2,7,8-dibenzanthracene.

α-Phenylnaphthalene was prepared by action of $AlCl_3$ on C_6H_5Br and $C_{10}H_3$. The distillates up to 342° C. containing the hydrocarbon were inactive but the residue in the flask was highly carcinogenic.

Cyclohexane, cyclohexene, styrene, hydrophenanthrene, hydrochrysene, hydroretene, perylene, naphthalene and various naphthalene derivatives all gave negative results.

62. Kennaway, E. L. and Hieger, I. Carcinogenic Substances and Their Fluorescence Spectra. Brit. Med. J., No. 3622, 1044-6 (1930)
This paper is a review of a large amount of work by the authors in an attempt to correlate fluorescence with carcinogenesis.

Tar oils, spirile and shale oils, which show carcinogenic properties are also strongly fluorescent.

63. Kewley, J. Cooperation. J. Inst. Pet. Tech., 18, 242 (1932)
Mention of the formation of a committee by the Institute of Petroleum Technologists to follow the work of the Manchester Cancer Committee.

64. Kling, A., Samssonov, N. and Heros, M. The Tarring of Highways as a Possible Agent in the Causation of Pulmonary Cancer. Bull. Acad. Med. 120, 130-43 (1938)
Expts. in mice showed that the tar, as used on roads, produces cutaneous tumors and malignancy in the lungs. A substance contg. the benzo (a) pyrene nucleus of decidedly cancerogenic properties has been sepd. from the tar.

65. Kling, A., Samssonov, N. and Heros, M. Possible Relationship between Tarring of Highways and the Increase of Incidence of Pulmonary Primary Cancer. Bull. Acad. Med., 121, 784-91 (1939)
Since tar contains benzopyrene, a recognized cancerigenic agent, it cannot be considered as inoffensive. Experiments on mice definitely confirm this assumption.

66. Koelsch, F. Cancer and Occupation. Monatschr. Krebsbekampf. 5, 7 (1937)
The author, in the form of an abstract, presents a survey of the relation between cancer and occupation. He includes bone cancer caused by radioactive substances, skin cancer from soot, tar, paraffin and lubricating oils (of which those boiling between 250-500° are of especial importance), skin cancer from arsenic as well as cancer and sarcoma from ultraviolet and sunlight.

67. Kunze, G. Mineral Oil and Cancer. Chem. Ztg., 59, 407-8 (1935)
A study of the map of Germany indicated that the number of deaths from cancer was always greatest in regions where mineral oil was found, refined or used. While no definite relation is established, the author suggests the possibility of the existence of such a relationship. Further research on this problem is indicated. It is pointed out that mineral oil by itself does not cause cancer. It may, however, become one of the contributing factors, together with others.

68. Lane, C. G. Occupational Dermatitis. Arch. Dermatol. and Syphil. 43, 184 (1941)
Describes the case of a 68 yr. old machinist who for 3 yrs. had a dermatitis of the face, arms, axillas and lower abdomen. There were scattered areas of tan-brown hyperkeratotic follicles and follicular plugs. Keratoses were present on the scrotum and there were keratotic areas on the arms. Autopsy revealed carcinoma of the oesophagus. Dr. Lane believes the skin changes to be due to oil to which the man was exposed in his 40 yrs. as a machinist, and that the condition is that described by White among machinists, oil workers and mule spinners in England. It apparently is rarely seen in this country, possibly because oils employed here are less carcinogenic.

69. Lauber, H. J., Hildebrand, E. and Schocke, H. Possible Therapeutic Action of Carcinogenic Hydrocarbons in Treatment of Cancer. Z. Ges. Exptl. Med., 105, 370-94 (1939)
Essentially less harmful therapeutic measures are available. The dangers are demonstrated on mice treated with methylcholanthrene.

70. Leitch, A. Mule Spinners' Cancer and Mineral Oils. Brit. Med. J., 2, 941-3 (1924)
Rendered an inert California oil very active by heating it. (No details as to temperature, etc.).

Crude oils from Assam, Borneo, Egypt, Burma and Badarpur produce malignant growths. Galician, Russian, Californian and Persian samples were negative.

71. Lyth, R. The Relation of Carcinogenicity of Mineral Oils to Certain Physical and Chemical Characteristics of These Oils. J. of Ind. Hyg. 15, 226-37 (1933)

72. Lyth, R. Molecular Distillation of Lubricating Oil. Nature, 139, 374 (1937)
A brief report is given of the distillation of a Scottish shale oil, using a specially designed molecular still. The most striking result is the inversion in the change in the physical properties going up the temperature scale, i.e., the first fractions show higher refractive indices and densities than the original oil, with gradually descending values from fraction four as the temperature is raised. Data on the properties

of the shale oil distillates are tabulated. These experiments are part of an investigation of the interrelation of refractive index and viscosity to activity on injection, and thereby carcinogenicity when applied to the skin.

73. Mioscher, G., Almasy, F, and Zehender, Z. Is There a Connection Between the Benzpyrene Content and the Carcinogenic Effect of Tar? Schweiz. Med. Wchnschr. 71, 1002-7 (1941)
The authors have examined the benzpyrene content of gas tar in various towns in Switzerland, using a method devised by Almasy. Then the tars were purified and their carcinogenic effect determined by painting on mice. The investigators tried to evaluate the results by means of a statistical method in order to overcome the difficulty offered by the fact that many mice die in the long period needed for the experiments. They find a simple, regular relationship between the benzpyrene content and the carcinogenicity of the tar,

74. Murray, J. A., et al. Discussion on Experimental Production of Malignant Tumors. Proc. Roy. Soc. (London) B113, 268-92 (1933).
A symposium in which some attention is paid to carcinogenic chem. compounds, and to the immunochemistry of cancer.

75. O'Brien, H. F. The Problem of Cancer and Oil. Petroleum Times, 27, 462 (1932)
An open letter to the editor of the Petroleum Times (London) in answer to an editorial in the issue of March 19th. The writer points out the humanitarian and scientific values derived from the cancer research of the Manchester Committee and criticizes the technological viewpoint of the editorial.

76. O'Donovan, W. J. Cancer from Handling Anthracene Coke in the Dye Industry. Br. J. Dermat. and Syph.,
Three cases of cancer in a factory employing only 25 men.

