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Carcinogens in the Human Environment (To Be Concluded).
W. C. Hueper 237

Production of Arteriosclerosis in the Rat. H. Gold 268

Zinc Protection Against Cadmium Injury to Rat Testis.
S. A. Gunn et al. 274

Fluorescence Microscopy in Exfoliative Cytology.
W. Liu.
I. General Considerations 282
II. Application to Gynecologic Cytology 286

Typing of Bronchogenic Carcinoma. W. Umiker 295

Diphenylthiocarbazone Blindness in Dogs. J. M. Budinger 304

Prevention of Bone Marrow Heterografting.
C. C. Congdon and D. B. Duda 311

Adrenal Hypoplasia. P. G. Winquist 324

Intraglomerular Mitosis in Rat Nephritis.
R. B. Jennings and M. H. Haber 330

Congenital Adrenal Hypoplasia. N. Kerenyi 336

Cystic Lymphangiectasis of the Spleen.
J. A. Harshman et al. 344

Human Plasma Cohn Fractions and Mouse Tumor.
P. A. Herbut et al. 349

Books 354

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VOLUME 71
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NUMBER 3
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MARCH 1961

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INDEX MEDICUS

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Carcinogens in the Human Environment*

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

Despite the fact that the existence of environmental carcinogens has been known for about 175 years, professional interest and appreciation of these pathogenic products of the modern industrial economy and their increasingly important role as causal agents of human cancers have remained at a rather low level. Only during the last decade has the general public been made aware of the presence of carcinogens in the human environment through the widespread publicity which radioactive fallout and cigarette smoking have received as potential environmental cancer hazards. The general population has been alerted also to such possible dangers to health from industry-related sources and products by the attention which lately has been given in the public press to carcinogenic hazards from air pollutants and food additives and contaminants. Since the modern economy of all countries will be based to an increasing degree on the growth and diversification of industrial activities and the greater use of industrial products, undesirable and dangerous carcinogenic health hazards from such sources will assume considerable stature as public health problems which will demand comprehensive organized study and extensive preventive control measures.

I. Significance of Environmental Cancer Hazards

Environmental carcinogens, i.e., physical, chemical, and parasitic agents being constituents of the human environment, are practically the only recognized causes of cancer in man.

(*a*) A few of these agents have been for ages constituents of the natural environment, such as ultraviolet radiation of sunlight (especially active in areas with dry and sunny climate and causing skin cancer), radioactive contaminants of the air, water, and foodstuffs from natural sources, particularly in restricted areas with highly radioactive soil and rocks (such as a certain

Submitted for publication May 5, 1960.
National Cancer Institute.

*This article will be concluded in the April issue.

region in the "Ore Mountains," Germany, where the population is said to have a generally increased cancer incidence), arsenical pollutants of drinking water obtained from arsenic-containing soil or rocks (such as a region near Cordoba, Argentina, where an endemic type of arsenic cancer of the skin exists), and infections with Schistosoma hematobium (such as those observed in Egypt, Iraq, and South Africa and causing there an endemic occurrence of cancer of the bladder).

(*b*) A second group of environmental carcinogens is man-made, and also has been a part of the human environment for many years. Exposure to soot containing cancer-producing aromatic hydrocarbons has doubtlessly existed as long as man has used carbon-containing matter for heating his living quarters and for cooking his food or for smoking foodstuffs for preservative purposes. Age-old habits, such as chewing betelnut quids or khaini quids, indulged in by inhabitants of certain oriental population groups, or smoking tobacco products, also have created cancer hazards affecting especially the oral cavity and respiratory tract for many generations.

