Carcinogens in the Human Environment*

W. C. HUEPER, M.D.
BETHESDA, MD.

III. Sources of Potential Environmental Cancer Hazards to the General Population

Many of the cancer hazards affecting the general population may have their origin in one or several industrially produced consumer goods or environmental industrial pollutants. The irregular and variable epidemiologic scatter pattern of cancers of different types among members of different population groups and in various geographic regions is at least in part a reflection of the influence of significant local fluctuations in the qualitative and quantitative composition of the environmental carcinogenic spectrum upon the cancer panorama. Among the consumer goods which may be involved in this respect, the following groups deserve critical analysis for the presence of carcinogenic agents (Table 7).

* This article is continued from page 269 of the last issue.

The abundant opportunities for intense and prolonged contact of the general population in many parts of the world with actually or potentially carcinogenic agents of diverse nature are not restricted to the increasingly widespread use of consumer goods but, recently, assume considerable proportions through the introduction of related occupational cancer hazards into the home through various hobbies, particularly those connected with the do-it-yourself movement (Hueper). The adherence to suitable and adequate precautionary measures which might provide protection against hazardous liquids, as well as gases, vapors, fogs, mists, sprays, fumes, and dusts generated during such activities is often totally lacking, especially if contact with such agents does not elicit immediate and serious discomfort. The possible cancer hazards to

TABLE 7.—*Environmental Pollutants and Consumer Goods as Potential Sources of Environmental Cancer Hazards*

I. Dietary agents such as:
  (a) food additives and contaminants including industrially polluted drinking water, packaging materials, and chemicals
  (b) naturally present ingredients and pollutants (alkaloids, arsenicals, selenium, radioactive substances)
  (c) chemicals generated during certain processing procedures (heat, radiation) of foodstuffs and during the preparation of foods from natural and artificial ingredients of foodstuffs (roasting, smoking, prolonged and repeated heating, grilling over an open fire, etc.)
  (d) dietary deficiencies and imbalances interfering and damaging organic function and the operation of normal metabolic defense mechanisms (vitamin B complex deficiencies, iron deficiency, protein deficiency, iodine deficiency, etc.)

II. Household goods, such as sanitary goods, over-the-counter drugs, home remedies, economic poisons, pesticides, cleaning agents, polishes, antirusting agents, paints and paint removers, detergents, solvents, dry cleaning agents, dyes, herbicides, contraceptives, cosmetics, etc.

III. Domestic and general air pollutants, such as aromatic and aliphatic hydrocarbons formed from the incomplete combustion of carbonaceous fuels, gasoline, diesel oil and coal (automobile exhaust, dust from tarred and asphalted roads, soot), chromate aerosols from air conditioning equipment and steam heating plants, pesticide sprays (mists and fogs) generated from domestic use of bombs or delivered from airplanes, radioactive substances of local or general atmospheric pollution, industrial and domestic effluents. Water pollutants from radioactive fallout, soot, automobile exhaust, industrial effluents, runoff from tarred and oil roads, from fields treated with pesticides and herbicides, detergents from industrial and domestic sources in sewage, water weed killers and water evaporation preventives.

IV. Occupational agents of chemical and physical types.

V. Habits and customs of certain kinds, such as tobacco smoking and chewing, sun bathing, chewing of quids, paraffin, gums, tar, etc., eating of arsenicals, use of special personalized heating devices (kangri, kairo), use of ultraviolet lamps.

VI. Medicinal chemical agents and chemicals and apparatus emitting ionizing radiation and ultraviolet radiation

VII. Infectious animate agents, such as Schistosoma haematobium, viruses, etc.

urban populations created by the inhalation of various carcinogenic industrial effluents and of carcinogenic hydrocarbons containing exhaust fumes from automobiles, trucks, and buses have properly been appreciated in only recent years. Such hazards, however, extend to farmers and gardeners not infrequently working in clouds of exhaust fumes given off from their gasoline- and diesel-engine-powered motorized equipment. It is also not rare that paints, pesticides, and herbicides are dusted, sprayed, or nebulized, respectively, without use of any type of mask or respirator to prevent or reduce the inhalation of the active ingredients of these preparations as well as of the various solvents and vehicles in which they are dissolved or suspended. It should be obvious from these considerations that the problem of actual and potential health hazards including cancer hazards from consumer goods presents various facts, most of which have attracted little or no attention in the past. Cancers resulting from such exposures, like the many others attributable to environmental carcinogens, therefore, have been included among the diffuse mass of cancers of so-called "spontaneous" origin, i.e., of cancers of unknown etiology.

Although the degree of exposure to many of the carcinogenic components of consumer goods is of relatively low order as represented by the dose and potency of the carcinogens involved, it is important that contact with many of them is usually very frequent and for some of them starts with birth and may last almost uninterruptedly for 24 hours a day until death. Carcinogenic air and water pollutants are most prominent in this respect. Serious consideration concerning the degree of exposure to environmental carcinogens must, moreover, be given to the fact that the general population often has contact with many f these agents for several reasons, i.e., th same carcinogen, such as arsenic, may be present in the atmosphere as an air pollutant, in the drinking water as a water contaminant, in foodstuffs as a pesticide residue, in medicines, cosmetics, wood preservatives, herbicides and insecticides as an active ingredient, and in paints and inks as a pigment or coloring matter. A corresponding situation arises whenever exposure conditions exist entailing contact with several different carcinogens which are syncarcinogens, i.e., there is a summation of the carcinogenic effects exerted by the individual agents, or there may occur occasionally even an accentuation of the added individual carcinogenic effects above this level. Such correlations can be expected to exist for hepatotoxic chlorinated hydro-

TABLE 8.—*Food Additives and Contaminants*

A. Food Additives
1. Natural and synthetic dyes
2. Antioxidants of fats and lipoids and vegetable matter
(a) destroyers of peroxides formed during auto-oxidation
(b) oxygen acceptors
(c) hydrogen donators
3. Natural and synthetic mucilages, thickeners, and gelatinous materials
4. Synthetic sweeteners
5. Synthetic flavoring agents
6. Surfactants (detergents, foaming agents)
7. Humectants
8. Preservatives and chemical sterilizing agents
9. Water conditioners (iodine, fluorides)
10. Antifoaming agents
11. Salt substitutes
12. Shortenings
13. Antistaling agents and softeners
14. Bleaches
15. Food modifiers and improvers (meat tenderizers, etc.)
16. Oil and fat substitutes and glazes and polishes of candy derived from petroleum
17. Organic solvents used as vehicles of some additives
18. Hydrogenated oils and fats (containing saturated, instead of the biologically important unsaturated, fatty acids and, possibly nickel as a contaminant).
19. Hygroscopic and antihygroscopic agents
20. Emulsifiers and solidifiers
21. Chelating agents

B. Food Contaminants
1. Pesticide Residues
(a) bactericides
insecticides — miticides
rodenticides
(c) molluscicides
(e) fungicides
(f) herbicides
(g) nematocides
(h) defoliants
2. Antisprouting and antimaturition agent of fruits and vegetables
3. Insect repellents
4. Hormonal fattening agents-estrogens
5. Antibiotics (fed to food animals and added to foodstuffs)
6. Antienzymatics
7. Enzymes
8. Pan-greases (silicones)
9. Pan-greases (mineral oils)
10. Water pollutants: coal tars and oils, petroleum tars, asphalts, oils, refinery and coke oven effluents, chromates, radioactive substances, arsenicals, etc.
11. Chemical sterilizing agents
12. Wrapping and coating materials (paraffin, waxes, resins, plastics)
13. Soot adherent to smoked foodstuffs and roasted and toasted products
14. Household detergents and their coloring agents (stilbene derivatives)
15. Non-ionizing radiation (ultraviolet) products
16. Ionizing radiation (radioactive) products and radiochemicals produced from natural and added chemicals in foodstuffs exposed to ionizing radiation
17. Radioactive substances taken up by plants and food animals from contaminated soil or water or adhering to them in the form of radioactive fall-out.
18. Water evaporation retardants

carbons, which are extensively used as solvents, paint removers, degreasing agents, aning fluids, anesthetics, and more recently particularly as pesticides and herbicides and found for this reason as residues in many foodstuffs. The existence of such relationships between exposures to carcinogens displaying additive effects must properly be appreciated whenever it should become necessary to establish a maximal permissible dose of a particular agent in specified types of products, if the same or similarly acting agents are present in many other products to which persons become exposed for occupational or other environmental reasons.

1. *Food Additives and Contaminants.*— The potential magnitude of the needed environmental carcinogenic sanitation program can be envisioned by establishing the scope of one segment of this problem related to food additives and contaminants only. The following groups of chemicals deserve consideration in such an undertaking (Table 8).

The extent to which foodstuffs contain additives and contaminants is evident from the facts that there is a list compiled by American (Food and Drug Administration; Food Protection Committee) and English investigators of some 800-1,000 food additives and that many foods daily consumed by the general public are contaminated with feed additives (estrogens, arsenicals) and pesticide residues of some type, such as arsenicals or chlorinated hydrocarbons (DDT, etc.). Only very fragmentary information is available as to the potential carcinogenic properties of a considerable number of these agents (Hueper).

The following tables and discussions briefly summarize the evidence available on established and potential human carcinogens used as food additives or present in foodstuffs as contaminants or generated in them by processing procedures in the United States (U.S.) and/or other countries (O.C.)

I. Intentional Food Additives: A. Food and cosmetic dyes. There exists some human, and a great deal of experimental evidence concerning the carcinogenicity of an appreciable number of synthetic dyes (Hecht; Symposium) (Table 9) formerly

TABLE 9.—*Recognized or Suspected Carcinogenic Food Dyes*

A. Human Carcinogens

Dye	Evidence Met	Target Organ	Animal	Route	Target Organ	Investigator
Auramine O (O.C.)	Occupat.	Bladder				Case
Magenta, Fuchsin (O.C.)	Occupat.	Bladder	Rat	Oral	Bladder (Papil)	Yoshida, et al.

B. Potential Human Carcinogens

Dye	Evidence	Target Organ	Animal	Route	Investigator
Triphenylmethane Compounds:					
Light Green SF (U.S.)	Experiment	Subcut. tissue Connect.	Rat	Subcut. Tissue	Schiller Gross Harris Nelson & Hagan Heckt
Brilliant Blue FCF (U.S.)	Exper.	Subcut. tissue Connect.	Rat	Subcut. Tissue	Nelson & Hagan Gross
Fast Green FCF (U.S.)	Exper.	Subcut. tissue Connect.	Rat	Subcut. Tissue	Nelson & Hagan
Acurbine VX (O.C.)	Exper.	Hematopoietic tissue	Mouse	Oral Cutan.	Miller & Pybus
Guinea Green B ? (U.S.)	Exper.	Subcut. tissue Connect.	Rat	Subcut. Oral	Nelson & Hagan Williams & Ivy
Rhodamine B (O.C.)	Exper.	Subcut. tissue Connect.	Rat	Subcut.	Umeda
Rhodamine 6G (O.C.)	Exper.	Subcut. tissue Connect.	Rat	Subcut.	Umeda
Fluorescein Sodium (not used)	Exper.	Subcut. tissue Connect.	Rat	Subcut.	Umeda
Eosin (water sol.) (O.C.)	Exper.	Subcut. tissue Connect.	Rat	Subcut.	Umeda
2-Hydroxynaphthalene Compounds:					
Sudan I (O.C.)	Experiment	Liver	Mouse	Subcut.	Kirby & Peacock
Orange SS (O.C.)	Experiment	Connect. tissue intestine	Mouse	Subcut.	Boone ?
Oil Yellow HA (O.C.)	Experiment	Liver	Mouse	Oral	Kirby & Peacock
Sudan IV (O.C.)	Experiment	Liver	Rat Mouse	Oral	Williams & Ivy Schmidt Heckmann
Sudan Brown RR (not used)	Experiment	Liver stomach hematopoietic tissue	Rat	Oral	Heckmann
2-Aminonaphthalene Compounds:					
Yellow AB (U.S.)? (2-amino-1-naphthol release)	Experiment	Bladder	Dog	Oral	Kemper et al. Conway et al.
Yellow OB (U.S.) ?	Experiment	Bladder	Dog	Oral	
Thiazin Brown R		Subcut. tissue	Rat	Subcut.	Heckt
Black 3416 (O.C.)	Experiment	Subcut. tissue	Rat	Subcut.	Heckt
Azo-Benzol Compounds:					
Butter Yellow (O.C.)	Experiment	Liver Bladder	Rat Dog	Oral Oral	Kinosita Nelson & Woodard

and/or presently used as food dyes in various countries.