77. Phillips, C. Relationship between Skin Cancer and Occupation in Texas: Review of 1569 Verified Lesions Occurring in 1190 Patients. Texas State J. Med., 36, 613-16 (1941)

78. Prosser-White, R. "The Dermatergoses" 195-238 (1934)
Dermatitis and cancer from petroleum products, shale and tars. Excellent review.

80. Roffo, A. H. Experimental Research on the Production of Pulmonary Tumors by the Distillates of Fuel Oil. Presse Med., 538 (1940)
The author demonstrated an oil, taken from the streets of Buenos Aires, identical to that from motor car exhaust, which contains carcinogenic substances. Roffo had rats inhale the combustion gases of fuel oil and later found a number of pulmonary cancers among the animals. By injecting a distillate of the fuel oil into the auricle of rabbits, he produced tumors in 80%.

81. Roussy, G. and Oberling, C. Can Tarring of Roads be Considered as a Cause of Pulmonary Cancer? Bull, Acad. Med. 120, 181-90 (1938)
The danger is not considered to be of significance although the possibility is admitted.

82. Schreus, H. T. and Zurhelle, E. Experimental Production of Tumors with Tars from Various Sources and with Paraffin. Deut. Med. Wochschr. 49, 633-4 (1923)
Author investigated the poisonous action of paraffin oil and tar constituents by painting mice twice a week. After six months a state of malignancy was obtained with paraffin oil. Coal tar readily develops malignant tumors. Various purified acid and basic fractions from coal tar give negative results. The neutral tar oil is most effective as a tumor inducer.

83. Schwartz, L. Skin Diseases in Oil Refineries. Safety Eng., 210 (Nov. 1934)
It has been found that workers in oil refineries have a percentage above the average for carcinoma of the cheek and of the lip. An unusual prevalence of pigmented papillomata on the hands, forearms and legs of workers in oil refineries and among machinists in contact with oil and grease was also noted. About 10% of such workers were found to have these growths.

The use of totally enclosed manufacturing systems and of protective ointments is suggested.

84. Schwartz, L. and Tulipan, L. "Occupational Diseases of the Skin", 1939, 514.

85. Scott, A. Occupational Dermatoses of the Paraffin Workers in Scottish Shale Oils. Brit. Med. J., 8.28.22, 381-5

86. Sequeira, J. H. Cancer and other Diseases of the Skin Caused by Mineral Oils. Konya and E. African Med. J., 6, 18-23 (1929)

87. Smyth, H. F. Review of Literature for 1926-1934, inc. Report of Committee on Industrial Skin Irritants to Am. Public Health Assn.

88. Southa m and Wilson. Cancer of the Scrotum. Brit. Med. J., 2, 971-3 (1922)

89. Speakman, J. B. and Chamberlain, N. H. Trans. Faraday Soc., 29, 367-8 (1933)
In a study of the carcinogenic potency of mineral oils, Twart has shown that the addition of glycerides reduces their potency, although no oil surpasses lanolin in this respect.

90. Toleky, L. Occupational Cancer. Acta d. Internat. Ver. f. Krebsbekampfung, 2, 253-75 (1936)
Several isolated cases of lung cancer among generator workers have been reported and among works exposed to coal dust, tar and tar distillates, but the number is small.

91. Teutschlaender, O. Industrial Cancer, especially the Types Occurring in Germany. Z. fuer Krebsforsch. 32, 614-27 (1930)
Discusses x-ray cancer, cancer of briquette workers, mule spinners' cancer, which has not appeared in Germany, and paraffin cancer among those who work in the petroleum industry.

92. Teutschlaender, O. Occupational Cancer, with Special Consideration of its Prevention and Legislation on the Subject. Med. Walt. 11, 1267-72 (1341-5 (1937)
Occupations in which there is danger of development of cancer are reviewed; many data are given regarding substances considered carcinogenic.

the location of malignant tumors, their latent period, protective measure of an industrial-hygienic type, questions of insurance, etc. There is no sp. agent common to all carcinogenic substances as a promoter of cancer growth.

93. Teuschlaender, O. Does Tar Require Ultra Violet Light to Produce Skin Cancer? Klin. Wchnschr., 16, 1284-5 (1937)
White mice were painted with tar. Cancers developed not only in the irradiated animals but also in those kept in a dark chamber so that not only a preparatory but also an independent cancerogenic effect must be ascribed to tar.

94. Teutschlaender, O. Light and Skin Cancer. Ztschr. f. Krebsforsch. 50, 81-92 (1940)
The author investigates the problem of whether or not a photodynamic influence is necessary in the genesis of tar cancer. He conducted experiments on tarred mice kept in a dark room. Since skin cancer developed on the painted skin, it is evident that ultra-violet light is not a requisite in tar cancer genesis. The same is shown by the development of spontaneous skin cancers in two wild grey house mice that lived in a briquet factory.

Nevertheless there is a widespread belief that both cancer of radiant source and tar cancer of the skin are caused by cyclic hydrocarbons. According to Roffo, both types are originated by oxidation and decomposition of cholesterol in the tissues which may be caused by radiation as well as by chemical influence--cancer-provoking cyclic hydrocarbons are finally generated. Prophylaxis must, therefore, guard against the influence of one or both factors.

95. Touraine, A. and Bour, H. Cancer from Lubricating Oils. Rev. Med. Franc. 20, 285-92 (1939)
A very complete review of cancer from lubricating oils, its occurrence, clinical symptoms and the medico-legal aspects of such cases.

96. Twort, C. C. and Ing, H.R. Mule Spinners' Cancer and Mineral Oils. Lancet 1, 752 (1928).

97. Twort, C. C. and Fulton, J. D. Experiments on the Nature of the Carcinogenic Agents in Mineral Oils. J. Path. and Bacteriol., 32, 149-161 (1929)
From a consideration of the chemical reactions involved, the authors are of the opinion that it is to benezenoid hydrocarbons that certain mineral oils owe their carcinogenic properties. Treatment of the oils with sulfuric acid led to almost total abolition of their carcinogenic properties, and similar results were obtained by the adoption of methods of oxidation and reduction.