(*c*) Another group of man-made environmental carcinogens, however, of recent date, is constituted of a rapidly increasing number and variety of chemical and physical agents which are the products of the modern industrial development. These agents are by far the largest number of environmental carcinogens of the so-far-known environmental carcinogenic spectrum. These new industry-related carcinogens are, in part, highly potent agents. They are encountered in a considerable number of occupational activities, are ingredients or contaminants of consumer goods (foodstuffs, cosmetics, household goods, sanitary goods, medicines, etc.) and are pollutants of the general air, water, and soil (industrial wastes, residues of pesticides, radioactive fallout). Human exposure to these recognized environmental carcinogens occurs thus from various sources and at numerous opportunities. All these contacts to specific carcinogens as well as to all carcinogens add to the total carcinogenic load to which persons and population groups become subjected to different degrees and for various reasons (Table 1).

TABLE 1.—*Recognized Human Carcinogens, Their Origin and Distribution in the Human Environment, and Cancer Caused by Them* *

Arsenic

Sites of Arsenic Cancers.—Recognized: Skin, Lung, Liver; Suspected: Mouth, Esophagus, Larynx, Bladder

Exposure Stigmata.—Dermatosis, Neuritis, Arteritis, Gastroenteritis, Liver Cirrhosis; Laryngitis; Perforated Nasal Septum, Bronchitis, Anemia.

Compounds of Economic Importance (tri- and pentavalent).—Arsenic metal and alloys; ores of silver, gold, copper, tin, lead, cobalt, nickel, antimony iron (pyrite); realgar, orpiment arsenic acid, arsenions, arsenic trioxide, arsenic pentoxide, sodium arsenite, calcium arsenate, copper arsenate, lead arsenate, cupric acetoarsenite (Paris Green), cupric arsenite (Scheele's Green), Schweinfurt Green, London purple, Wolman's salt, arsine (Arseniuretted Hydrogen), arsanilic acid, cacodylates, arsphenamines, lewisite, etc., tryparsamide; carbarsone; arcetarsone (Stovarsol).

Operations and Products with Contact to Arsenic for Producers, Processers, Users, Consumers, Residents.—Copper alloy; lead shot; dust, fumes, mist, vapors in and around *metal ore smelters and refineries; dust and water draining off slag heaps* of mines and smelters; *water from arsenic-containing rock;* pigments in paints, ink, glazes, glass, soap, and dyes of textiles and paper; decolorizer of glass; mordant; *preservative of wood, pelts, furs, hides;* dehairing agent of pelts; *herbicide; pesticide* (cattle and sheep dip, grasshopper and mosquito bait, insecticide of potato beetle, Japanese beetle, cotton boll weevil, codling moth, gypsy moth); algicide; rodenticide; gas purification by Thylox process; war gases (lewisite, etc.) hair lotion; animal feed additive; *pharmaceuticals* (tonics, antianemic preparations, Fowler's solution, Donovan's pills, Asiatic pills, cacodylates, arsphenamines, caustic ointments, etc.).

* Table 1 continued thru page 27/249

Population Groups with Occupational and Environmental Exposure to Arsenic.—Occupational Groups: Airplane pilots, arsenic roasters, artificial flower makers, book binders, bronze workers, cannery workers peeling fruit treated with insecticides, citrus fruit orchard workers, cotton plantation workers, cut-glass workers, dyers, dyestuff makers, electroplaters, enamelers, *farmers, fur handlers and preparers,* galvanizers, gardeners, glass mixers, glass workers, glue manufacturers, gold refiners, ink manufacturers, *insecticide makers, insecticide sprayers and dusters,* japan makers, jewelers, lead factory workers, lead shot workers, linoleum color workers, lithographers, *miners of arsenic, copper,* zinc, silver, lead ores; oil cloth manufacturers, oil refinery workers, paper (colored) makers, paper glazers, paper hangers, paper printers, pelt and hair factory workers, pencil (colored) makers, pharmaceutical workers, photographers, poison bait makers, pottery decorators, pottery plant glaze dippers and mixers, printers, pyrites burners, rotogravure workers, rangers, rubber compounders, mordant mixers, rubber pressers, rubber tire manufacturers, sealing wax makers, seamstresses handling fabrics dyed or treated with arsenicals, *sheep dip manufacturers, smelter workers,* sulfur burners, sheep wool cutters, sulfuric acid workers, stevedores, tannery workers, taxidermists, textile printers, tinners, tobacco processers, velvet makers, *vinery workers, vineyard workers,* war gas manufacturers, weavers of yarns dyed with arsenical pigments, weed killer producers, wire drawers, wood preservers, wax goods manufacturers, zinc mixers, zinc smelter chargers, felt hat carroters, ferrosilicon workers.