The evidence indicating that a few of the dyes used for coloring foodstuffs are human carcinogens under dietary conditions of exposure is at present still of circumstantial nature, i.e., it is derived from observations made among workers engaged in the production of such dyes (magenta, auramine [Case and Pearson]). The recently re-

orted observations of Radomski and Deichmann concerning the absence of β-aphthylamine in the stomach of rabbits ollowing an intragastric introduction of ellow AB are in this connection without ignificance, because only 60% of the dye dministered could be accounted for and he urine was not studied. Rabbits are nown to produce a metabolite from β-aphthylamine which apparently is non-arcinogenic (2-amino-6-naphthol) (Booth nd Manson; Hueper), while the canine nd human urinary metabolite (2-amino-1-aphthol) has such properties for the ladder. Similarly, potentially misleading in his respect are the negative observations of Allmark, Grice, and Lu, who used rats in heir long-term studies of oral feeding of ellow AB and OB, because also rats and ice are refractory to the carcinogenic ac-on of β-naphthylamine as well as of the dyes, yellow OB and AB (Badger, Cook, Hewett, Kennaway, Martin and Robinson; ugin—).

otential danger of a carcinogenic ffect from these 2 lipoid-soluble dyes, how-ver, is not entirely restricted to the possible roduction of 2-amino-1-naphthol following he liberation of β-naphthylamine from the ye by a metabolic splitting of its azo-nkage, which has been demonstrated for he chemically related dye, Orange I, under he influence of the bacterial intestinal flora n dogs yielding sulfanilic acid and α-aphthylamine (Sisley et al.). Recent ana-tic studies of the 2 yellow dyes by Conway and Lethco have shown that some of the β-naphthylamine used in the production of Yellow AB and Yellow OB remains unreacted and appears as an impurity in certified lots of these dyes (Table 10). That a frequent ingestion of these dyes with foodstuffs might represent an actual human cancer hazard is suspected by Williams on the basis of experiences made with exposures to β-naphthylamine among dye workers. Williams, moreover, noted also in support of this concept that minute amounts of β-naphthylamine present in coal tar and pitch from gas plants might account for the excessive incidence of bladder cancers prevailing among English gas workers (Henry, Kennaway and Kennaway). Mention must be made also of the carcinogenic properties possessed by some aminostilbene derivatives and of the fact that members of this general group of compounds are generally being used as whiteners or brighteners in household detergents.

It may be noted in this connection that the substitution of synthetic carotene in place of Yellow AB and Yellow OB also may carry a potential cancer hazard, if diphenylamine should be used as a stabilizer of this synthetic vegetable dye, because diphenylamine often is contaminated with 4-amino-diphenyl which is a highly potent carcinogen for the bladder of man and dogs and for the intestine of rats (Deichmann et al.; Walpole, Williams, and Roberts; Melick, Escue, Narvka, Mezera, and Wheeler).

TABLE 10.—*β-Naphthylamine Content of FD&C Certified Yellow AB* *

Manufacturer	Safety Certified Lot No. by FDA	Total Aromatic Amine Content Computed as β-Naphthylamine (by Color Test), PPM.	β-Naphthylamine Content (Chromatographic Method), PPM.
A	E7044	276	263
	G7275	188	165
B	H3604	1,080	600 †
C	H3609	198	187
D	W6328	203	175
E	H6589	104	Approx. 82

* W. Conway and B. Lethco. † Twice the permitted amount.

mediates (β-naphthylamine ? sulfate) allowed by Food and Drug regulations is 0.05%, or 500 ppm.

Apart from the fact that almost all of the food, drug, and cosmetic dyes used in this and other countries have not adequately and competently been studied for possible carcinogenic properties in experimental animals, no pertinent reliable and valid information has ever been published concerning such possibilities by surveying occupational groups and other specially exposed population groups (gasoline handlers, dye manufacturers, textile and paper dyers, colored-smoke producers) for carcinogenic effects from these agents when present in a considerably more impure state than that required for food dyes. Such investigations, however, are urgently needed because claims have been advanced, based on epidemiologically deficient evidence, that the use of butter yellow in Austria and in some oriental countries for coloring foodstuffs was responsible for an increased or excessive death rate from primary liver cancer among the populations consuming such foods (Zeitlhofer; Sta. Crug; Peller). Some of the dyes listed as well as a few others (toluidine blue, pontamine sky blue, pyridium, Evans blue, trypan blue, fluorescein, methylene blue, 10-tolidine) are employed for medical purposes (Holoubek, Hendrick and Hollis; Bickers; Weinberg et al.), or as insecticides (Phenothiazine, azobenzene) (DeEds, Wilson and Thomas) giving rise to allergic and photosensitizing reactions and/or cancerous reactions (Marshall; Gillman; Simpson; Brown and Thorson; Brown and Norlind; Allen et al.; Spitz et al.).

The evidence on hand indicates that (1) several food and cosmetic dyes are probably human carcinogens; (2) that others are potential carcinogens; (3) that many additional ones have not adequately been investigated, (4) that contact of members of the general population and of special worker groups with some of these and many related dyes exists for other reasons, and (5) that all dyes which may give rise to the formation of orthohydroxyamines should be suspected of possessing carcinogenic properties (Clayson; Walpole, Williams and Roberts; Badger).

B. Emulsifying agents and shortenings. An emulsifying agent prepared from a vegetable oil by the application of heat and oxygen, containing highly oxidized and highly polymerized aliphatic compounds, and used for the processing of vegetable and animal fats, was recently shown to produce sarcomas in rats at the site of subcutaneous introduction (Symposium). Distinct caution, therefore, is indicated in the future concerning the incorporation of highly oxidized and polymerized oils, such as those probably formed in deep-fat frying processes, into products of human consumption or in consumer goods providing prolonged and frequent cutaneous and respiratory exposures. Mention may be made in this connection of observations recently reported by Jardetzky et al., who obtained hepatomas in 40% of mice fed a commonly used shortening and in 65% f mice given orally a specific solvent fraction of this foodstuff.

In recent experiments with several emulsifiers Fitzhugh, Bourke, Nelson, and Frawley noted that one of them, namely polyoxyethylene (8) stearate, proposed for use in bread and rolls, produced when fed at a 25% level in the diet not only bladder stones in 25 out of 150 rats but in 13 of them also bladder tumors (9 papillomas and 4 carcinomas). Despite this evidence the Food Protection Committee of the Food and Nutrition Board declared this food additive as safe for human consumption (Publication 646) by arguing that the tumors were not caused directly by the chemical, but by a chronic irritative effect exerted by the stones, which were found in all animals with tumors. Although polyoxyethylene (8) stearate is converted by this allegation from a direct carcinogen into an indirect carcinogen, the fact remains, even if this scientifically unsound argument is adopted, that the oral consumption of this chemical is followed by a carcinogenic response in the bladder of some of the rats and thus must be considered as potentially dangerous and objectionable to man. The scientific validity of the argument that

chronic irritation of the bladder mucosa by the stones was the direct cause of cancerous reactions must, moreover, seriously be doubted, since neither observations on rats and mice nor on man support the view that bladder stones are involved in the causation of bladder cancer as a primary causal factor (Zeppa and Womack; Willis; Gruber; Podilchak; Angrist; Capurro and Moumgis; Dalton, Morris, and Dubnik). It may be pointed out, moreover, in this connection, that the Food and Drug Administration has prohibited at a former occasion the further use of diethylene glycol as a humectant in tobacco because this chemical when fed to rats produced benign and malignant tumors of the bladder in addition to bladder stones.

C. Synthetic mucilages, thickeners, and stabilizers. The recent demonstration of various cancerous responses in rats by the parenteral introduction of water-soluble, highly polymerized compounds, such as [redacted]yl pyrrolidone, carboxymethylcellulose and dextran (Hueper, Lusky, and Nelson), should provide an indication for an extensive and competent investigation into potential similar responses elicited by some of the chemically similar synthetic polyglucoses (methyl cellulose), polyvinyl compounds (polyvinyl alcohol), and polysilicones employed as substitutes for gelatine and cream in some foods and food preparations in this and other countries (Hueper). Since such products have no nutrient value, it would be wise to eliminate them for the time being from the list of permitted food additives (Eichholtz), if they should be found to have carcinogenic properties upon parenteral introduction into experimental animals.

D. Synthetic sweeteners. The sweetening agent Dulcin (*p*-phenetylurea), which for many years was commercially available, was recently found to elicit cirrhosis and tumors of the liver and bladder in rats given this chemical by mouth (Fitzhugh and Nelson, Lettré; Griepentrog), necessitating its withdrawal from the open market in the United [redacted]. Similar studies made on saccharin (2,3-dihydro-3-oxobenzo-sulfonazole) and various cyclamate compounds (calcium and solium cyclo-hexysulfamate) gave negative results.

E. Flavoring agents. No comprehensive information is available concerning potential carcinogenic properties of the approximately 300 flavoring agents employed. Lemon oil, however, has recently been reported to be a cocarcinogen (Roe). While as a rule, such chemicals are present in foodstuffs in very small amounts, this condition does not exclude the possibility of cancer hazards from such sources, since experimental investigations as well as experiences made with a few occupational carcinogens have established the fact that prolonged exposures to minute amounts of potent carcinogens may result after a long latent period in the development of cancers in exposed experimental animals and workers. The advisability of such investigations is indicated because of the demonstration of liver tumors in rats fed red pepper (Capsicum) (Hoch-Ligeti) and Senecio alkaloids which are used by South-Africans as home remedies (Schoental; Cook, Duffy, and Schoental) and which have given rise to chronic poisonings among the population of South Africa due to the consumption of bread contaminated with seeds of Senecio plants. Such cases of "bread poisoning" exhibited at necropsy degenerations and cirrhosis of the liver with ascites (Steyn). Similarly, ergot alkaloids which are contaminants of rye flour, and which are used medicinally, have not only caused poisonings in persons and groups of people resulting in vascular and gangrenous lesions of extremities, but when fed to rats, caused the development of neurofibromas of the ear (Fitzhugh, Nelson, and Calvery).

F. Surfactants. Surfactants are employed in foodstuffs as antifoaming agents, emulsifiers, and dispersants or may be introduced unintentionally into them as residues of detergents used for cleaning cooking utensils and dinnerware. In experiments on animals it has been shown that some chemicals of this type exert a cocarcinogenic or weakly carcinogenic effect on the action of known

polycyclic aromatic hydrocarbons given by mouth and facilitate the penetration of these agents through the mucosa of the alimentary tract and the skin (Setälä, Shubik; Saffioti and Shubik; Shubik and Sicé; Della Porta, et al.; Umeda; Setälä et al.; Eckardt; Horton et al.). Special attention in this respect should be given to the various polyoxyethylene sorbitan fatty acid compounds (Tweens) used as dispersants and emulsifiers (Lusky and Nelson). A definite amount of caution, therefore, should be exercised in the choice of such agents for the purposes mentioned and in the amounts which may be permitted in foodstuffs (candies, soft drinks, dill pickles, vitamin preparations, ice cream, cream whip, cakes, bread, rolls).

G. Humectants. Humectants are incorporated in marshmallows, pastilles, shredded coconut, confections, ice cream, chocolates, and jelly-like candies, as well as cigarette tobacco. Diethylene glycol, a humectant formerly used in tobacco, when fed to rats over many months, elicited the formation of stones, fibropapillomas, and one carcinoma of the bladder (Nelson, Fitzhugh, and Calvery).

H. Preservatives. Thiourea, thioacetamide, acetamide, and various thiouracil derivatives find extensive use for various purposes (preventives of orange decay, antithyroid drugs, rubber accelerators, plastics). Thiourea and thiouracil fed to rats caused the development of thyroid adenomas (Bielschowsky; Purves and Griesbach), while the oral administration of thiourea and thioacetamide, like that of acetamide (Dessau and Jackson), to this species was followed by the appearance of hepatomas (Fitzhugh and Nelson; Dupta). The use of the last 2 mentioned chemicals in processing citrus fruits, therefore, has been prohibited in this country.

Another of the various preservatives of foodstuffs, 8-hydroxyquinoline, is present also in contraceptives, ointments, hair lotions, and rectal suppositories and used in Germany as a tobacco fungicide. This chemical has shown carcinogenic properties for mice when implanted into the bladder lumen (Boyland and Watson) and has produced uterine cancers when introduced into their vaginas. Hoch-Ligeti noted also that a contraceptive containing this chemical when fed or intravaginally applied to rats kept on a protein-deficient diet produced cancers of different types in several organs including the uterus and the brain. Its use in American dairy products was recently discontinued by voluntary action of the industry concerned.

I. Petroleum Derivatives Used as Polishes, Glazes, Fat Substitutes, and Coating of Food Containers. Liquid paraffin (mineral oil) and solid paraffin are employed as polishes and glazes of candy. Liquid paraffin and petrolatum-like material have been employed in the past at various times and in different countries as substitutes for vegetable and animal fats and oils during periods when these nutrients were in short supply, in reducing diets, and in pan greases. They are ingested also as laxatives, ingested and inhaled when used as vehicles in nose drops and throat sprays, as well as when present as air pollutants for occupational reasons in exposure to sprayed or nebulized cooling and cutting oils.

While the former practice of injecting paraffin into breasts, noses, penis, etc., for cosmetic purposes has now been discontinued, such deposits have given rise not only to the production of paraffinomas, but occasionally also to cancers, such as of the scrotum and breast (Hueper, Bauer, Schmähl and Reiter; Baader; Rose). Similar carcinogenic effects on the lungs have been recorded in a few cases from the inhalation or ingestion of paraffin oil used in laxatives and throat and nasal sprays (Wood; Santé).

Foodstuffs such as milk, cream, cheese, butter, margarine, and citrus fruit have, moreover, contact with paraffin and petroleum waxes (microcrystalline wax) used for the impregnation of food containers, wrapping paper, and coatings of cheeses, fruits, vegetables, as well as in cosmetics and medicines. Fat-containing foods may

either extract fat-soluble constituents present in these paraffins and waxes, or may become contaminated with them through scaling of wax from the walls of such containers. In the home manufacture of citrus fruit marmalade not only the dye often used for coloring the rind of citrus fruits but also the wax employed for delaying evaporation of water may become incorporated in the finished product. The depilation of fowl is commercially accomplished by dipping the birds into liquefied paraffin.

The urgent need for the establishment of adequate safety standards on paraffins and waxes used by the food processing industries was recently demonstrated by the chemical study of 24 different dairy waxes (Flemming). It was noted that some of these waxes were not white in color but distinctly greyish or yellowish, suggesting that they were not "fully refined" but contained still some oily residue. These waxes represent mixtures of paraffins with microcrystalline waxes for increasing the tensile strength of the end-product and for preventing cracking of paraffin coats of waxed food containers. It is likely that the contamination of the waxes with oily residues mainly comes from the crystalline waxes. These are branched and cyclic paraffins which do not release readily all the originally present oily carcinogenic materials by the application of the commercially used separation methods.