98. Twort, C. C. and Twort, J. M. Studies on the Origin of Cancer. Ztschr. f. Krebsforsch., 32, 491 (1930)
This is a general survey of the work of the Tworts, and is based on experiments on 45,000 mice, a smaller number of rats, guinea-pigs, and rabbits, and on the use of some hundreds of varieties of tars and oils of various capacities to cause cancer. There is but little probability that an acquired physiological immunity against cancer-producing substances exists. The authors' various substances are divided according to their

cancer-forming capacity in mice, so that every group has about ten times the power of the preceding one.

99. Twort, C. C. and Twort, J. M. Classification of Four Thousand Experimental Oil and Tar Skin Tumours of Mice.
The study from which this classification was made was based upon 29,100 animals.

100. Twort, C. C. and Fulton, J. D. Further Experiments on the Carcinogenicity of Synthetic Tars and Their Fractions. J. Path. Bact. 33, 119-43 (1930).

101. Twort, C. C. and Twort, J. M. The Carcinogenic Potency of Mineral Oils. J. Ind. Hyg. 13, 204-22 6 (1931)
Painting mice with refined shale oil induces cancer more readily than painting with refined petroleum well oil. The most potent fraction from shale oil is unfinished lubricating oil from which most of the paraffin wax has been removed but which had not been treated with H_2SO_4 and filtered. The heavier grade oils are less potent than spindle oils. The Cancer-producing property of oils appears to be related to fluorescence. Oils having a blue fluorescence seem more active than those having a green fluorescence. Chrysene dissolved in oleic acid possesses carcinogenic properties.

102. Twort, C. C. and Twort, J. M. The Relative Potency of Carcinogenic Tars and Oils. J. Hyg., 29, 373-9 (1931)
A method has been devised whereby the potency of any given carcinogenic agent can be compared with that of a standard agent. A unit of carcinogenicity- U.C. - has been established, and a concentration of 500 carcinogenic units per cubic centimeter is considered to induce the maximum relative response in animals when the agent is applied twice a week.

The carcinogenic powers of oils rate as follows, in descending order: Shale, Venezuelan, Borneo, Rumanian, Persian, Californian, Mexican, Mid-Continental, Texan, Pennsylvanian, and Russian.

Hypothetical standard agent	100.0
Penn. oil	0.1
Cal. pet. oil	3.0
Oil No. 3	0.6
Shale Oil	48.0
Pitch	25.0
Gas tar	94.0
Pinene synthetic tar	706.0
Effect of refining	
Penn. oil	0.1
Methyl sulfite extract	22.0
Oil No. 3	0.6
Distillate 300-380°C./12mm	12.0
Methyl sulfite extract	53.0
Shale oil	48.0
Oxidized at 150-160°C.	0.3
Pinene synthetic tar concentrate	3745.0
Oxidized at 100°C.	2369.0
Oxidized at 150-160°C.	58.0

103. Twort, C. C. and Fulton, J. D. Concentration of the Carcinogenic Principle in Oils and Tars. J. fuer Krebsforsch. 35, 543-73 (1932)

In the attempt to assess U.C. by physical and chemical characteristics, the specific gravity, refractive index and iodine number appeared most promising, though other features may also ultimately prove to be of value.

104. Twort. C. C. and Lyth, R. The Selection of Non-carcinogenic from Carcinogenic Oils. J. Hyg., 33, 464-73 (1933)

All the animal and vegetable oils tested by the authors on animals have proved to be incapable of inducing tumor formation during the life of their animals. On the other hand, oleic acid and linoleic acid, unsaturated fatty acids which may be present in commercial saponifiable oils, have frequently induced tumor formation; observations which in their opinion are of the highest importance in relation to many cancers other than those of the skin, and possibly even of those of the skin itself.

It has been found that the carcinogenic constituents of a given crude are not equally distributed in the various products of distillation obtained from this crude. The activity of the first products to come over in the still, the motor spirits, etc., is negligible, and that of the lamp oils, burning oils, light fuel, etc., is also of little account, but when we reach the boiling range of the lubricating oils a definite carcinogenic activity may become manifest. Among the latter the most active grades are, on the whole, the spindle grades, closely followed by oils of a Redwood viscosity of 500 to 1500 at 70° F., with a gradual decrease in activity as one approaches the internal combustion engine (motor car) grades. The crude oils themselves, as a rule, are somewhat less potent than the motor car oils, but of course, it will necessarily depend upon the amount of refining to which the latter have been subjected before being marketed.

105. Twort, C. C. and Twort, J. M. Carcinogenicity of Spindle Oils. Oil and Colour Trades J., 92, 1193-4 (1937)

A physical and an animal test for carcinogenicity and a physical and an animal test for dermaticity of mineral textile oils are described. The average results of these tests on 66 oils (excluding shale oils) collected 5-10 yrs. ago and on 66 oils collected recently are tabulated. (The animal test for carcinogenicity is not yet completed for the recent oils.) These results indicate that the original oils are definitely worse than the recent oils in both the dermatitis tests, while in the cancer physical test there is no significant difference. It is expected that the figures for the recent oils in the animal test of carcinogenicity will be lower than those of the original oils.

It is concluded, however, that little is being done to improve mule spindle oils from the biological standpoint. There are also indications that the average oil used in some of the cotton-spinning towns is more dangerous than that used in others.

106. Twort, C. C. and Twort, J. M. Notes on Some of the Procedures Adopted for Assessing the Biological Activity of Mineral Oils. Oil Colour Trades J., 94, 251-5 (1938)

Mineral oils may induce dermatitis or cancer of the skin. In dotg. the carcinogenic aspect 3 essential detns. are made: d., n and kinetic

viscosity (KV). The data collected are based on the utilization of formulas for assessing the biol. activity, especially from its carcinogenic aspect. In Formula A, R = (n-1)/d where R = sp. refractivity, n = refractive index and d = density. In Formula B, R = n-(d/2). Formula A is used in obtaining the cancer refractivity CR from Formula C which is CR = R+ 3(d-0.900)/20. In Formula D the refined cancer refractivity RCR = CR - (KV/50). Results, where those mineral oils have been employed, are shown in tables in which mineral oils are grouped according to toxicity and according to the n drop. The significance of d. in relation to the n drop among oils of similar toxicity and the significance of viscosity in relation to the n drop among oils of apparently similar toxicity are shown. The real difficulty in arriving at the true biol. activity with greater accuracy is the lack of uniformity of the inert fully hydrogenated constituents. There is quite good correlation between carcinogenicity, refractivity, n drop and toxicity.