Nonoccupational Groups: Residents in vicinity of metal smelters and of orchards, fields and woods dusted and sprayed with arsenical pesticides; *persons consuming drinking water and foodstuffs contaminated with arsenical algicide* and insecticide residues; persons smoking tobacco with arsenical residue and inhaling arsenical air pollutants from burnt coal; *veterans with war-gas poisoning; patients given prolonged treatments with arsenical preparations* (anemia, psoriasis, syphilis, trypanosomiasis, etc.); inhabitants of rooms with arsenic-containing wall paint or wallpaper.

Asbestos

Sites of Asbestos Cancers.—Recognized: Lung

Exposure Stigmata.—Chronic fibrosing pneumonia involving first lower lobes (asbestosis), asbestos bodies in sputum, asbestos warts of skin (fingers).

Compounds of Economic Importance	Operations and Products with Contact to Asbestos for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Asbestos
Chrysotile, Amphibole, Amosite, Crocidolite, Tremolite containing Magnesium, Aluminum, Calcium, Iron, Silica	Asbestos rock mining, loading, shipping, crushing, milling; *asbestos spinning, weaving,* mixing, cutting, pressing, molding, plastering, cementing. clothes, cloths, sheets, blankets, curtains, brake linings, yarns, cords, ropes, twines, ribbons, artificial snow, filler in rubber goods, plastics and roof coatings, filter cloths, filter pads, filter paper, artificial wood, tiles, shingles, card boards, wall boards, partitions, panels, paper, clutch facings, clapboard, pipe coverings, pipes, insulation blocks, insulation jackets, gaskets, pump packings, electric wire insulation, structural heat insulation, facings of acoustical building materials, catalyst supports in sulfuric acid production, putties	Occupational Groups: Asbestos rock miners, loaders, truckers, crushers, millers; *asbestos spinners, weavers;* electrical appliance and wire manufacturers, masons, carpenters, heating equipment workers, rubber workers, shingle and tile manufacturers, building material manufacturers, filtering material manufacturers, molders of asbestos products, asbestos-asphalt makers, putty manufacturers, asbestos cement makers, asbestos paper, cardboard, and *brake-lining producers, asbestos felt insulation workers,* asbestos sound insulation worker, asbestos insulator, pipe coverer, asbestos tube wrapper, asbestos cork insulation worker Nonoccupational Groups: Residents in vicinity of asbestos processing and textile mills inhaling plant effluents polluted with asbestos dust.

Chromium

Sites of Chromium Cancers.—Recognized: lung, nasal cavity; Suspected: stomach

Exposure Stigmata.—Dermatitis, cutaneous "chrome holes," ulcerated and perforated nasal septum, laryngitis, tracheitis, bronchitis, chronic fibrosing pneumonia, chronic gastritis, indolent intestinal ulcers

Compounds of Economic Importance (Di-, Tri- and Hexavalent).—Chromite ore, chromium metal, chromium alloys (iron, nickel, cobalt), chromium oxide, chromium trioxide, chromous chloride, chromic chloride, chromyl chloride, chromic nitrate, chromium oxychloride, chromium boride, chromium carbide, ammonium chromate, sodium chromate, potassium chromate, strontium chromate, calcium chromate, barium chromate, lead chromate, zinc chromate, sodium dichromate, potassium dichromate, chrome sulfate, chrome alum, ammonium chrome alum, potassium chrome alum, stearate chromium chloride, chromium acetate, chromic acid, ammonium dichromate, copper chromate, chrome hydroxide, chrome phosphate, chromite ore roast, chromate roast leached residue, stearatochromic chloride