When these waxes were examined under ultraviolet light many showed a strong bluish-white fluorescence indicating the presence of aromatic hydrocarbons and characteristic of but not specific for carcinogenic aromatic polycyclic hydrocarbons. When isooctane solutions of these waxes were spectroscopically studied, 4 showed strong absorption at the 290 mμ wavelength, while for 11 waxes the absorption at this wavelength was of moderate degree. It is significant that the absorption maxima of most carcinogenic polycyclic hydrocarbons lie between 288 and 298 mμ. These observations also suggested that the waxes studied might contain carcinogenic chemicals. In subsequent analytical studies it was established spectrophotometrically that the "dirtiest" wax contained about 45μg. of 1,2,5,6-dibenzanthracene, a known carcinogenic hydrocarbon, in 100 grams of wax (Falk, Kotin, and Miller; Lijinski and Shubik). A possible cancer hazard to the consumer of foodstuffs from waxed containers may result from the elution of the carcinogens into the contents as well as from the desquamation of the wax or its penetration into foodstuffs such as cheese or fruits.

The apparent reality of this danger to human health from such sources is indicated by recent observations of Falk, Miller, and Kotin, who were able to elute 3,4-benzpyrene adsorbed to carbon particles (soot) by plasma proteins and succeeded in subsequent experiments to elute within 55 hours almost the entire amount of 3,4-benzpyrene and 1,2,5,6-dibenzanthracene added to dairy wax and contained in paraffin films by the use of milk proteins.

The crude oil fraction from which paraffin is obtained in the processing of crude petroleum, shale oil, or lignite oil is a potent carcinogen, being the cause of the well-known scrotal and skin cancers of paraffin pressers and mule spinners. The crude oils, moreover, contain potent aliphatic cocarcinogens (Horton et al.). It is noteworthy, also, that some of the mineral oils sold for human consumption and obtained from catalytically cracked stocks are highly fluorescent because they contain aromatic polycyclic hydrocarbons. It is, moreover, known that technical difficulties are encountered in freeing completely microcrystalline waxes from residues of oils which are long-established human carcinogens. A competent examination of paraffins and waxes used for medicinal and commercial purposes, including food containers and wrapping material, is indicated because of recent observations on a tumorigenic action of presumably purified paraffin when implanted into the bladder of rodents (Bonser, Clayson, Jull, and Pyrah; Query, and

Meigs). Schmähl and Reiter, moreover, recently reported that the intraperitoneal or subcutaneous injection of liquid paraffin and yellow petrolatum into rats resulted in the development of sarcomas at the site of injection in some animals. The studies of Boyd and Doll on the relationship between the use of liquid paraffin as purgatives and the occurrence of gastrointestinal cancers indicated that liquid paraffins contribute to the carcinogenic process. A similar conclusion was reached by Wolff on the basis of experimental evidence.

Serious consideration should also be given to the possibility that carcinogenic hydrocarbons may be generated in originally noncarcinogenic paraffins and waxes when these become exposed to high temperatures such as those encountered during frying.

A vivid illustration of the cancer hazards which may arise from the consumption of food contaminated with carcinogenic material present in petroleum or coal tar derivatives was recently reported by Burrell. It was known for many years that members of liquor-producing and liquor-consuming trades have an excessive liability to esophageal cancer. Some investigators had ascribed this phenomenon to the practice of charring liquor barrels on the inside, thereby producing wood tar which may be eluted by the alcohol into the liquor and thereby create an exposure to carcinogenic aromatic polycyclic hydrocarbons contained in the tar. Burrell observed that in a South African area esophageal cancer was more than 6 times as frequent among the local Bantus as among the Europeans. He traced this striking discrepancy to the practice of the Bantus to consume liquor obtained by fermenting the mash in drums previously used for distributing petroleum asphalt with which the drums were still lined, thereby permitting the alcohol to dissolve carcinogens from the residue of the asphalt in the drums. In recent experiments with 4 petroleum asphalts used for paving roads and obtained from different oil fields in the Americas, it was sh wn that they display weak carcinogenic properties when applied to the skin of mice and when injected into the thigh muscle of rats.

Comment: The evidence presented indicates that some food additives in use in this country and/or other countries possess carcinogenic properties not only for experimental animals but in some instances also for man. Although the evidence on the carcinogenic potency of some of these agents has been obtained in experimental animals by exposing them to these chemicals through nonphysiologic routes and in unusually high amounts, the observations made, nevertheless, are of significance in terms of potential human health hazards. Serious consideration, moreover, should be given to the fact that the great majority of the additives either have not adequately been investigated for carcinogenic qualities or have not been studied at all in this respect.

It is evident, moreover, that some carcinogenic food additives are present in other consumer goods or are constituents f the human environment with which large parts of the general population have frequent and intimate contact (cosmetics, drugs, household and sanitary goods, clothing, building materials, pesticides, environmental poisons, occupational agents, environmental pollutants).

2. *Food Contaminants and Products of Food Processing Procedures.*—To the potential cancer hazards which may be associated with some intentional food additives must be added those which are related to unintentional additives, i.e., food contaminants (pesticides, water and soil contaminants, inks, packaging materials) and products of processing procedures (smoking, toasting, frying, roasting, irradiation). They form another part of th total carcinogenic load placed upon the general population from various sources (occupational activities, air and water pollution, habits, customs, climate, infections, endogenous factors).

A. Pesticide Residues: (a) Arsenicals. Among the various pesticides which may remain attached as residues to foodstuffs, especially such as fresh fruits and vege-

...and the various processed foods (wine, juices, preserves, jellies, marmalades, dried fruits and vegetables, canned fruits and vegetables, frozen fruits and vegetables), the different arsenical and chlorinated hydrocarbon insecticides, rodenticides, fungicides, and herbicides deserve principal attention. Arsenicals in foods have been responsible for a considerable number of chronic arsenic poisonings among consumers of contaminated foodstuffs—especially wine. Recent reports from Germany indicate that vineyard workers who drank wine contaminated with considerable amounts of arsenical pesticides developed, more than 10 years after cessation of exposure to these agents, cancers of the skin, lung, and liver (Roth; Hess; Rockstroh; Butzengeiger). These observations on dietary arsenic cancer parallel those previously recorded from the Reichenstein region in Germany and from Cordoba Province, Argentina (Arguello; Tello) where the consumption of drinking water poll...d with arsenicals caused the de...ent of cancers of the skin. Such neoplastic sequelae have repeatedly been observed after a medicinal consumption of arsenicals (Arhelger and Kremen; Sommers and McManus) as well as in workers occupationally exposed to arsenicals, particularly in the production and use of arsenical pesticides (Hill and Faning) and in the smelting of arsenical ores (Neubauer; Rogh; Liebegott; Goldblatt; Butzengeiger; Hueper). Vegetables and fruits previously sprayed or dusted with arsenical pesticides, therefore, should be thoroughly cleaned before they are eaten, and proper precautions should always be taken to prevent any undue contact with arsenicals when employing arsenical pesticides so as to keep the unavoidable exposure with arsenicals at a minimum. Air-borne arsenic in urban atmospheres and arsenical residues in tobacco smoke are among frequent contributors to human exposure (Satterlee; Goulden et al.; Daff and Kennaway; Holland et al.).

(*b*) Chlorinated hydrocarbons. Among the numerous newer pesticides, various chlorinated aliphatic and aromatic hydrocarbons have come into extensive use (von Oettingen). Many of them have distinct hepatotoxic properties (Ortega et al.; Barnes). Prolonged feeding of rats with DDT and Aramite (β-prime-chlorethyl-β-para-*tert.*-butyl-phenoxy-α-ethyl-methyl-sulfide) was followed by the development of hepatomas. While DDT has a minimal tumorigenic effect when given to rats and dogs with the feed in doses highly excessive to those encountered under ordinary exposure conditions (Fitzhugh and Nelson), Aramite causes benign and malignant liver tumors in the majority of rats and dogs fed this chemical in the feed at a concentration as low as 5,000 parts per million (Sternberg. Popper, Oser and Oser). These observations gain in significance since other hepatotoxic chlorinated hydrocarbons (chloroform, carbon tetrachloride) when administered to mice also elicit hepatomas and thus may exert a synergistic action (Eschenbrenner and Miller; Rudali and Mariani; Edwards and Dalton). Mention may also be made of an observation of Gardner and Boddaert concerning the occurrence of hepatomas and testicular interstitial-cell tumors in mice subcutaneously injected with an estrogenic chlorinated ethylene compound (tri-*p*-anisyl-chloroethylene).

The widespread use of aliphatic and aromatic chlorinated hydrocarbons in industry, agriculture and in the home (dry cleaning fluids, paint removers, solvents, degreasing agents, medicines, fire extinguishers, fumigants of grain, cable coating, (von Oettinger; Hardin; Hughes), and their distribution as pesticides from airplanes, create frequent contacts from various sources with these hepatotoxic agents for members of the general population, apart from those associated with the presence of pesticide residues in foodstuffs of vegetable and animal nature. Since DDT and other chlorinated pesticides (heptachlor epoxide) are excreted in the milk, even infants are bound to have some degree of exposure to these agents. They, moveover, exert a cu-

mulative effect, being stored in various tissues, particularly fat tissue (Hayes et al.; Davidow et al.; Lange et al.).

Several of the chlorinated hydrocarbons (carbon tetrachloride, chlorophenothane, benzene hexachloride) have elicited in man aplastic anemia and panmyelophthisis (Friberg and Martensson; Straus). Consideration should be given to the possibility that they may have, like other similarly acting agents, such as benzol and ionizing radiation, leukemiogenic properties (Hueper), or that such effects are attributable to the solvent vehicles used, which may contain benzol as an impurity (Elkins and Pagnotto).

(c) Carbamates. Urethan (ethyl carbamate) is capable of inducing pulmonary adenomas and carcinomas in mice and rats (Nettleship and Henshaw; Guyer and Claus; Jaffe; Mostofi and Larsen; Malmgren and Saxen; Orr). It also exerts, in conjunction with a cocarcinogenic, an initiating carcinogenic effect on the skin of mice (Roe and Salaman: Salaman and Roe; Berenblum and Haran). Carbamate derivatives used as insecticides, weed killers, plasticizers, fish dope, medicines, textile finishes, and resins, therefore, should be studied for carcinogenic properties (Hueper; van Esch, van Genderen and Vink; Shabad and Naumova). Since urethan is capable of transmitting transplacentally the tumorigenic action from the maternal organism to the offspring (Larsen; Klein) of mice, populations exposed to carbamates deserve attention also for the occurrence of tumors in infants of exposed mothers (Baló). Polyurethan foam implanted into rats caused sarcomas and adenocarcinomas of the intestine around intra-abdominal deposits (Hueper).

B. Plant Growth Regulators: The various chemicals used in agriculture and horticulture for controlling the growth of plants can be placed into 2 classes, those which favor this process, i.e., the auxins and sprouting agents, and the plant growth inhibitors, antiauxins, or antisprouting and antimaturition agents or herbicides. The specific, hormone-like action of these chemicals is related to their influence upon the cellular proliferative mechanisms, i.e., they have a mitotic or antimitotic effect. Sprouting agents are benzotriazole, p-chlorophenoxy acid (CIPA), 3-indolacetic acid (IA) and α-cyano-β-(2,4-dichlorphenyl)-acrylic acid (Ethyl-214), while antisprouting agents are maleic hydrazide, α-naphthalene acetic acid, 2,4,5-trichl rophenoxyacetic acid (2,4,5 T), 2,4-dichlorophenoxyacetic acid (2,4-D), β-naphthylalanine, β-indolylalanine (trytophane), and others. Some of these agents (maleic hydrazide) are excreted in cow's milk and are retained in organs.

A few have been tested for long-term effects in experimental animals for possible carcinogenic action. Truhaut and Vernes injected α-naphthylacetic acid into mice over many months without obtaining tumors. Maleic hydrazide fed to rats also gave negative results concerning abnormal tumor formation. Tumors also were not observed in dogs fed for one year with this particular chemical. While these few observations are reassuring to some extent, they scarcely represent an adequate study of the many chemicals used for the purposes stated in regard to potential cancer hazards to man, especially since Fukui et al., who calculated the electronic structure of a number of plant growth compounds, such as benzoic acid derivatives, have found that the electronic distributions of some special positions in the molecule are intimately correlated with the auxine activity of the compounds and show a strong resemblance to carcinogenic polycondensed aromatic hydrocarbons. Recent experimental studies on rats given by mouth large amounts of the herbicide, 3-amino-1,2,4-triazole, which is taken up into fruits, have shown, moreover, that this herbicide causes the development of thyroid cancers (Editorial: Flemming).

In performing such tests in the future, consideration also should be given to the fact that the active ingredients are solubilized by the addition of surfactants (triethylamine, diethylolamine, Triton X100,

Dreft; Triton B1956), in fuel oil, diesel oil, or other petroleum oils, which may be carcinogenic by themselves. Negative observations made on livestock exposed to contaminated vegetation do not provide any valid evidence as to the innocuousness of these agents, since such animals are only rarely kept alive for a sufficiently long period to show any cancerous effects.