107. Twort, J. M. and Lyth, R. The Concentration of Carcinogenic Materials in Mineral Oils by Distillation Processes. J. Hyg. 39, 161-9 (1939)

Twelve acid-treated lubricating cuts of a crude, Borneo mineral oil, were tested for carcinogenic activity. The whole range was biologically active, which activity had been foreseen from an examination of the physical characteristics. The peak activity was around a viscosity of 200-250 Centipoises at 25° C. Molecular distillation gave a greater concentration of the carcinogenic material than ordinary distillation at from 3-10 mm. In confirmation of previous findings, the middle fractions of a Borneo crude oil were mostly responsible for pathological changes in the organs—fatty infiltration of the liver and hyaline degeneration of the spleen. Lung tumors were more prevalent than is usual when this type of agent is used for testing carcinogenity for the skin. Their incidence was rather higher in the more viscous fractions: this incidence was apparently not correlated with carcinogenity for the skin.

108. Twort, J. M. and Lyth, R. Skin Cancer due to Handling Coal Tars Used for Preservation of Fishing Nets. Nature, 144, 446 (1939)

Several fishermen contracted cancer of the skin after handling the tars. Mouse expts. showed that different coal tars differed in their carcinogenic activity, although all produced some cancers. Creosote oil and anthracene oil were also carcinogenic. Only coal tar made in vertical low-temp. retorts should be used on nets.

109. Twort, C. C. Mule-Spinners' Cancer: The Need for Using the Correct Oils. Oil-colour Trades J., 8.29.41, 326

The cancer-producing powers of mineral oils used in the cotton industry from different fields of origin, in the crude and refined states, were thoroughly examined and the resul ts showed that there is a danger of any one producing cancer of the skin if applied long enough but the oils from certain fields are the more likely to do so. Special attention was paid to the examination of the physical characteristics of various mineral oils, and it was proved that a knowledge of their refractive index and viscosity provides a more reliable estimate of their cancer-producing powers than the application of the sample to the skin. This test is accurate, rapid and inexpensive, while that with the skin is variable, lengthy and costly.

The chief line of investigation has been a continuation of the work on the molecular distillation of mineral oils with the object of isolating the substances responsible for their carcinogenic activities. Animal experiments with fractional distillates from a Venezuelan oil are in progress. Fractions obtained by molecular distillation of a carcinogenic shale oil have been subjected to chromatographic absorption and two apparently pure hydrocarbons have been isolated in small quantity; these are being investigated chemically. Painting experiments with fractions obtained by this method have shown that many of them are highly toxic for mice. None of the substances so far tested has been shown to possess a high carcinogenic activity.

A few spindle grade oils and three oils intended as vehicles for insecticides have been tested for carcinogenicity.

A colloidal material intended as a protective against carcinogenic oils has been tested. There are indications that it has some protective action.

The carcinogenic activity of two products formed during the purification of carbonisation has been tested, and found to be less than that of the average gas tar.

110. Ullmann, K., Oppenheim, M. and Rille, J. H. J. Ind. Hygiene, 8, 288, 364 (1926)

The lesions caused by crude petroleum are the same as those caused by crude coal tar, showing the analogous substances must be present in both. The final products of distillation are the most active, especially paraffin oil. The carcinogenic agent is present in fractions from 200° C. to 450° C., but it is not certain that the same substance causes both dermatitis and epitheliona.

111. Valade, P. Cancer of the Human Lung from Dust from Tarred Roads. Presse Med., 2.1.39, 161

112. Van Themische, M. E. Chemical Cancer. Ing. Chim., 20, 30-5 (1936)

More than twice as many cases of cancer due to soot were found among sweepers than among any other occupation. Personal cleanliness and clothing that fits tightly around the extremities and around the neck are the best preventives. Similar care will do much toward preventing cancer due to exposure to gasoline and its derivatives, paraffins, oils, and greases. Such precautions are even more necessary in cases exposed to tar, pitch, rosin or aniline dyes. Strict medical supervision and the use of processes which avoid contact of the workers with the product will further reduce the danger.

113. Wampler, F. J. Occupational Diseases of the Skin (by L. Schwarz). "Industrial Medicine", 1943, 327-9

Chimney sweeps' cancer has been reported in England more frequently than in any other country. It is said that the incidence of cancer among chimney sweeps is eight times more common than among the general population. Cancer of the scrotum of chimney sweeps, however, is on the decline in England and it is reported as being practically non-existent in other countries, except for an isolated case or two in Germany. The local irritation and rubbing in of the soot as the sweep is cramped in descending the chimney is said to be the cause.

Tar is used in building roads, in making roofing paper and felt. Pitch is used for making conduits, lacquers, insulating material, greases, and mineral cements, and workers at these occupations are affected with comedones, tumors, warts, keratoses, and epithelioma, mostly of the scrotum, lip, face and hands.

No cases of mule spinners' cancer have been reported from France, Germany, Russia, or Poland. The author made examinations of thousands of mule spinners employed in the United States and did not find any cases of scrotal cancer, although there were many cases of folliculitis and keratoses of the thighs caused by oil-soaked trousers.

114. Wariek, H. Melanoderma and Keratoses from the Action of Asphalt. Arztl. Sachverst. Ztg., 66, 49 (1940).
In the preparation of cork plates (heat-insulation plates of asphalt and cork) much dust develops under very unfavorable working conditions. Two workers, who had been working for three months, suffered from pigmentation, inflammatory changes and hyperkeratoses of the face, forearms and hands. The hyperplastic processes were intensified in the older workers. The symptoms were aggravated by light. The intensive action of asphalt dust is considered to be the cause.

115. Watson. A. F. Tar Cancer in Mice, III, An Apparatus for the Preparation under Standard Conditions of a Highly Potent Carcinogenic Agent of Low Toxicity. Brit. Jour. Exper. Path., 12, 441-7 (1931)
With an ada ptation of the apparatus of Hague and Wheeler the author has succeeded in making from purified turpentine, at 850° C. a relatively non-toxic tar which elicited tumors after 210 days in 90% of the survivors from a group of 37 mice; most of these growths were malignant.