Operations and Products with Contact to Chromium for Producers, Processers, Users, Consumers, Residents.—Mining, grinding, mixing, *chromate manufacture*, electrometallurgical chrome production, stainless steel manufacturing and processing industries, *production of chromium compounds* for tanning, photographic, paint, ink, textile, shingle, rubber, plastic, glass, petroleum, pyrotechnical, pottery, printing, wood preserving industries; electroplating plants, aviation-, railroad-, shipbuilding industries; dye manufacturing industry, chemical and pharmaceutical industries, explosive-manufacturing plants, match manufacturers, wax and wax-product industries; oil and fat industry; Fiberglas manufacturers and processers; cement industry; blue print industry; metal wares and machinery, electrical appliances, anti-corrosive and antirusting agent, polymerization catalyst, oil cracking catalyst, anticorrosive primer paint pigment, pigment in paints, inks, glass, plastics, rubber, shingles, linoleum; glazes, enamels, etc.; glass and pottery frosting and etching agent; chemical cleaning fluid; textile mordant; oxidizing agent in dye production, bleaching agent for fats and oils; leather tannery and finishing chemicals; dry battery chemicals; wood preservative and staining agents; Fiberglas coupling agent; corrosion retarder in refrigeration brines; in air washers, in cooling water of diesel engines, locomotives, automobiles, boilers; ingredient of match-heads, explosives, cements, water-repellent for fabrics, felt hats, glass fiber, drapes, paper.

Population Groups with Occupational and Environmental Exposure to Chromium.—Occupational Groups: abrasive makers, abrasive workers and polishers, airplane sprayers; bleachers, blue print makers, colored candle makers, cement manufacturers; chemical workers, *chromate and chrome pigment producers;* chrome platers; chrome-steel manufacturers and processers; chrome ore miners, loaders, shippers, grinders and mixers, chrome-alloy producers and processers, crayon makers, *dye manufacturers,* dock workers, electroplaters, electrometallurgical workers, enamelers, enamel makers; explosive manufacturers, Fiberglas producers and processers, furniture polishers, glass and pottery frosters, ink makers, linoleum workers, lithographers, match producers, mordanters, paint manufacturers, painters, metal cutters and welders, oil refinery workers, pyrotechnical workers, printers, paper dryers, paper waterproofers, photoengravers, photographic workers, pottery glaze makers, pottery glazers, refractory brick makers and masons, railroad engineers, rubber workers, plastic manufacturers, soap makers, stainless steel producers, processers, buffers and polishers, pyrotechnical workers, shingle manufacturers, leather finishers, tannery workers, textile printers and mordanters, textile waterproofers, wax ornament workers, welders, wood stainers and preservers, boiler scalers, dry battery makers, colored glass producers, fat bleachers

Nonoccupational Groups: Residents in vicinity of chromate plants, airplane manufacturing and maintenance establishments, railroad yards, shipping building plants, scrap metal smelters, oil refineries; home users of paints containing chrome pigments and of chromate-containing antirusting agents in steam heating plants; consumers of drinking water containing industrial wastes polluted with chromates and of fats bleached with sodium dichromate.

Nickel

Sites of Nickel Cancers.—Recognized: nasal cavity, paranasal sinuses, lung
Exposure Stigmata.—Dermatitis, nasal polyps, chemotoxic pneumonia