C. Estrogens: The growing use of estrogenic chemicals, especially diethylstilbestrol, for an accelerated fattening of food animals (fowl, hogs, cattle, sheep) in the form of pellets either subcutaneously implanted or added to the feed, deserves consideration because estrogens are recognized carcinogens for several species, causing upon prolonged administration cancers of various organs and tissues (breast, uterus, testis, kidney, hematopoietic tissue, bladder). Practical experience has shown that farmers and poultry men do not always follow the instructions regulating the commercial use of these [illegible]ally highly potent substances, i.e., [illegible]o not always insert the estrogen pellets in parts of animals (neck) which usually are discarded, but in parts which are eaten; they implant more than one pellet of 15 mg. of estrogenic chemical, and they sell their animals for human consumption before the safety period of 6 weeks after implantation has elapsed, while cattle estrogenized by both routes are slaughtered, as a rule, without observing a 60-hour estrogen-free waiting period. It is noteworthy, moreover, that at least one synthetic estrogen, namely tri-*p*-anisolchloroethylene, is stored in the human fat tissue after oral administration and thus appears to be most objectionable from a carcinogenic viewpoint because of its prolonged effect (Greenblatt and Brown).

Since members of the general population may have appreciable contacts with exogenous estrogens from other sources (medicines, cosmetics, production of estrogens, handling of estrogenic preparations, preparation and handling of estrogenic feed), such exposures or the possibility of such [illegible]s, especially when they are avoidable and not essential or justified, appear to be objectionable, even if it is still controversial whether or not estrogens cause cancers in man (uterus, breast). It is well established that often prolonged anatomic and functional reactions to medicinal, occupational, and environmental hyperestrinism have been attributable to such contacts and have affected male and female adults and children (Watrous and Olsen; Scarff and Smith; Fitzsimons; Fisk; Pagani; Klavis; Katzenellenbogen; Kloprain and Bartini; Green; Stoppelman and Van Valkenburg).

The view of a primary or contributory role of estrogens in the causation of cancers in both women and men is being held by an increasing number of competent investigators and clinicians (Eller and Wolff; Corscaden; Terp; Jüptner; Gusberg, Burrows and Horning; Bromberg et al.; Mühlbock; Meissner and Sommers; DeWaard; Hertz; Speert; Novak; Hueper). Reports on the occurrence of endometrial carcinomas following a prolonged treatment of estrogens have become more frequent in recent years (Riehm and Stoll; Vass; Stokes; Emge); so have the observations on the development of uterine adenocarcinomas in coexistence with estrogen-producing granulosa-cell ovarian tumors (Ayre; Corbet, Miller and Tod; Walz) as well as those concerning an excessive frequency of cancers of the breast in men given large amounts of estrogens for medical reasons (Hueper), or suffering from hyperestrinism because of functional and/or anatomic impairment of the liver (hepatic cirrhosis) (Symeonidis; Davies; Coodley and Molle).

It is rather remarkable that biologically potent chemicals which are obtainable for medicinal reasons only on prescription by a licensed physician can be used freely in large quantities by persons without any proper training concerning the potential health hazards associated with the handling and consumption of large quantities of these hormonal substances. Such practices are difficult to control adequately on a nation-wide basis in foodstuffs handled in interstate and intrastate commerce by thousands of in-

dividual producers in quantities of several millions of animals. It is, therefore, commendable that the food processing industry has agreed to discontinue voluntarily the further production of estrogen pellets for implantation into fowl.

D. Water and Soil Pollutants: Since water is the most important foodstuff, the possibility of cancer hazards from this source deserves serious consideration, inasmuch as natural or industrial carcinogenic pollutants may enter the drinking water supply as well as be absorbed by and accumulated in vegetables, fruits, and food animals using water contaminated with such materials (arsenicals, selenium, radioactive substances, wastes from coke ovens, tar refineries, oil refineries, textile dyeing plants, paper manufactures, cellulose factories, domestic and industrial detergents and others). Tarry and oily materials, moreover, may be washed by rain into bodies of water; so may radioactive fall-out and pesticides dusted and sprayed on fields and orchards, and atmospheric effluents from industrial establishments containing carcinogenic matter (soot, arsenicals, chromates, aliphatic hydrocarbons, beryllium, asbestos, etc.) (Hueper; Hueper and Ruchhoft; Tollo; Goldblatt and Goldblatt).

In fact, experimental investigations have demonstrated the presence of carcinogenic matter in water serving as sources of drinking water or food supply (cancer of the skin in mice painted with carbon adsorbates of effluents of an oil refinery) (Hueper and Ruchhoft), sarcoma in mice receiving subcutaneous implants of a polycyclic aromatic hydrocarbon fraction of barnacles growing in waters polluted with ship fuel oil, (Shimkin, Koe, and Zechmeister), demonstration of several carcinogenic polycylic aromatic hydrocarbons in extracts of oysters obtained from similarly contaminated waters (Cahnmann and Kuratsune).

The most recent addition to the spectrum of industry-related pollutants and additives to water serving as reservoirs for drinking water are the evaporation retardants forming a monomolecular film on the surface of the water. So far only the use of hexadecanol, but not of cocarcinogenic dodecanol, has been approved for this purpose (Hollis). There is no published evidence that either one has been studied for untoward effects upon human health for other than toxic aspects. In view of th fact that dodecyl compounds are in part cocarcinogens or weak carcinogens this new practice of chemicalizing the human food supply is in urgent need of thorough and competent investigation for delayed carcinogenic sequelae among consumers.

Mention may also be made of the practice introduced during recent years of employing chemicals, such as sodium arsenite, orthodichlorobenzene, trichlorbenzol, dichlorbenzol, naphtha, 24-D,2,4,5-T, and copper sulfate as algicides (Bartsch). Sodium arsenite is considered as one of the cheapest and "safest" products for such purposes because of its "toxicity"; its use in water supply reservoirs, however, should be considered with extreme care, according to Bartsch, wh failed to mention and to consider the likely cancer hazards which would result from such a practice.

Selenium, a soil contaminant in the United States and South Africa (Steyn) causing chronic selenosis (alkali disease) among livestock characterized by liver cirrhosis, elicits, when fed to rats, liver cirrhosis, hepatic adenomas and carcinomas (Nelson, Fitzhugh and Calvery). It is at present not known whether similar neoplastic sequelae occur in populations consuming seleniferous food.

It is at present purely speculative but worth investigating whether the marked differences in gastric cancer mortality among different countries of similar racial and cultural nature and among different areas of the same country (England and Wales, Netherlands) (Tromp; Daires and Griffith) are in part causally related to local dietary factors (Torgensen and Petersen).

E. Wrapping and Coating Materials: Various chemicals either obtained from materials carcinogenic to man and animals, such as crude petroleum, shale and lignite

oils used in the production of paraffins and microcrystalline waxes, discussed above (Hueper; Goldblatt and Goldblatt) or synthesized from carbon or silicon compounds and forming polymerization products, such as polyethylene, cellophane, polyvinyl chloride, polyacrylates, polysilicones, polyamides, polytetrafluoroethylene, and Bakelite, which are carcinogenic when implanted into rats and mice, are employed at an increasing scale in the manufacture of food containers, as inner linings of cans, and as wrapping and coating materials of foodstuffs, including sausage casings which are apt to be eaten (Oppenheimer et al.; Druckrey et al.; Nothdurft; Hueper). Richmond and Hadlow et al. produced cancers in rats by the parenteral introduction of a water-soluble iron-dextran complex used as an antianemic.

Although there exist as yet no direct counterparts in man to the "polymer cancers" elicited in rats and mice by the parenteral implantation of the various macromolecular plastics, this may be due to the fact that the industrial, commercial, and medicinal use of these chemicals is of rather recent date. A latent period sufficiently long for the development of cancers following the parenteral introduction of these polymers into man has not elapsed for most cases. The existence of asbestosis cancers of the lung, however, attests to the fact that the human organism may react to the presence of a silicon polymer with a cancerous manifestation in the exposed tissue. No evidence, on the other hand, is available from experiences in man and experimental animals whether the ingestion of any one of these polymers or the ingestion of foodstuffs being in direct contact with them entail any carcinogenic hazard. It appears to be a wise precaution to keep all occupational groups having cutaneous, respiratory, and ingestive contact with these macromolecular chemicals under close surveillance for any evidence suggesting a carcinogenic action on man.

Similar considerations should be extended to persons who have received parenteral administrations of iron-dextran complex, [redacted]ic preparations, and the various synthetic macromolecular plasma extenders, such as polyvinyl pyrrolidone and dextran, since several polyvinyl pyrrolidones implanted and intravenously injected into rats produced reticulum-cell sarcomas, Kupffer-cell sarcomas, and carcinomas of the uterus and skin in about 30% of the animals treated. Distinct caution is also indicated in the industrial (felt, rubber) and medical (virucidal) use of a polymer chain-termination and cross-linking agent, β-propiolactone, since it is capable of eliciting carcinomas of the skin in mice and subcutaneous sarcomas in rats (Walpole et al.; Roe and Salaman; Roe and Glendenning).

F. Incomplete Combustion Products of Carbonaceous Materials: Recent observations indicate that foodstuffs when exposed to wood smoke, such as that used in smoking meats and fishes or when subjected to high temperatures causing charring of the foodstuffs (roasting, toasting, baking) may become contaminated with a known carcinogenic aromatic hydrocarbon, 3,4-benzpyrene (Dickens and Weil-Malherbe; Gorelova, Dikun and Lapshin; Shabad and Dikun; Kuratsune; Sula and Dobes; Valade; Sulman and Sulman; Bailey and Dungal). Kuratsune, and Kuratsune and Hueper recently added to this evidence by demonstrating that the soot produced when roasting coffee beans by direct or indirect exposure to a gas flame contains, among other polycyclic aromatic hydrocarbons, not-inappreciable amounts of this carcinogen, confirm-

TABLE 11.—*Rough Estimation of Polycyclic Hydrocarbons in a Coffee Soot Produced by the Direct Application of Heat**

Hydrocarbons	Amount, µg/Kg
Phenanthrene	128
Pyrene	257
Fluoranthene	240
Chrysene	634
Benz (a) anthracene	16
Perylene	270
Benzo (e) pyrene	187
Benzo (a) pyrene	200
Benzo (g, h, i,) perylene	98
Benzo (k) fluoranthene	66

* M. Kuratsune and W. C. Hueper

ing thereby previous, not entirely reliable, claims of Roffo, which, however, were denied by Druckrey (Table 11).

In subsequent experiments on coffee beans roasted to different degrees, it was found that 3,4-benzpyrene was not demonstrable in the watery extracts of coffee beans of light as well as dark roasts (Kuratsune and Hueper; Dansi and Zanini), although very small amounts of this carcinogenic were present in a special brand of black roasted coffee where the surface of the beans is burnt.

The practical importance of these observations, however, remains uncertain at the present time because of conflicting experimental evidence concerning the carcinogenicity of these soots and their effects upon experimental animals. Eichler and Vollmer failed to produce cancers of the skin in rabbits and mice painted with coffee tar. Similarly negative results were reported by Schmähl and Reiter in rats fed heavily smoked bacon for up to 1,000 days. Fark, on the other hand, obtained tumors in 8 of 20 mice fed smoked bacon, but none in 50 mice used in a repeat experiment. None of these observations is of convincing value concerning a carcinogenic action of smoked foodstuffs in man because cancers of the alimentary tract cannot consistently be produced in rats and mice even when large amounts of 3,4-benzpyrene or other similar potent carcinogens are fed (Waterman; Rorei and Gummel; Shay, Harris and Gruenstein; Lorenz and Stewart) unless some cocarcinogenic or procarcinogenic vehicle is used in the administration of these carcinogens. It is moreover not definitely established that 3,4-benzpyrene is carcinogenic to man.

Nevertheless, recent epidemiologic studies of Voitelovich et al. on the cancer incidence among 2 population groups, one representing the inhabitants of 2 coastal villages, the second of 6 inland villages in Latvia, provide important evidence supporting the view that carcinogenic factors in the smoke used for smoking foodstuffs may play a significant role in the production of cancers of the alimentary and respiratory tracts. It was found that the population of the coastal villages engaged in fishing and consuming large amounts of fresh, salted, and smoked fish had about 3 times as much cancer of the alimentary and respiratory tract as the people living in inland villages, and engaged in agricultural activities. While the villagers of the inland villages also eat smoked meat, those of the coastal villages are engaged in smoking fish almost the whole year around and conduct such work not only in special smoking plants but also at home, since practically every house has its own smoking oven in which fish are smoked for domestic use.

There exists a great deal of equivocal and contradictory evidence concerning the role of ingested heated fats and cholesterol in the production of cancers of the stomach and intestine in mice and rats (Peacock; Roffo; Kirby; Falk et al.; Peacock et al.; Chalmers; Lane, Blickenstaff and Ivy). While the subcutaneous injection of one type of polymerized and peroxidized vegetable oil has been shown to produce sarcomas in rats, the injection of another similarly altered vegetable oil into mice was not followed by the appearance of tumors (Chalmers). It may be pointed out in this connection that the physicochemical conditions prevailing in deep-fat frying processes favor the development of oxidized and polymerized products, especially when the fat or oil once heated remains in permanent use.

A similar uncertainty exists in regard to the alleged carcinogenicity of normal cholesterol. While Hieger and Badger note that cholesterol has a definite, although weak, carcinogenic potency, Fieser states that cholesterol itself, which is so widely distributed in the body, could hardly have the properties of a carcinogen of even low-order potency but that tumors appearing at the site of the injected material must have been initiated by some transformation product of cholesterol or some unknown companion substance. The extreme rarity of primary cancers of the arterial system in which cho-

esterol and its esters are deposited and retained for decades supports Fieser's views, at least as far as man is concerned. Kirby failed to produce cancers in rats fed cholesterol esters of unsaturated fatty acids as well as in mice painted with such materials or subcutaneously injected with them. Bischoff et al., on the other hand, reported that a combination of sesame oil and certain oxidation products of cholesterol is carcinogenic to mice, eliciting fibrosarcomas. It is noteworthy finally in this connection that he reported occasional occurrence of tumors in nonalimentary organs following the ingestion of carcinogens might be related to the fact that chylomicrons may act as carriers of ingested carcinogenic hydrocarbons, thereby causing their general hematic distribution, and under suitable dietary and metabolic conditions become arrested in specific organs (Setälä and Ermälä). The possible existence of such correlations is supported by observations of Andervont and Lorenz, who [redacted]ed tumors of the lung of mice by an intravenous injection of dibenzanthracene dispersed in lipemic dog serum.