116. Welwart. Cancer from Paraffin Wax and Mineral Oils. Seifens. Ztg., 62, 792-3 (1935)
Most chemists and dermatologists believe that workers in paraffin factories got cancer from the paraffin itself while Scherber and Teutschlaender claim that cancer does not come from paraffin but from mineral oils.

117. Windaus, A. and Rennhak, S. Some Derivatives of 3,4-Benzopyrene. Z. Physiol. Chem. 249, 256-66 (1937)
By analogy to x-rays("x-rays produce and x-rays cure cancer") carcinogenic hydrocarbons should be tested for possible therapeutic values. Suggestive results have been obtained with 3,4-benzopyrne (I).

118. Wood, F. C. The Non-Carcinogenic Nature of Purified Mineral Oils. J. Am. Med. Assn., 94, 1641 (1930)
The general clinical evidence that there exists no relation between the therapeutic use of refined petroleum products and the occurrence of cancer is confirmed by experimental studies.

119. Wood, H. B. Paraffin Not Productive of Cancer. J. Cancer Res., 13, 97-102 (1929)

120. Wood H. B. Skin Lesions Among Tar Workers. J. Cancer Res., 13, 54-9 (1929)
Different types and composition of tars are discussed. Only tar obtained from the distn. of coal at high temps. contains a substance

carcinogenic to certain lab. animals. Workmen handling coal tar showed tar warts as a result, but no other effect. No irritant action on the human skin was found from low temp. distillate tar or from petroleum tar.

121. Woodhouse, D. L. Carcinogenicity of Synthetic Lubricating Oils. J. Inst. Pet. Tech., 20, 1057-63 (1934)

122. Yamagiwa and Ichikawa. Experimental Study of the Pathogenesis of Carcinoma. J. Cancer Res., III, 1-21 (1918)
In 1915 produced cancer by the experimental application of tar to the ear of a laboratory animal.

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A CONTRIBUTION OF INFORMATION TO MEMBERS OF THE A.P.I. MEDICAL ADVISORY COMMITTEE

SHELL OIL COMPANY, INCORPORATED

WOOD RIVER RESEARCH LABORATORIES

REPORT NO. M-1247

JULY 2, 1945

SUBJECT: CARCINOGENIC HYDROCARBONS AND RELATED COMPOUNDS

A LITERATURE REVIEW

AUTHOR: H. H. ZUIDEMA

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Industrial cancer was first recognized in England in the latter part of the eighteenth century, when it was established that chimney sweeps were particularly liable to cancer of the scrotum.[10] This was caused by soot. Progress in this field of study was very slow at first, and it was not until 1915 that two Japanese investigators announced the first case of carcinoma in an experimental animal. They produced first papillomas and then true cancer of the epidermis on the ears of rabbits by painting with tar over long periods of time.[35] During the thirty years that have elapsed since that discovery, a great deal of work has been done with various coal tar and petroleum fractions and pure compounds either occurring in these fractions or prepared synthetically. Numerous species of test animals, including mice, rats, fowl, rabbits, and dogs have been used, and many methods of application, including oral administration, intramuscular, intravenous, and subcutaneous injection, and painting on the skin. The method that appears to be the most widely used at present consists of painting a solution on the skin of a special inbred strain of mice. Mice are preferred over animals having longer life-spans since they respond more rapidly. The special strains are used to increase the precision of the test. Painting is preferred to other methods of application because there is less likelihood of interference by simultaneous spontaneous carcinomata. The carcinogenicity of a given compound is influenced by many factors including the genetic constitution of the animal species and strain, its age and sex, the diet, the physical condition of the animal, the purity of the compound, the dose, the physical state of the compound, the solvent used, and the route or site of application.[25]

While carcinogenic properties are generally associated with certain polynuclear aromatics and their derivatives, there are many substances entirely unrelated to these compounds which have been reported as having similar cancer-producing ability. Among these may be mentioned asbestos[34,37], inorganic compounds of arsenic and of zinc[25], aqueous potassium hydroxide and aqueous hydrochloric acid[25], ethyl alcohol[25], glucose[25], fructose[25], and a number of nitrogen compounds, most of which contain one or more benzene rings[25]. Radioactive elements and compounds are not included in this discussion since the mechanism of their producing cancer is probably quite different, i.e., physical rather than chemical. Materials which have been reported

as carcinogenic and whose carcinogenicity is probably due to the presence of polynuclear aromatics include coal tar and pitch[26,27] blue shale oil[5], mineral oils and asphalt[4], tobacco tar[39], tars obtained in the destructive distillation of tea[42] and coffee[40], diesel fuel[52], distillates from Borneo crude petroleum[54], combustion gases from fuel oil[41], the SO_2 extract from a spindle oil produced from a paraffinic crude petroleum[54], the products obtained by heating acetylene, isoprene, yeast, a non-carcinogenic petroleum fraction, or human skin to 700 - 900°C[30], and the products obtained by treating acetylene, xylene, naphthalene, or tetrahydronaphthalene with aluminum chloride[31]. The carcinogenicity of tars produced by heating various substances tends to increase with increasing temperature.[30,45] It is probable that the carcinogenic hydrocarbons present in certain coal tar and petroleum fractions were to a large extent formed during the process steps and were not present in the coal or crude petroleum from which they were derived. However, the carcinogenicity of a given fraction depends upon the source as well as the method of processing. According to the Manchester Committee on Cancer[49], the following order of increasing carcinogenicity prevails: Russian, Pennsylvania, Texas, Mid-Continent, Mexican, California, Persia, Romanian, Borneo, Venezuela, and shale. This corresponds roughly to the order of increasing aromaticity.