Conclusions

1. The growing pollution of the human environment with chemical and physical agents associated with the modern industrial development poses serious problems to medicine, public health, sociology, economy, natural sciences, and technology.

2. Because of the still far-reaching lack of factual knowledge on the carcinogenic agents already present in the human environment and the distinct difficulties encountered in discovering and identifying them by epidemiologic, medical, and experimental procedures, definite efforts should be made to prevent, as much as possible and practicable, any further addition of new industry-related carcinogens to the human environment.

3. Cancer hazards associated with exposure to these agents represent a segment of the general toxic health hazards con[redacted] with the production, distribution, and [redacted]nption of industrial products and the release of industrial wastes into the environmental air, water, and soil.

4. In view of the rapid growth of industrial activities and of population, the complex problems created by these developments deserve serious and urgent attention by all parties concerned so as to keep them within controllable limits.

5. Cancer hazards of industry-related causation should not be considered as unimportant and unavoidable calculated risks of modern living. They are as amenable to sanitary control measures as communicable diseases have proved to be in past decades. The recently advanced argument that the prophylaxis of environmental cancers can cut us off from all our amusements and that it is best, therefore, to enjoy life and take the small risks attached to these things (Wright) reflects a philosophy which denies the best traditions of medical practice and public health, and would open the way for an indiscriminate introduction of any number of highly toxic and carcinogenic materials into the human environment. While the risks to health and life resulting from such exposures would be of the "calculated" variety, distinct differences would exist between the parties who would run the risks and those who would do the calculations.

9307 Rockville Pike, Bethesda 14, Md.

BIBLIOGRAPHY

Allen, M. J.; Boyland, E.; Dukes, C. E.; Horning, E. S., and Watson, J. G.: Cancer of the Urinary Bladder Induced in Mice with Metabolites of Aromatic Amines and Tryptophan, Brit. J. Cancer 11:212-228, 1957.

Allmark, M. G.; Grice, H. C., and Lu, F. C.: Chronic Toxicity Studies on Food Colours, J. Pharm. & Pharmacol. 7:590-601, 1955.

Andervont, H. B., and Lorenz, E.: Dibenzanthracene Tumors in Mice, Pub. Health Rep. 52:637-647, 1937.

Angrist, A.; Capurro, P., and Mourgis, B.: Relative Roles of Vitamin A Deficiency, Foreign Body Irritation, and Estrogen Administration in the Production of Squamous Metaplasia in the Rat Bladder, Proc. Am. A. Cancer Res. 3:3, 1959.

Arguello, R.; Tello, E. E.; Macola, B. A., and Manzano, L.: Los cancers cutaneos en el [redacted] cronico regional endemico en la

provincia de Cordoba, R. A., Rev. Fac. cienc. med. Univ. Cordoba 8:409-432, 1950.

Arbelger, S. W., and Kremen, A. J.: Arsenical Epitheliomas of Medicinal Origin, Surgery 30: 977-986, 1951.

Ayre, J. E.: Cervical Cancer, Am. J. Obst. & Gynec. 54:363-390, 1947.

Badger, G. M.: The Carcinogenic Hydrocarbons: Chemical Construction and Carcinogenic Activity, Brit. J. Cancer 2:309-350, 1948.

Miscellaneous Chemical Carcinogens, Brit. J. Cancer 10:330-356, 1956.

Bailey, E. J., and Dungal, N.: Polycyclic Hydrocarbons in Icelandic Smoked Food, Brit. J. Cancer 12:348-350, 1958.

Baló, J.: Lungenkarzinom und Lungenadenom, Budapest Verlag der Ungarischen Akademie der Wissenschaften, 1957, p. 363.

——Juhasz, J., and Kendry, G.: Über die geschwulsterzeugende Wirkung des Urethan in Schlafmitteln, Ztschr. Krebsforsch. 59:561-567, 1953.

Barnes, J. M.: Toxic Hazards of Certain Pesticides to Man, Geneva, World Health Organization, 1953, p. 129.

Bauer, K. H.: Das Krebsproblem, Berlin, Springer-Verlag, 1949, p. 304.

Bartsch, A. F.: Practical Methods for Control of Algae and Water Weeds, Pub. Health Rep. 69:749-757, 1954.

Berenblum, I.: A System of Grading Carcinogenic Potency, Cancer Res. 5:561-564, 1945.

——and Shubik, P.: A New Quantitative Approach to the Study of the Stages of Chemical Carcinogenesis in the Mouse's Skin, Brit. J. Cancer 1:383-391, 1947.

——and Haran, N.: The Initiating Action of Ethyl Carbamate (Urethane) on Mouse Skin, Brit. J. Cancer 9:453-456, 1955.

Bickers, W.: Toluidine Blue—An Evaluation in the Treatment of Uterine Bleeding, Am. J. Obst. & Gynec. 66:1313-1317, 1953.

Bielschowsky, F.: Tumors of the Thyroid Produced with 2-Acetyl-Amino-Fluorene and Allythiourea, Brit. J. Exper. Path. 25:90-95, 1945.

Bischoff, F.; Lopez, G.; Rupp, J. J., and Gray, C. L.: Carcinogenic Activity of Cholesterol Degradation Products, Fed. Proc. 14:590, 1955.

Bischoff, F.: A Cocarcinogenic Fraction from Sesame Oil, Fed. Proc. 16:155, 1957.

Cocarcinogenic Activity of Cholesterol Oxidation Products and Sesame Oil, J. Nat. Cancer Inst. 19:977-985, 1957.

Bonser, G. M.; Clayson, D. B., and Jull, J. W.: Induction of Tumours with 1-(2-Tolylazo)-2-Naphthol (Oil Orange TX), Nature, London 174:879, 1954.

——Clayson, D. B.; Jull, J. W., and Pyrah, L. N.: The Experimental Aspects of Industrial Bladder Cancer, Brit. J. Urol. 26:49-52, 1954.

Induction of Tumours of the Bladder Epithelium by the Implantation of Paraffin Wax Pellets, Brit. J. Cancer 7:456-459, 1953.

Booth, J., and Monson, D.: Metabolism of 2-Naphthylamine in the Intact Animal and in Isolated Tissues, Ann. Rep. Brit. Emp. Cancer Campgn. p. 22-23, 1953.

Boyd, J. T., and Doll, R.: Gastro-Intestinal Cancer and the Use of Liquid Paraffin, Brit. J. Cancer 8:231-237, 1954.

Boyland, E.; Harris, J., and Horning, E. S.: The Induction of Carcinoma of the Bladder in Rats with Acetamidofluorene, Brit. J. Cancer 8: 647-653, 1954.

Boyland, E., and Watson, G.: 3-Hydroxyanthranilic Acid, a Carcinogen Produced by Endogenous Metabolism, Nature, London 177:837-838, 1956.

Brewer, J. I., and Foley, T. J.: Endometrial Carcinoma and Hepatic Cirrhosis, Obst. & Gynec. 1:67-73, 1953.

Bromberg, Y. M.; Liban, E., and Laufer, A.: Early Endometrial Carcinoma Following Prolonged Estrogen Administration in an Ovariectomized Woman, Obst. & Gynec. 14:221-226, 1959.

Brown, D. V., and Thorson, T. A.: Reticulum-Cell Sarcoma of Rats: Experimental Production with Trypan Blue, J. Nat. Cancer Inst. 16: 1181-1195, 1956.

——and Norlind, L. M.: Trypan Blue-Induced Tumors in Rats: Morphologic, Hematologic, and Serologic Observations, Am. J. Path. 35: 696-697, 1959.

Burrell, R. J. W.: Oesophageal Cancer in the Bantu, South African M.J. 31:401-409, 1957.

Burrows, H., in Burrows and Horning: Oestrogens and Neoplasia, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 189.

Butzengeiger, K. H.: Die chronische Arsenvergiftung der Winzer, Aerztl. Wchnschr, 4: 365-369, 1949.

Cahnmann, H. J., and Kuratsune, M.: Polynuclear Aromatic Hydrocarbons in Oysters Collected in Polluted Water, Proc. Am. A. Cancer Res. 2:99, 1956; Anal. Chem. 29:1312-1317, 1957.

Cantarow, A.; Stasney, J., and Paschkis, K. E.: Influence of Sex Hormones on Mammary Tumors Induced by 2-Acetaminofluorene, Cancer Res. 8:412-417, 1948.

Campbell, M.: Urology, Vol. 2, Philadelphia, W. B. Saunders Company, 1954, p. 1045.

Case, R. A. M.; Hosker, E.; MacDonald, D. B., and Pearson, J. T.: Tumors of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Brit. J. Indust. Med. 11:75-104, 1954.

——and Hosker, M. E.: Tumour of the Urinary Bladder as an Occupational Disease in the Rubber Industry in England and Wales, Brit. J. Prev. & Social Med. 8:39-50, 1954.

——and Pearson, J. T.: Further Consideration of the Role of Aniline and of the Manufacture of Auramine and Magenta (Fuchsine) as Possible Causative Agents, Brit. J. Indust. Med. 11:213-216, 1954.

Chalmers, J. G.: Heat Transformation Products of Cottonseed Oil, Biochem. J. 56:487-492, 1954.

Clayson, D. B.: A Working Hypothesis for the Mode of Carcinogenesis of Aromatic Amines, Brit. J. Cancer 7:460-471, 1953.

Conway, W. D., and Lethco, E. J.: Aromatic Amine Impurities in Yellow AB and Yellow OB, Anal. Chem. 32:838-841, 1960.

Cook, J. W.; Duffy, E., and Schoental, R.: Primary Liver Tumours in Rats Following Feeding with Alkaloids of Senecio Jacobaea, Brit. J. Cancer 4:405-410, 1950.

——: Azo-Dyes and Experimental Liver Tumours, Brit. J. Nutrition 1:245-253, 1947.

Coodley, E. L., and Molle, W. E.: Metabolic Study of Gynecomastia Associated with Liver Disease, Am. J.M. Sc. 218:531-539, 1949.

t, R. M.; Miller, A. A., and Tod, W. H.: ndometrial Carcinoma Associated with Feminizing Tumours of the Ovary, J. Obst. & Gynaec. Brit. Emp. 59:369-371, 1952.

Corscaden, J. A.: Gynecologic Cancer, Ed. 2, Baltimore, The Williams & Wilkins Company, 1956, p. 546.

Daff, M. E., and Kennaway, E. L.: The Arsenic Content of Tobacco and of Tobacco Smoke, Brit. J. Cancer 4:173-182, 1950.

Dalton, A. J.; Morris, H. P., and Dubnik, C.: Changes in the Thyroid and Other Organs in Mice Receiving Thiouracil, Fed. Proc. 5:219, 1946.

Dansi, A., and Zanini, C.: Sul significato pratico della presenza di idrocarburi policiclici nel caffe torrefatto, Tumori 45:65-70, 1959.

Davies, J. N. P.: Sex Hormone Upset in Africans, Brit. M.J. 2:676-679, 1949.

Davies, R. L., and Griffith, G. W.: Cancer and Soils in the County of Angelsey, Brit. J. Cancer 8:56-66; 594-598, 1954.

Davidow, B.; Radomski, J. L., and Ely, R.: Excretion of Heptachlor Epoxide in Milk of a Dairy Cow Fed Heptachlor, Science 118: 383-384, 1953.

DeEds, F.; Wilson, R. H., and Thomas, J. O.: Photosensitization by Phenothiazine, J.A.M.A. 114:2095-2097, 1940.

Deichmann, W. B.; Coplan, M. M.; Woods, F. M.; Anderson, W. A. D.; Heslin, J., and Radomski, J.: The Carcinogenic Action of *p*-Aminobiphenyl in the Dog, A.M.A. Arch. Indust. Health. 13:8-12, 1956.

Della Porta, G.; Pietra, G.; Terracini, B., and Shubik, P.: Studies on the Promoting Action of Tween 60, Proc. Am. A. Cancer Res. 3:16, 1959.

DeWaard, F.: On the Aetiology of Endometrial Carcinoma, Acta endocrinol. 29:279-294, 1958.

Dessau, F. I., and Jackson, B.: Acetamide-Induced Liver Cell Alterations in Rats, Lab. Invest. 4: 387-397, 1955.

Dickens, F., and Weil-Malherbe, H.: Investigation into the Possible Carcinogenic Activity of Wood Smoke, Cancer Res. 1:679-684, 1942.

Druckrey, H.: Kaffeeroestprodukte und Krebs, Med. Klin. 35:614, 1939.

Harmful and Harmless Dyes for Foods, Voeding 16:667-681, 1955.

——and Schmaehl, D.: Carcinogenic Activity of Synthetic Products, Ztschr. Naturforsch. 7b:353-356, 1952.

Dupta, D. N.: Thiourea, Thioacetamide Liver Tumors in Rats, Nature, London 175:257, 1955.

Cranberry Smash, Editorial, Science 130:3387, 1959.

Edwards, J. E., and Dalton, A. J.: Induction of Cirrhosis of the Liver and of Hepatomas in Mice with Carbon Tetrachloride, J. Nat. Cancer Inst. 3:19-41, 1942.

Eichholtz, F.: Die toxische Gesamtsituation auf dem Gebiet der menschlichen Ernährung, Berlin, Springer-Verlag, 1956, p. 178.

Eichler, O., and Vollmer, H.: Versuche zum Nachweis carcinogener Substanzen, die beim Roestprozess auftreten koennen, Klin. Wchnschr. 26: 634, 1948.

Elkins, H. B., and Pagnotto, L. D.: Benzene Content of Petroleum Solvents, A.M.A. Arch. Indust. Health 13:51-54, 1956.

Eller, J. J., and Wolff, S.: Hormones and Vitamins in Cosmetics, J.A.M.A. 114:1865-1875; 2005-2010, 1940.

Emge, L. A.: Endometrial Cancer and Feminizing Tumors of the Ovaries: Significance of their Coexistence, Obst. & Gynec. 1:511-51[illegible] 1953.

van Esch, G. J.; van Gelderen, H., and Vink, H. H.: The Production of Skin Tumours in Mice by Oral Treatment with Urethane, Isopropyl-*N*-Phenyl Carbamate or Isopropyl-*N*-Chlorophenyl Carbamate in Combination with Skin Painting with Croton Oil and Tween 60, Brit. J. Cancer 12:355-362, 1958.

Eschenbrenner, A. B., and Miller, E.: Liver Necrosis and the Induction of Carbon Tetrachloride Hepatomas in Strain A Mice, J. Nat. Cancer Inst. 6:325-341, 1946.

Falk, H. L.; Goldfein, S., and Steiner, P. E.: The Products of Pyrolysis of Cholesterol at 360 C and Their Relation to Carcinogens, Cancer Res. 9:438-447, 1949.

Falk, H. L.; Miller, A., and Kotin, P.: Elution of 3,4-Benzypyrene and Related Hydrocarbons from Soots by Plasma Proteins, Science 127: 474-475, 1958.

Falk, H. L.; Kotin, P., and Miller, A.: Milk and an Eluent of Polycyclic Aromatic Hydrocarbons Added to Wax, Nature, London 163: 1184-1185, 1959.

Fark, G.: Cancerogene Wirkung von geräuchertem Speck, Ztschr. Krebsforsch. 56:583-586, 1950.

Fieser, L. F.: Some Aspects of the Chemistry and Biochemistry of Cholesterol, Science 119:710-716, 1954.

Friberg, L., and Martensson, J.: Case of Panmyelophthisis after Exposure to Chlorophenothane and Benzene Hexachloride, A.M.A. Arch. Indust. Hyg. 8:166-169, 1953.

Fitzhugh, O. G., and Nelson, A. A.: Comparison of the Chronic Toxicities of Synthetic Sweetening Agents, Fed. Proc. 9:272, 1950.

Fitzhugh, O. G., and Nelson, A. A.: Liver Tumors in Rats Fed Thiourea and Thioacetamide, Science 108:626, 1948.

Fitzhugh, O. G., and Nelson, A. A.: Comparison of the Chronic Toxicity of Triethylene Glycol with That of Diethylene Glycol, J. Indust. Hyg. and Toxicol. 28:40-43, 1946.

Fitzhugh, O. G., and Nelson, A. A.: The Chronic Oral Toxicity of DDT (2, 2-Bis (*p*-Chlorophenyl-1,1,1-Trichloroethane), J. Pharmacol. & Exper. Therap. 89:18-30, 1947.

The Chronic Toxicity of Ergot, J. Pharmacol. & Exper. Therap. 82:364-376, 1944.

——Bourke, A. R.; Nelson, A. A., and Frawley, J. P.: Chronic Oral Toxicities of Four Stearic Acid Emulsifiers, Tox. & Appl. Pharmacol. 1:315-331, 1959.

Fitzsimons, M. P.: Gynaecomastia in Stilboestrol Workers, Brit. J. Indust. Med. 1:235, 1944.

Fisk, G. H.: Oestrogen Absorption and Toxicity in Male Workers in a Chemical Plant, Canad. M.A.J. 62:285, 1950.

Flemming, A. S.: Warning on Cranberries, J.A.M.A. 172:28, 1959.

Food Protection Committee, Food and Nutrition Board: The Use of Chemical Additives in Food Processing, Publ. No. 398, National Research Council, Washington, D.C. 1956, p. 91.

The Safety of Polyoxyethylene (8) Stearate for Use in Foods, Bull. 646, National Academy of Sciences, Washington, D.C., 1958, p. 19.

Problems in the Evaluation of Carcinogenic Hazard from Use of Food Additives, Bull. 749, National Academy f Sciences, Washington, D.C. 1959, p. 44.

Food and Drug Administration: Report of the Food and Drug Administration Advisory Committee to Consider Aramite, 1955, p. 6.

Food Standard Committee, Ministry of Food: Report on Coloring Matters, H. M. Stationery Office, London, 1954, p. 27.

Foulds, L.: The Experimental Study of Tumor Progression: A Review, Cancer Res. 14:327-351, 1954.

Fukui, K.; Nagata, G., and Yonezawa, T.: On the Analogy Between Carcinogenic Compounds in the Mechanism of Their Biological Actions, Gann 49:43-48, 1958.

Gamble, C. L.: An Improved Test of Spermicidal Activity Without Dilution or Mixing, J.A.M.A. 152:1037-1041, 1953.

Gardner, W. U., and Boddaert, J.: Testicular Interstitial Cell Tumors in Hybrid Mice Given Tri-*p*-Anisyl Chloroethylene, Arch. Path. 50: 750-764, 1950.

Gillman, J.; Gillman, T., and Gilbert, C.: Reticulosis and Reticulum Cell Tumours of the Liver Produced in Rats by Trypan Blue with Reference to Hepatic Necrosis and Fibrosis, South African J.M. Sc. 14:21-83, 1949.

Goldblatt, E. R. A., and Goldblatt, J.: Industrial Carcinogenesis and Toxicology, in Merewether, E. R. A.: Industrial Medicine and Hygiene, Vol. 3, London, Butterworth & Co., Ltd., 1956, p. 185-562.

Gorelova, N. D.; Dikun, P. P., and Lapshin, I. I.: 3,4-Benzopyrene in Liquids Used to Produce Smoked Foodstuffs, Vop. Onkol. 5:341-346, 1959.

Goulden, F.; Kennaway, E. L., and Urquhart, M. E.: Arsenic in the Suspended Matter of Town Air, Brit. J. Cancer 6:1-7, 1952.

Green, M.: Gynecomastia and Pseudoprecocious Puberty Following Diethylstilbestrol Exposure, A.M.A. J. Dis. Child. 95:637, 1958.

Greenblatt, R. B., and Brown, N. H.: Storage of Estrogen in Human Fat After Estrogen Administration, Am. J. Obst. & Gynec. 63:1361, 1952.

Griepentrog, F.: Tumoren der Harnwege und Harnsteine in chronischen Versuchen mit dem Susesstoff *p*-Phenetylcarbamid, Arzneimittelforsch. 9:123-125, 1959.

Graffi, A.; Vlamynck, E.; Hoffmann, F., and Schulz, I.: Untersuchungen über die geschwulstauslösende Wirkung verschiedener chemischer Stoffe in der Kombination mit Crotonöl, Arch. Geschwulstforsch. 5:110-126, 1953.

Gross, E.: Über den Triphenylmethanfarbstoff Lichtgruen-SF als Sarkomerreger bei der Ratte, Arch. Exper. Path. u. Pharmak. 225: 175-179, 1955.

Colorants, les faits concernant les risques d'effects cancerigènes (Lebensmittelfarben), Acta Unio internat. contra cancrum 13:323-336, 1957.

Gruber, G. B.: Wege der Harnableitung mit Ausnahme der Harnroehre, in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1934, Vol. 6, Pt. 2, p. 320.

Gusberg, S. B.: Precursors of Corpus Carcinoma, Estrogens and Adenomatous Hyperplasia, Am. J. Obst. & Gynec. 54:905-1094, 1947.

Geyer, M. F., and Claus, P. E.: Effects of Urethane (Ethyl Carbamate) on Mitosis, Proc. Soc. Exper. Biol. & Med. 64:3-5, 1947.

Habel, J. M.: Indiscriminate Use of Estrogens in Menopause, Virginia M. Monthly 75:517-521, 1948.

Hackmann, C.: Untersuchungen über die cancerogene Wirkung einiger fettlöslicher Azofarbstoffe, Ztschr. Krebsforsch. 57:530-541, 1951.

Haddow, A., and Horning, E. S.: On the Carcinogenicity of an Iron-Dextran Complex, J. Nat. Cancer Inst. 24:109-147, 1960.

Haley, J., and Stolarsky, Fr.: A Study of the Acute and Chronic Toxicity of Toluidine Blue and Related Phenazine and Thiazine Dyes, Stanford M. Bull. 9:96-100, 1951.

Hard[illegible] B. L.: Carbon Tetrachloride Poisoning: [illegible]view, Indust. Med. 23:93-105, 1954.

Ha[illegible], P. N.: Production of Sarcoma in Rats with Light Green SF, Cancer Res. 7:35-36, 1947.

Hartwell, J. L.: Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Ed 2, Public Health Service Publ. No. 149, U.S. Govt. Printing Office, Washington, D.C., 1951, p. 583.

Hayes, W. J., Jr.; Durham, W. F., and Cueto, C., Jr.: The Effect of Known Repeated Oral Doses of Chlorosphenothane (DDT) in Man, J.A.M.A. 162:890-897, 1956.

Hecht, G.: Toxikologische Daten von Farbstoffen und ihre Zulassung fuer Lebensmittel in verschiedenen Laendern, Mitteilung 6, Deutsche Forschungsgemeinsch. 1955, p. 119.

——and Wingler, A.: Die biologische Untersuchung und der geeignete chemische Aufbau einiger Azofarbstoffe zur Lebensmittelfaerbung, Arzneimittel-forsch. 2:192-196, 1952.

Henry, E. A.; Kennaway, N. M., and Kennaway, E. L.: Incidence of Cancer of the Bladder and Prostate in Certain Occupations, J. Hyg. 31: 125-137, 1931.

Hess, H.: Arseninhalation und Bronchialcarcinom bei Winzern, Arch. klin. Chir. 283:274-279, 1956.

Hieger, I.: Chemical Carcinogenesis: A Review, Brit. J. Indust. Med. 1:1-23, 1949.

The Carcinogenic Activity of Preparations Rich in Cholesterol, Acta Unio internat. contra cancrum. 6:27-33, 1948.

Carcinogenic Substances in Human Tissues, Brit. M. Bull. 4:360-363, 1947.

Carcinogenic Activity of Lipoid Substances, Brit. J. Cancer 3:123-139, 1949.

——and Orr, S. F. D.: On the Carcinogenic Activity of Purified Cholesterol, Brit. J. Cancer 8:274-290, 1954.

Hill, B. A., and Faning, E. L.: Mortality Experience in the Factory: Cancer from Inorganic Arsenic Compounds, Brit. J. Indust. Med. 5: 2-6, 1948.

Hoch-Ligeti, C.: Production of Liver Tumours by Dietary Means: Effect of Feeding Chillies (Capsicum Frutescens and Annum Linn.) to Rats, Acta Unio internat. contra cancrum 7:606-611, 1951.

Effects of Spermicidal Contraceptives on the Uterus of Rats, Proc. Am. A. Cancer Res. 2:118, 1956.

Effect of Prolonged Administration of Spermicidal Contraceptives on Rats Kept on a Low-Protein or a Full Diet, J. Nat. Cancer Inst. 19:661-686, 1957.

Holland, H.; Wilson, R. H.; Acevedo, A. R.; McCall, M. S.; Clark, D. A., and Lanz, H. C.: The Cigarette Smoke-Arsenic-Cancer of the Lung Problem, Acta Unio internat. contra cancrum 15:608-611, 1959.

Hollis, M. D.: Toxicological Aspects of Using Hexadecanol and Dodecanol on Reservoirs, Newsletter, Office of Engineering Resources for Engineering Chief Professional Officer, Jan. 15, 1958, p. 2.

Horton, A. W., and Denman, D. T.: Carcinogenesis of the Skin: A Reexamination of Methods for the Quantitative Measurements of the Potencies of Complex Materials, Cancer Res. 15:701-709, 1955.

——Denman, D. T., and Trosset, R. P.: Carcinogenesis of the Skin: II. The Accelerating Properties of Aliphatic and Related Hydrocarbons, Cancer Res. 17:758-766, 1957.

Holoubek, J. E.; Hendrick, J. V., and Hollis, W. J.: Toluidine Blue in Bleeding Associated with Thrombopenia, J.A.M.A. 139:214-216, 1949.

Hueper, W. C.: Studies on Growth Factors of Embryo Extract, Am. J. Cancer 17:74-105, 1933.

Occupational Tumours and Allied Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 897.

Carcinogenic Studies on Isopropyl-*N*-Phenyl-Carbamate, Indust. Med. & Surg. 21:71-74, 1952.

Environmental Cancer: A Review, Cancer Res. 12:691-697, 1952.

Recent Developments in Environmental Cancer, A.M.A. Arch. Path. 58:360-399, 474-523, 645-682, 1954.

——and Ruchhoft, C. C.: Carcinogenic Studies on Adsorbates of Industrially Polluted Raw and Finished Water Supplies, A.M.A. Arch. Indust. Hyg. 9:488-495, 1954.

Hueper, W. C.: Considerations for the Selection of Chemicals for Carcinogenic Screening, A.M.A. Arch. Indust. Health. 11:494-504, 1955.

Potential Role of Non-Nutritive Food Additives and Contaminants as Environmental Carcinogens, A.M.A. Arch Path. 62:218-249, 1956.

Carcinogenic Studies on Water-Soluble and Insoluble Macromolecules, A.M.A. Arch. Path. 67:589-617, 1959.

Hueper, W. C.: Über die histologischen Veraenderungen im menschlichen Gewebe nach Injektion von Paraffin, Frankfurt. Ztschr. Path. 29:268-286, 1923.