A large number of compounds have been tested for carcinogenicity. Hartwell has published a survey[25] which includes 696 compounds tested. Of these, 146 were carcinogenic, and 23 additional ones produced papillomas but no true cancers. While some of these compounds have been tested under only one or two sets of conditions, others have been studied very extensively. The three compounds that have received the most detailed study are the three derivatives of 1,2-benzanthracene: 1,2,5,6-dibenzanthacene, 3,4-benzpyrene, and 20-methylcholanthrene. All three are potent carcinogens. It has been estimated that they have been investigated in 60 different laboratories.[20]

A list of most of the known carcinogenic compounds is given in Table 1, pages 5-10. Structures, complete with numbering systems, are included, since lack of uniformity among various investigators in this field has led to some confusion. There is fortunately less deviation in the current papers than in the case of those written ten to fifteen years ago. The numbering used in this report corresponds to that used by Hartwell[25]. It should be understood that the carcinogenicity of the compounds shown in Table 1 varies considerably in degree and that the results have been verified by several laboratories in some cases while in others the results of only one or two experiments are available. The reader is referred to Hartwell for more detailed information and for reference to the original experiments. It will be observed that most of the compounds are either hydrocarbons or their derivatives containing at least three benzene rings or nitrogen compounds containing at least two benzene rings. More specifically, the first of these classes consists, with only three exceptions, of derivatives

of phenanthrene. The exceptions are tetraphenylmethane, triphenylbenzene. and triphenylethylene. In Table 1 the hydrocarbons are subclassified further as derivatives of 1,2-benzanthracene, 3,4-benzpyrene, cholanthrene, and other derivatives of phenanthrene. Examination of the structures shows that all of these are derivatives of phenanthrene.

While the work that has been done on the production of cancer by exposure to various compounds has made it possible to draw certain conclusions regarding the effect of chemical structure, it is not as yet possible to predict with any degree of certainty the carcinogenicity of a given compound from its structure. A phenanthrene derivative may or may not, for example, be carcinogenic depending upon such factors as the length of an alkyl side chain, the position of a benzene ring, or the position of an alkyl group. However, a paraffinic or naphthenic hydrocarbon or one containing only one or two benzene rings may with a reasonable degree of confidence be assumed to be non-carcinogenic.

The amount of compound required to produce an experimental cancer on a test animal is surprisingly small. Doses of 1,2,5,6-dibenzanthracene and 3,4-benzpyrene as small as 2.5 and 4 micrograms, respectively, give positive results when applied to mice.[1,2,3] Discontinuous application, e.g., once a week, of a given total quantity of material is more effective than continuous exposure.[15] A single application of 20-methylcholanthrene in 0.6% benzene solution is capable of producing cancer on the skin of mice.[45] When different carcinogenic hydrocarbons, e.g., methylcholanthrene, benzpyrene, and dibenzanthracene, are applied successively the effect is additive[33]. The investigators who made this observation offer the hypothesis that carcinogenisis is essentially an accumulation of abnormal protein within the cell.

Since so many compounds have been tested for carcinogenicity it is only natural that several attempts have been made to correlate this property with other properties, either physical or chemical. Such a correlation would be extremely useful in that the determination of the physical or chemical property would be much simpler than the rather long and tedious process of exposing experimental animals to the substance in question. Fluorescence spectra have received more study in this regard than any other property[5,7,28,32]. The author of a recent paper made the statement that all known carcinogenic chemicals are fluorescent.[43] However, it is obvious from a glance at Table 1 or Hartwell's tabulation that this is too broad a claim. However, many investigators have used fluorescence spectra to good advantage in this field, and there appears to be a definite correlation with carcinogenicity, at least with certain types of compounds. The correlation may be due in part to the fact that fluorescence spectra have been used as a guide in selecting fractions from coal tar for physiological tests; it is conceivable that other carcinogenic compounds, which are not fluorescent, exist or could be synthesized.

A rough parallelism between the carcinogenicity of polynuclear aromatics and the diazo coupling reaction has been observed.[21,22] Attempts have also been made to correlate refractive index, or more specifically, specific refraction, with the carcinogenicity of oils.

The Manchester Committee on Cancer[19] recommended that spindle oils of various ranges of specific gravity have specific refraction values below certain limits to assure the absence of carcinogenic properties. However, it is obvious that there can be no general correlation between a physical property of this nature and carcinogenicity, for slight changes in structure, such as the position of a methyl group, which would have little effect upon optical properties, affect carcinogenic properties profoundly; furthermore the presence of a large concentration of a non-carcinogenic aromatic would raise the specific refraction of a mixture much more than would the presence of a small amount of a potent carcinogen.

The probability of obtaining a general correlation between carcinogenicity and some more easily determined property would be greatly enhanced if there were a clearer understanding of the mechanism of the action of carcinogenic compounds. It is, of course, very difficult to obtain such an understanding, for so little is known about cancer itself.

Whether or not carcinogenisis by hydrocarbons and related compounds is in any way connected with spontaneous cancer is a question that has received much conjecture. That such a relationship does exist is suggested by the fact that certain derivatives of estradiol (see Table 1) which is closely related to the sex hormone estrone, are carcinogenic. Spontaneous cancer quite often occurs in the reproductive organs. Furthermore, the very potent carcinogen, 20-methylcholanthrene, can be produced by the degradation of desoxychclic acid, cholic acid, or cholesterol, the first two of which are normal constituents of human bile and the last of which is present in all tissues of the human body.[22] These degradation reactions were, however, conducted under drastic conditions which are in no manner related to those prevailing physiologically, and there is no evidence that 20-methylcholanthrene is formed in the body through the degradation of bile acids or cholesterol. The possible connection between cancer produced spontaneously and carcinogenisis by methylcholanthrene or related compounds therefore remains a matter of conjecture, at least for the present.

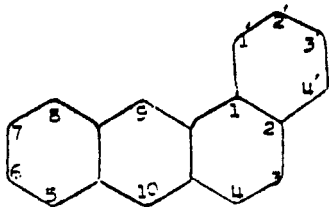
There has, for obvious reasons, been little attempt to induce cancer in human beings through exposure to the various compounds that are carcinogenic to mice. There is, therefore, no direct correlation between the susceptibility of man and the test animals. There is, of course, an indirect correlation of occupational cancer largely through exposure to coal tar and dye intermediates caused by materials which are carcinogenic to mice. However, many of the compounds shown in Table 1 do not occur in any products known to have caused occupational cancers, and it is conceivable that some compounds harmful to mice are innocous to man. Until that can be proved, the only safe policy is to regard all compounds which are harmful to mice as dangerous and to avoid exposure by humans.

HEZ:VAC

TABLE 1

CARCINOGENIC COMPOUNDS

All compounds listed by Hartwell[25] unless otherwise indicated.

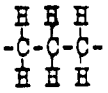
1. Derivatives of  1,2-benzanthracene

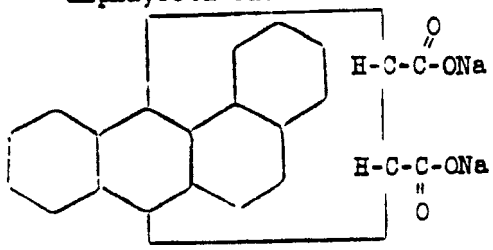
The following derivatives of 1,2-benzanthracene:

3-methyl
5-methyl
6-methyl
9-methyl
5-ethyl
10-ethyl
5-n-propyl
5-n-butyl[2]
5-n-amyl[2]
5-n-hexyl[2]
6-i-propyl
3-hydroxy
10-hydroxy
10-aldehyde, $-\overset{H}{\underset{|}{C}}=O$
10-methyleneacetoxy, $-\overset{H}{\underset{H}{\overset{|}{C}}}-O-\overset{O}{\overset{\|}{C}}-CH_3$
10-methylenecarbomethoxy, $-\overset{H}{\underset{H}{\overset{|}{C}}}-\overset{O}{\overset{\|}{C}}-O-CH_3$
10-cyanomethyl, $-\overset{H}{\underset{H}{\overset{|}{C}}}-CN$
3-methoxy
10-methoxy
4,9-dimethyl
4,10-dimethyl
5,6-dimethyl
5,9-dimethyl
5,10-dimethyl
6,7-dimethyl
9,10-dimethyl
6,7-dimethyl
9,10-dimethyl
5-chloro, 10-methyl
7-chloro, 10-methyl
5-cyano, 10-methyl
7-cyano, 10-methyl
1,2,7,8-dibenzanthracene[31]
1,2,5,6-dibenzanthracene

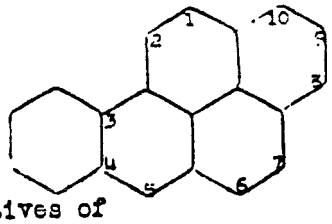
The following derivatives of 1,2,5,6-dibenzanthracene:

9-methoxy
2′-methyl
3′-methyl
4-methyl
9-methyl
1′,9-methylene
4,10-dimethylene, 
3,4′-dimethylene (phenanthra-acenaphthene)
8,9-dimethylene

5,6-cyclopenteno 
6,7-cyclopenteno
1′,2′,3′,4′-tetrahydro
Na salt of 9,10-endo alpha,beta succinic acid:



2. Derivatives of 3,4-benzpyrene



3,4-benzpyrene

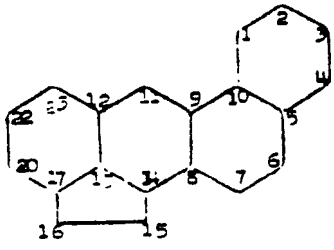
The following derivatives of 3,4-benzpyrene:

5-aldehyde
4′-methyl
5-methyl
1′,2′-dihydro, 4′-methyl

1′,2′,3′,4′-tetrahydro
10-acetyl

3,4,8,9-dibenzpyrene
5,10-dihydro-3,4,8,9-dibenzpyrene
7-methyl,1,2,3,4-dibenzpyrene

3. Derivatives of Cholanthracene



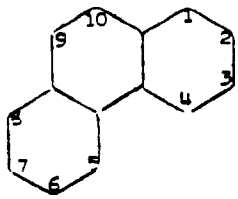
Cholanthrene

The following derivatives of cholanthrene:

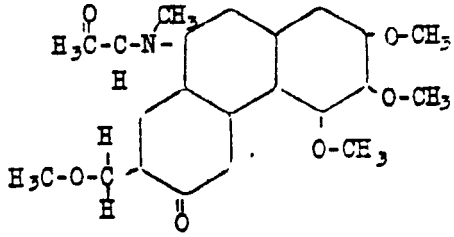
20-methyl
20-ethyl
20-isopropyl
20-tert-butyl

15,20-dimethyl
16,20-dimethyl
15-hydroxy, 20-methyl
15-keto, 20-methyl

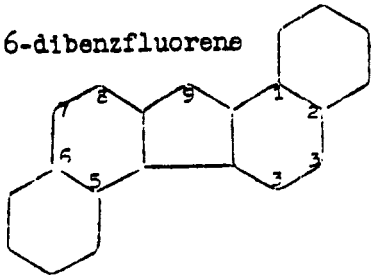
4. Other Derivatives of Phenanthrene



Colchicine



3,4-benzphenanthrene

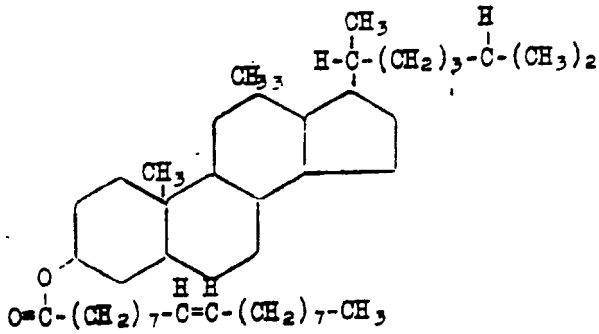


1,2,5,6-dibenzfluorene

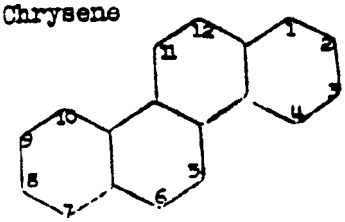
The following derivatives of 3,4-benzphenanthrene

1-methyl[2]
2-methyl[2]
2-ethyl[2]
2-isopropyl[2]
7-methyl[2]
8-methyl[2]
2,9-diethyl
2-methyl, 1,2,3,4-dibenzphenanthene