Experimental Studies on Potential Carcinogenic Effects by Foodstuffs Exposed to Ionizing Radiation, in Proceedings of the Contractors' Annual Meeting on Radiation Preservation of Foods Project 1957, p. 38-42.

Experimental Carcinogenic Studies in Macromolecular Chemicals: I. Neoplastic Reactions in Rats and Mice Following Parenteral Introduction of Polyvinyl Pyrrolidone, Cancer 10:8-18, 1957.

Berufskrebse, in Handbuch der gesamten Arbeitsmedizin, edited by E. Baader, Urban & Schwarzenberg, Munich, Vol. 2, to be published.

——and Itami, S.: Effects of Neoarsphenamine on Spontaneous Breast Tumours of Mice, Am. J. Cancer 17:106-113, 1933.

Hughes, J. P.: Hazardous Exposure to Some So-Called Safe Solvents, J.A.M.A. 156:234-237, 1954.

Jaffé, W. G., and Jaffé, R.: Carcinogenic Action of Ethyl Carbamate on Rats, Including Histological Findings in Lungs and Livers, Cancer Res. 7:107-112, 1947.

Jardetzky, O.; Visscher, M. D., and King, J. T.: Effects of Fractionation of Dietary Fat on the Incidence of Hepatomas in C3H Male Mice, Proc. Am. A. Cancer Res. 1:22-23, 1954.

Jull, J. W.: Effects of Oestrogens and Progesterone on Chemical Induction of Mammary Cancer in Mice of IF Strain, J. Path. & Bact. 68:547-559, 1954.

Jüptner, W.: Estrogenic Substance During Menopause, Med. Klin. 46:1-32, 1951.

Katzenellenbogen, I.: A Dermato-Endocrinological Syndrome and Problems Connected with the Production and Use of Stilboestrol, Harefuah 50:239, 1956.

Kinosita, R.: Studies on the Carcinogenic Chemical Substances, Tr. Soc. path. jap. 27:665-725, 1937.

Kirby, A. H. M.: Biological Tests with Cholesterol Esters of Unsaturated Acids, Brit. J. Cancer 2:70-74, 1948.

The Effects of (*a*) a Residue of Cholesterol Heated to 300 C and (*b*) 3,5-Cholestadiene, Cancer Res. 4:94-97, 1944.

——and Peacock, P. R.: Liver Tumours in Mice Injected with Commercial Food Dyes, Glasgow M.J. 30:364-372, 1949.

Klavis, G.: Kasuistischer Beitrag zur Frage der Ausfallserscheinungen bei Arbeiten mit Stilboestrol, Zentralbl. Arbeitsmed. u. Arbeitsschutz 4:46, 1954.

Kloprain, L, and Bartini, B.: Intoxication by Diethylstilboestrol of Workers in a Pharmaceutical Factory, Members of the Families and a Poulterer. Harefuah 51:57, 1956.

Klein, M.: The Transplacental Effect of Urethan on Lung Tumorigenesis in Mice, J. Nat. Cancer Inst. 12:1003-1010, 1952.

Kotin, P., and Falk, H. L.: Production of Skin Tumors in Mice with Oxidation Products of Aliphatic Hydrocarbons, Cancer 9:905-909, 1956.

——Experimentally Weak Carcinogens, Cancer Res. 18:1-3, 1958.

Kuratsune, M.: Benzo(*a*)Pyrene Content of Certain Pyrogenic Materials, J. Nat. Cancer Inst. 16:1485-1496, 1956.

——and Hueper, W. C.: Polycyclic Aromatic Hydrocarbons in Coffee Soots, J. Nat. Cancer Inst. 20:37-51, 1958.

Lamb, J. H., and Lain, E. S.: Occurrence of Contact Dermatitis from Oil Soluble Gasoline Dyes, J. Invest. Dermat. 17:141-146, 1951.

Lane, A.; Blickenstaff, D., and Ivy, A. C.: The Carcinogenicity of Fat "Browned" by Heating, Cancer 3:1044-1051, 1950.

Larrick, G. P.: Tolerances and Exemptions from Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities (Aramite), Fed. Reg. 20:4593, 1955; 20:1177, 1955.

Larsen, C. D.: Pulmonary-Tumor Induction by Transplacental Exposure t Urethane, J. Nat. Cancer Inst. 8:63-70, 1947.

Laug, E. P.; Kunze, F. M., and Prickett, C. S.: Occurrence of DDT in Human Fat and Milk, Arch. Indust. Hyg. 3:245-246, 1951.

Laug, E. P.; Nelson, A. A.; Fitzhugh, O. G., and Kunze, F. M.: Liver Cell Alteration and DDT Storage in the Fat of the Rat Induced by Dietary Levels of 1 to 50 P.P.M. DDT, J. Pharmacol. & Exper. Therap. 98:268-273, 1950.

Lettré, H., and Wrba, H.: Die Wirkung des Süsstoffes Dulcin bei Langdauernder Fütterung, Naturwissenschaft 42:217-218, 1955.

iebegott, G.: Pathologische Anatomie der chronischen Arsenvergiftung, Deutsche med. Wchnschr. 74:855-856, 1949.

.orenz, E., and Stewart, H. C.: Tumors of Alimentary Tract Induced in Mice by Feeding Olive Oil Emulsions Containing Carcinogenic Hydrocarbons, J. Nat. Cancer Inst. 7:227-238, 1947.

.usky, L. M., and Nelson, A. A.: Fibrosarcomas Induced by Multiple Subcutaneous Injections of Carboxymethyl Cellulose (CMC), Polyvinylpyrrolidone (PVP), and Polyoxyethylene Sorbitan Monostearate (Tween 60), Fed. Proc. 16:518, 1957.

Malmgren, R. A., and Saxen, E. A.: Studies of the Carcinogenic Effect of Urethan on Transplanted Lung Tissue in Strain A Mice, J. Nat. Cancer Inst. 14:411-421, 1953.

Marshall, A. H. E.: The Production of Tumors of the Reticular Tissue by Di-Azo Vital Dyes, Acta path. et microbiol. scandinav. 33:1-9, 1953.

Meigs, J.: Personal communication to the author, 1956.

Meissner, A., and Sommers, S. C.: Endometrial Hyperplasia and Carcinoma Produced by Estrogen, Am. J. Path. 31:571-572, 1955.

[illegible] V. F.; Escue, H. M.; Naryka, J. J.; [illegible]a, R. A., and Wheeler, E. P.: The [illegible]t Reported Cases of Human Bladder Tumors Due to a New Carcinogen-Xenylamine, J. Urol. 74:760-766, 1955.

Mellors, R. C.: Cancer, in Mellors, R. C.: Analytical Pathology, New York, McGraw-Hill Book Company, Inc., 1957, pp. 1-126.

Miller, W. C.; Proctor, B. E., and Goldblith, S. A.: Recent Developments in Radiation Sterilization of Foods, J. Milk & Food Technol. 17:161-163, 1954.

Miller, E. W., and Pybus, F. C.: Test for Carcinogenic Activity, Ann. Rep. Brit. Emp. Cancer Campgn, pp. 246-247, 1954.

Morris, H. P., and Eyestone, W. H.: Tumors of Liver and Urinary Bladder of Dog After Ingestion of 2-Acetylaminofluorene, J. Nat. Cancer Inst. 13:1139-1165, 1952.

Mostofi, F. K., and Larsen, C. D.: Carcinogenic and Toxic Effects of Urethane in Animals, Am. J. Clin. Path. 21:342-348, 1951.

Mostofi, F. K., and Larsen, C. D.: The Histopathogenesis of Pulmonary Tumors Induced in Strain A Mice by Urethan, J. Nat. Cancer Inst. 21:1187-1221, 1951.

Mühlbock, O.: Hormones and Carcinogenesis, Nederl. tijdschr. geneesk. 103:949-952, 1959.

Nagasawa, H. F., and Gutmann, H. R.: Acylation and Deacylation of Carcinogenic Fluorene Derivatives by Rat Tissue, Fed. Proc. 16:224, [illegible]

Nelson, A. A., and Woodard, G.: Tumors of the Urinary Bladder, Gall Bladder and Liver in Dogs Fed *o*-Aminoazaotoluene or *p*-Dimethylaminoazobenzene, J. Nat. Cancer Inst. 13: 1497-1905, 1953.

——and Hagan, E. C.: Production of Fibrosarcomas in Rats at Site of Subcutaneous Injection of Various Food Dyes, Fed. Proc. 12: 397-398, 1953.

——Fitzhugh, O. G.; Morris, H. J., and Calvery, H. O.: Neurofibroma of Rat Ears Produced by Prolonged Feeding of Crude Ergot, Cancer Res. 2:11-15, 1942.

——and Davidow, B.: Injection Site Fibrosarcoma Production in Rats by Food Colors, Fed. Proc. 16:367, 1957.

Nettleship, A., and Henshaw, P. S.: Induction of Pulmonary Tumors in Mice with Ethyl Carbamate (Urethane), J. Nat. Cancer Inst. 4: 309-319, 1943.

Neubauer, O.: Inorganic Arsenical Cancer, Brit. J. Cancer 1:192-251, 1947.

Nothdurft, H.: Über die Sarkomausloesung durch Fremdkoerperimplantation bei Ratten in Abhaengigkeit von der Form der Implantate, Naturwissenschaft 42:106, 1955.

Die experimentelle Erzeugung von Sarkomen bei Ratten und Maeusen durch Implantation von Rundscheiben aus Gold, Silber, Platin oder Elfenbein, Naturwissenschaft 42:75-76, 1955.

Experimentelle Sarkome durch reizlos einheilende Fremdkoerper, Krebsforsch. u. Krebsbek. 34:14-27, 1955.

Experimentelle Sarkomausloesung durch eingeheilte Fremdkoerper, Strahlentherapie 100:192-210, 1956.

Novak, E. R.: Relationship of Endometrial Hyperlasia and Adenocarcinoma of the Uterine Fundus, J.A.M.A. 154:217-220, 1954.

Oettel, H.: Gesundheitsgefaehrdung durch Kunststoffe, Arch. Exper. Path. u. Pharm. 232:77-132, 1958.

von Oettingen, W. F.: The Halogenated Aliphatic, Olefinic, Cyclic, Aromatic, and Aliphatic-Aromatic Hydrocarbons Including the Halogenated Insecticides: Their Toxicity and Potential Dangers, U.S. Dept. of Health, Education and Welfare, Public Health Service Publ. No. 414, Government Printing Office, Washington, D.C., 1955, p. 430.

Oppenheimer, B. S.; Oppenheimer, E. T.; Danishefsky, I.; Stout, A. P., and Errich, F. R.: Further Studies of Polymers as Carcinogenic Agents in Animals, Cancer Res. 15:333-340, 1955.

Orr, J. W.: The Induction of Pulmonary Adenomata in Mice by Urethane, Brit. J. Cancer 1: 311-322, 1947.

Oretega, P.; Hayes, N., Jr., Durham, W. H., and Mattson, A.: DDT in the Diet of the Rat, Public Health Monograph No. 43, Pub. Health Service Publication No. 484, Government Printing Office, Washington, D.C., 1956, p. 27.

Pagani, C.: Sindromi iperestriniche de origine esogenal osservazioni in lavoratori addetti alla sintesi di sostanze estrogene a quadri sperimentali sull-animale, Ann. di ostet. et ginecol. 75:1173, 1953.

Peacock, P. R.; Beck, S., Chalmers, J. G.: Gastric Cancer: Possible Dietary Carcinogens, J. Nat. Cancer Inst. 13:931-947, 1953.

——and Beck, S.: Investigations of Heated Cottonseed Oil as a Possible Dietary Carcinogen, Acta Unio internat. contra cancrum 7:612-614, 1951.

——and Kirby, A. H. M.: The Action of Carcinogenic Hydrocarbons on Stock Mice, Cancer Res. 4:88-93, 1944.

Peller, S.: Cancer in Man, New York, International Universities Press, Inc., 1952, Chap. II, p. 77.

Podilchak, M. D.: The Part Played by Chronic Inflammation in the Pathogenesis of Cancer of the Bladder, Urology 6:14-19, 1957.

Poel, W. E.: Effect of Carcinogenic Dosage and Duration of Exposure on Skin-Tumor Induction in Mice, J. Nat. Cancer Inst. 22:19-43, 1959.

Wax as Carcinogenic Factor, Query, J.A.M.A. 170:2148, 1959.

Purves, H. D., and Griesbach, W. E.: Studies on Experimental Goitre: VII. Thyroid Carcinomata in Rats Treated with Thiourea, Brit. J. Exper. Path. 27:294-297, 1946.

Studies on Experimental Goitre: VIII. Thyroid Tumors in Rats Treated with Thiourea, Brit. J. Exper. Path. 28:46-53, 1947.

Radomski, J. L., and Deichmann, W. B.: Cathartic Action and Metabolism of Certain Coal Tar Dyes, J. Pharmacol. & Exper. Therap. 118: 323-327, 1956.

Rarei, B., and Gummel, H.: Beeinflussung des Tumorwachstums durch 3,4-Benzpyren, insbesondere durch Cholestenonsulfosäure Benzpyrenlösung, Ztschr. Krebsforsch. 48:355-365, 1939.

Redgrove, H. S.: Carcinogenic Colouring Matters, Nature, London 145:672, 1940.

Reinl, W.: Über Erkrankungen bei der Verarbeitung von Kunststoffen auf der Basis der Polyurethane, Zentralbl. Arbeitsmed. u. Arbeitsschutz 3:103-107, 1953.

Remmaes, S., and Østberg, E. W.: Cancer Ventriculi Mortality in Different Population Groups: Cancer Ventriculi Mortality in Various Parts of Oslo 1930-1956, Brit. J. Cancer 9:7-20, 1955.

Richmond, H. G.: Induction of Sarcoma in the Rat by Iron-Dextran Complex, Brit. M.J. 1:947-949, 1959.

Riehm, H., and Stoll, P.: Korpuskarzinom nach 17 jähriger Follikelhormon-Medikation, Geburtsh. u. Frauenh. 12:985-992, 1952.

Rockstroh, H.: Zur Aetiologie des Bronchialkrebses in arsenverarbeitenden Nickelhuetten, Arch. Geschwulstforsch. 14:151-162, 1959.

Roe, F. J. C.: Oil of Sweet Orange: A Possible Role in Carcinogenesis, Brit. J. Cancer 13:92-93, 1959.

——and Salaman, M. H.: A Quantitative Study of the Power and Persistence of the Tumour-Initiating Effect of Ethyl Carbamate (Urethane) on Mouse Skin, Brit. J. Cancer 8:666-676, 1954.

Further Studies on Incomplete Carcinogenesis: Triethylene Melamine (T.E.M.), 1,2-Benzanthracene and β-Propiolactone, as Initiators of Skin Tumour Formation in the Mouse, Brit. J. Cancer 9:177-203, 1955.

The Carcinogenicity of Beta-Propiolactone for Mouse Skin, Brit. J. Cancer 10:357-362, 1956.

Roffo, A. H.: Tumeurs malignes developpées dans l'appareil digestif par l'ingestion des graisses oxydées par chauffage, Bull. Assoc. franç. cancer 28:556, 558, 1939.

Caracteres fisicoquimicos de la colesterina irradiada por el sol ultravioletas es sus relaciones can la etiologia del cancer, Bol. inst. med. exper. cancer 43:409-427, 1936.

Rose, E.: Sequels of Paraffin Injections, Beitr. klin. Chir. 134:244-264, 1925.

Roth, F.: Über die chronische Arsenvergiftung der Moselwinzer unter besonderer Berücksichtigung des Arsenkrebses, Ztschr. Krebsforsch. 61:287-319, 1956.

Rudali, G., and Mariani, P. L.: Sur la production de tumeurs du foie, chez la souris XVII Ivry, á l'aide du tétrachlorure de carbone, Compt. rend. Soc. biol. 144:1626, 1950.

Saffiotti, U., and Shubik, P.: The Effects of Low Concentrations of Carcinogen in Epidermal Carcinogenesis: A Comparison with Promoting Agents, J. Nat. Cancer Inst. 16:961-969, 1956.

Salaman, M. H., and Glenlenning, O. M.: Tumour Promotion in Mouse Skin by Sclerosing Agents, Brit. J. Cancer 11:434-444, 1957.

——and Roe, F. J. C.: Incomplete Carcinogens: Ethyl Carbamate (Urethane) as an Initiator of Skin Tumour Formation in the Mouse, Brit. J. Cancer 7:472-481, 1953.

Santé, L. R.: The Fate of Oil Droplets in the Lung and Their Possible Relationship to the Development of Bronchiogenic Carcinoma, Am. J. Roentgenol. 62:788-797, 1949.

Satterlee, H. S.: The Problem of Arsenic in American Cigarette Tobacco, New England J. Med. 254:1149-1154, 1956.

Scarff, R. W., and Smith, C. P.: Proliferative and Other Lesions in the Male Breast with Notes on 2 Cases of Proliferative Mastitis in Stilbestrol Workers, Brit. J. Surg. 29:393, 1942.

Schiller, W.: Rat Sarcoma Produced by the Injection of Light, Green, S. F., Am. J. Cancer 31:486-490, 1937.

Schmähl, D., and Reiter, A.: Prüfung von Räuchereiprodukten auf krebserzeugende Wirkung, Ztschr. Krebsforsch. 59:397-401, 1953.

Versuche zur Krebserzeugung mit flüssigem Paraffin, gelber Vaseline und Wollfett, Arzneimittel-forsch. 3:403-406, 1953.

Schmorl, S.: Paraffingranulome, München med. Wchnschr. 69:215, 1922.

Schoental, R., and Head, M. A.: Pathological Changes in Rats as a Result of Treatment with Monocrotaline, Brit. J. Cancer 9:229-237, 1955.

Schoental, R.: Liver Lesions in Young Rats Suckled by Mothers Treated with the Pyrrolizidine (Senecio) Alkaloids, Lasiocarpine and Retrorsine, J. Path. & Bact. 77:485-495, 1959.

Herbal Medicines and Disease, J. Trop. Pediat. 2:208-214, 1957.

[redacted]rkor-Like Syndrome and Other Pathological Changes in Rats as a Result of Feeding with Senecio Alkaloids (Isatidine), Voeding 16:268-285, 1955.

——Head, M. A., and Peacock, P. R.: Senecio Alkaloids: Primary Liver Tumours in Rats as a Result of Treatment with (1) A Mixture of Alkaloids from S. Jacobaea Lin.; (2) Retrorsine; (3) Isatidine, Brit. J. Cancer 8:458-465, 1954.

Setälä, K., and Ermala, P.: Chylomicrons as Carriers for Carcinogenic Hydrocarbons, Science 114:151-152, 1954.

——Setälä, H., and Holsti, P.: A New and Physicochemically Well-Defined Group of Tumor-Promoting (Cocarcinogenic) Agents for Mouse Skin, Science 120:1075-1076, 1954.

——Merenmies, L.; Stjernvall, L.; Aho, Y., and Kajarne, P.: Mechanisms of Experimental Tumorigenesis: I and II, J. Nat. Cancer Inst. 23:925-977, 1959.

Setälä, H.: Tumor Promoting and Co-Carcinogenic Effects of Some Non-Ionic Lipophylic-Hydrophylic (Surface-Active) Agents, Acta path. et microbiol. scandinav. (Suppl. 115):1-93, 1956.

Shabad, L. M., and Dikun, P. P.: Air Pollution with Carcinogenic Substances: 3,4-Benzopyrene, 1959, p. 239.

——and Natunova, L. P.: Investigation of Possible Blastomogenic Action of Certain Substances Inhibiting Sprouting of Vegetables in Storage, Vop. Pitan. 15:27-32, 1956.

Shay, H.; Harris, C., and Gruenstein, M.: Effect on Male Rats of the Gastric Instillation of Methylcholanthrene in "Heated" and "Unheated" Olive Oil, Cancer 4:988-993, 1951.

Shimkin, M. B.; Koe, B. K., and Zechmeister, L.: Instance of Occurrence of Carcinogenic Substances in Certain Barnacles, Science 113:650, 1951.

Shubik, P.: Personal communication to the author.

——and Sice, J.: Chemical Carcinogenesis as a Chronic Toxicity Test: A Review, Cancer Res. 16:728-742, 1956.

——and Della Porta, G.: Carcinogenesis and Acute Intoxication with Large Doses of Polycyclic Hydrocarbons, A.M.A. Arch. Path. 64:691-703, 1957.

Simpson, C. L.: Trypan Blue-Induced Tumours of Rats, Brit. J. Exper. Path. 33:524-528, 1952.

Sisley, P.; Poncher, C., and Panisset, L.: De l'Action des microbes sur quelques types de materiéres colorantes, Compt. rend. Acad. sc. 152:1794-1796, 1911.

——and Poncher, C.: Du Sort des materiéres colorantes dans l'organisme animal, Compt. rend. Acad. sc. 152:1062-1064, 1911.

Smith, M. I.: The Influence of Diet on the Chronic Toxicity of Selenium, Pub. Health Rep. 54:1441-1453, 1939.

Sommers, S. C., and McManus, R. G.: Multiple Arsenical Cancers of Skin and Internal Organs, Cancer 6:347-359, 1953.

Speert, H.: Corpus Cancer, Cancer 1:584-603, 1948.

Spitz, S.; Maguigan, W. H., and Dobriner, K.: The Carcinogenic Action of Benzidine, Cancer 3:789-804, 1950.

Sta. Cruz, J. Z.: Experimental Liver Cancer in Rats Produced by Butter Yellow, Philippine M.A.J. 24:1, 1948.

Sternberg, St. S.; Popper, H.; Oser, B. L., and Oser, M.: Gall Bladder and Bile Duct Adenocarcinoma in Dogs: Following Chronic Feeding of Aramite, Am. J. Path. 35:691-692, 1959; Cancer 13:780-789, 1960.

Steyn, D. G.: Poisoning of Human Beings and Animals by Senecio Plant Varieties, Farming in South Africa 1-11, 1941-1942.

Stoppelman, M. R. H., and van Valkenburg, R. A.: Pigmentaties en gynaecomastie ten gevolge van het gebruik van stilboestrol bevattend haarwater bij kindern, Nederl. tijdschr. geneesk. 99:3925, 1955.

Stokes, E. M.: Association of Estrogenic Administration and Adenocarcinoma of Endometrium, Western J. Surg. 56:494-497, 1948.

Straus, B.: Aplastic Anemia Following Exposure to Carbon Tetrachloride, J.A.M.A. 155:737-739, 1954.

Sugiura, K.: Observations on Rats Fed with Yellow AB, Proc. Soc. Exper. Biol. & Med. 61:301-302, 1946.

Sula, J., and Dobes, M.: Benzopyrene Fractions in Wood Smoke from Meat Smoking Chambers, Casop. lék. česk. 90:985-988, 1951.

Sulman, E., and Sulman, F.: The Carcinogenicity of Wood Soot from the Chimney of a Smoked Sausage Factory, Cancer Res. 6:366-367, 1946.

Symeonidis, A.: Poststarvation Gynecomastia and Its Relationship to Breast Cancer in Man, J. Nat. Cancer Inst. 11:656, 1950.

Tello, E. E.: Hidroarsenicismo cronico regional endemico (Hacre), Cordoba, Argentina, Imprenta de la Universidad Cordoba, 1951, p. 157.

Terp, A.: Estrogens in Development of Cancer of the Uterus, Ugeskr. Laeg. 112:1277-1310, 1950.

Torgersen, O., and Petersen, M.: The Epidemiology of Gastric Cancer in Oslo, Brit. J. Cancer 10:292-306, 1956.

Tromp, S. W.: The Geographical Distribution of Cancer of the Stomach in the Netherlands (Period 1946-1952), Brit. J. Cancer 10:265-291, 1956.

Truhaut, R.: Sur l'Action cancerigéne de certaines matiéres colorantes: Importance en hygiéne alimentaire, en thérapeutique et en hygiene générale, Ann. Pharm. Franç. 13: 1-40, 1955,

Umeda, M.: Experimental Study of Xanthene Dyes as Carcinogenic Agents, Gann 47:51-78, 1956.

Production of Rat Sarcoma by Injections of Tween 80 Solution of Scarlet Red, Gann 49: 27-31, 1958.

Valade, P.: Note au sujet de l'action cancérigène du goudron de bois, Bull. Assoc. franç. cancer 28:849-951, 1939.

Vasa, A.: Occurrence of Uterine Fundus Carcinoma After Prolonged Estrogen Therapy, Am. J. Obst. & Gynec. 58:748-751, 1949.

Voitelovich, E. A.; Dikun, P. P.; Dymarskii, L. U., and Shabad, L. M.: A Comparative Study of the Incidence of Malignant Tumours in the Tukum District of the Latvian SSR, Problems of Oncology 3:351-356, 1957.

Walpole, A. L.; Williams, M. H. C., and Roberts, D. C.: The Carcinogenic Action of 4-Aminodiphenyl and 3:2-Dimethyl-4-Aminodiphenyl, Brit. J. Indust. Med. 9:255-263, 1952.

Tumours of the Urinary Bladder in Dogs After Ingestion of 4-Aminodiphenyl, Brit. J. Indust. Med. 11:105-109, 1954.

——Roberts, D. C.; Rose, F. L.; Hendry, J. A., and Homer, R. F.: Cytotoxic Agents: IV. The Carcinogenic Actions of Some Monofunctional Ethyleneimine Derivatives, Brit. J. Pharmacol. 9:306-323, 1954.

Walz, W.: Beitrag zur Karzinomentstehung im Corpus uteri durch Überfollikulinisierung, Zentralbl. Gynäk. 74:1256-1264, 1952.

Watrous, R. M., and Olsen, R. T.: Diethylstilbestrol Absorption in Industry: A Test for Early Detection as an Aid in Prevention, Am. Indust. Hyg. A. Quart. 20:469-472, 1959.

Weinberg, J. A.; Greaney, E. M.; Rawlings, R., and Haley, T. J.: The Use and Toxicity of Pontamine Sky Blue, Science 114:41-42, 1951.

Willheim, R., and Ivy, A. C.: A Preliminary Study Concerning the Possibility of Dietary Carcinogenesis, Gastroenterology 23:1-19, 1953.

Wingler, A.: Über Farbstoffe zur Lebensmittelfärbung: Zur Frage der Krebsgefährdung, Ztschr. Krebsforsch. 59:134-135, 1953.

Wolf, G.: Chemical Induction of Cancer, Harvard University Press, Cambridge, Mass., 1952, p. 250.

Wright, A. D.: Cancer Scares, J.A.M.A. 162:832, 1956.

Wood, E. H.: An Unusual Case of Carcinoma of Both Lungs Associated with Lipoid Pneumonia, Radiology 40:193-195, 1943.

Willis, R. A.: Pathology of Tumours, Ed. 2, London, Butterworth & Co., Ltd., 1953, p. 472.

Williams, M. H. C.: Occupational Tumours of the Bladder, in Raven, R. W.: Cancer, Vol. 3, London, Butterworth & Co., Ltd., 1958, pp. 337-380.

Zeppa, R., and Womack, N. A.: Carcinoma of the Gallbladder: Attempt at Experimental Induction, Southern Med. J. 50:1267-1271, 1957.

Zeitlhofer, J.: Zur Frage der Häufigkeit und Form der primären Leberkrebse, Krebsarzt 6:154-160, 1951.