Cholesterol oleate

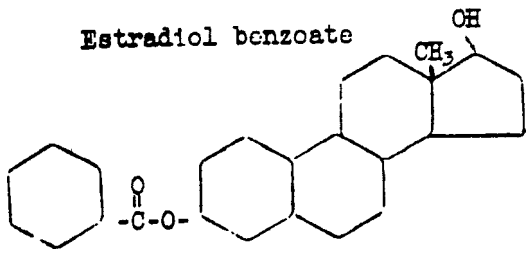


Chrysene

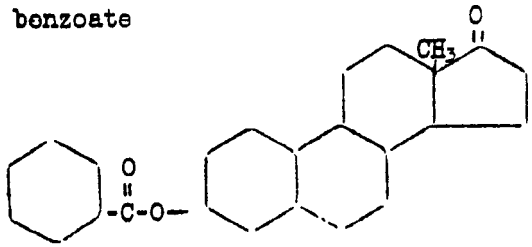


1,2-dimethyl chrysene[2]
5-methyl chrysene[17]
4,5-methylene chrysene[17]
5,6-dimethyl chrysene[17]

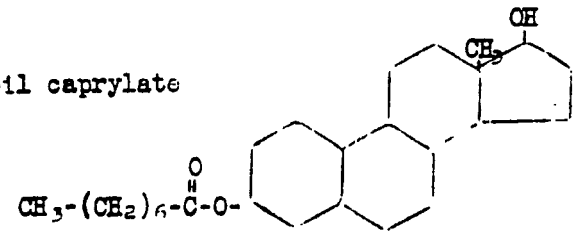
Estradiol benzoate



Equilenin benzoate

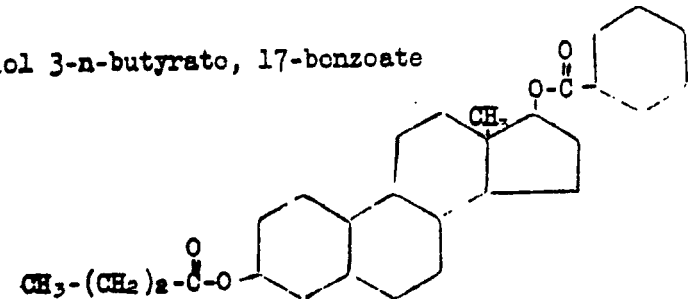


Estradoil caprylate



1,2-cyclopentene phenanthrene[2]

Estradiol 3-n-butyrate, 17-benzoate

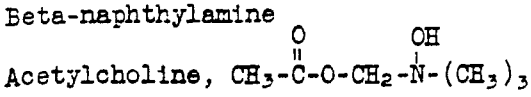


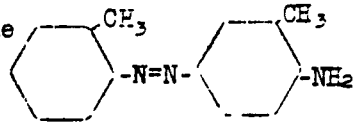
5. Other Aromatic Compounds

Tetraphenylmethane
1,3,5-triphenylbenzene
Triphenylethylene[33]

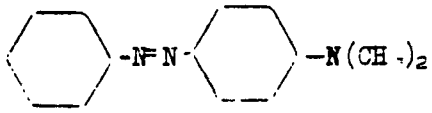
6. Organic Compounds Containing Nitrogen

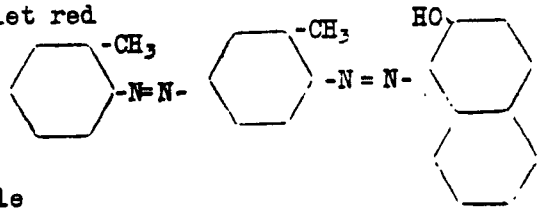
2-amino, 1-naphthol
Alpha naphthylamine[13]
Beta-naphthylamine

Acetylcholine, 

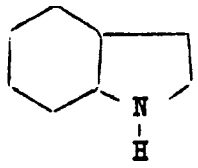
o-amino azotoluene 

p-dimethyl aminoazobenzene (butter yellow)

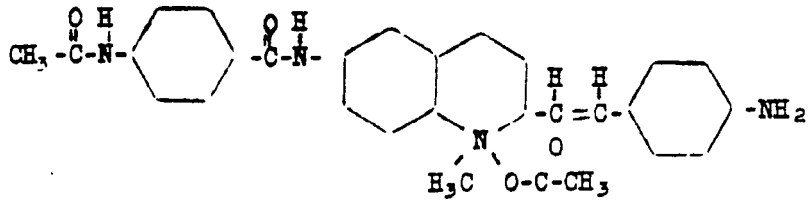


Scarlet red 

Indole

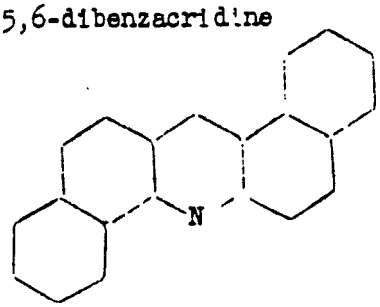


Syyryl 430

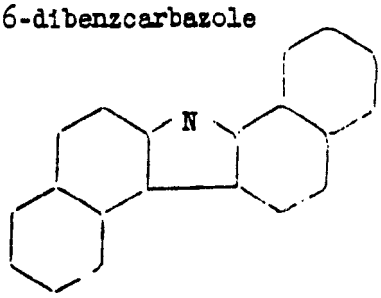


Benzidine[13]

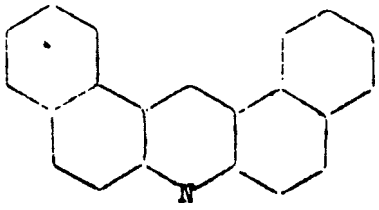
1,2,5,6-dibenzacridine



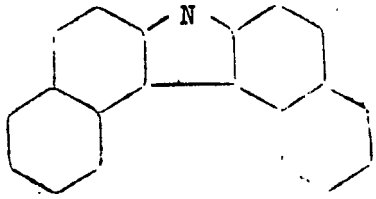
1,2 5,6-dibenzcarbazole



1,2,7,8-dibenzacridine



3,4,5,6-dibenzcarbazole



7. Miscellaneous

Arsenic trioxide
Potassium arsenite
Aqueous hydrochloric acid
Aqueous potassium hydroxide
Zinc chloride
Zinc sulfate
Ethyl alcohol
Fructose
Glucose
Galactose

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For those wishing to acquire a more extensive background in this field, a review by Fieser[20] is recommended as a good starting point, followed by the original papers by Cook and co-workers. For a detailed tabulation of carcinogenic compounds Hartwell's book[25] should be consulted.