Compounds of Economic Importance (divalent, uni-, tri-, tetravalent)	Operations and Products with Contact to Nickel for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational & Environmental Exposure to Nickel
Nickel-Copper Matte Nickel Ore, Metallic Nickel Alloys (Copper, Iron, Chromium), Nickel Oxide, Nickel Sulfate, Nickel Sulfide, Nickel Nitrate Nickel Hydroxide, Nickel Chloride, Nickel Ammonium Sulfate, Nickel Carbonyl, Nickel Formate, Nickel Acetate, Nickel Carbonate, Nickel Naphthenate-, Oleate, Stearate, Nickel Ammine; Nickel Carbamate, Nickel Oxime, Nickel Ferrite	Nickel ore mining, shipping, loading, grinding, smelting, refining, nickel carbonyl production, metallic nickel production, Monel metal and stainless steel manufacture and processing, nickel alloy production and processing, nickel plating, powder metallurgy, anodizing aluminum, acrylic plastic production, hydrogenation of vegetable oils, hydrogenation catalysis in chemical industry and synthetic coal oil production, enamel and glaze production and application (ceramic industry), glass production, electronic industry, electrotype manufacture, German silver production, electric appliance industry, alkaline storage battery production, flash-coating of metal surfaces, textile mordant for stabilizing metallized dyes, nickel soaps as additives to crankcase oils, sealing agent for anodizing aluminum	Occupational Groups: Acrylic plastic producers, abrasive manufacturers, aluminum anodizers, ceramic glaze makers and glazers, coin makers, electroplaters, electronic appliance workers ("Fly-Back" transformers, dipolar antennae), enamelers, painters, paint manufacturers, German silver manufacturers and silversmiths, hydrogen manufacturers, Monel metal producers and processers, margarine manufacturers, glass producers, metal flash coat operators, nickel alloy (copper, silver, aluminum) producers and processers, nickel-chrome alloy workers, nickel extractors, nickel ore miners, loaders, shippers, grinders, and mixers, nickel smelter and refinery workers, nickel polishers and buffers, stainless steel workers and processers, nickel carbonyl manufacturers, powder metallurgy workers, oil refinery workers, storage battery manufacturers, textile dyers and workers, talc manufacturers Nonoccupational Groups: Users of nickel-containing kitchen utensils and tableware

Aromatic Amines

Sites of Aromatic Amino Cancers.—Recognized: bladder, ureter, renal pelvis; suspected: intestine, lung, liver, prostate.

Exposure Stigmata.—Excretion of aromatic amino compounds and their metabolites in urine, hematuria, often no symptoms of prodromal character.

Compounds of Economic Importance.—α-naphthylamine, β-naphthylamine, benzidine, xenylamine, auramine (magenta, phenetidine, chloronitroanilines, 4-nitrodiphenyl, *o*-tolidine, diphenylamine, naphthylamine aldehyde condensate, phenyl-α-naphthylamine, xenylamine antioxidant, yellow AB, yellow OB, α-naphthylamine thiourea, β-naphthalene-azo-β-naphthol, etc.), naphthol pitch (β-naphthylamine still coke), aminostilbenes, coal tar petroleum fuel additives (oxidation inhibitors).

Operations and Products with Contact to Aromatic Amines.—*Production, handling, loading, processing, using of these amines, cleaning of stills,* handling of *tars of stills, their use in lacquer production, repair and maintenance activities on equipment, emptying and disposal of barrels and containers, use in production of dyes and rubber antioxidants, production of rubber, rodenticides, pharmaceuticals, lipsticks, colored margarine, butter, baked goods, cheese crackers, etc., dyeing* and use of textiles and leathergoods with dyes with carcinogenic aromatic amine ingredients or impurities, red sky writing, rat catching, production and handling of security paper, use as reagents in tests for chlorine, and other inorganic ions and metals, for separation

of phenol mixtures, laboratory use in tests for occult blood and for folliculinization, in biologic stains, in quantitative and qualitative analysis for various metals, handling of coal tar, patent fuel and crude anthracene; stabilizer of carotenes, industrial chemical antioxidants; azo-dyes, di- and triphenylmethane dyes, etc., molding compositions, lacquers, detergent manufacturers using whiteners, manufacturers of gasoline and aviation fuel, gasoline dyes (Sudan IV, butter yellow).

Population Groups with Occupational and Environmental Exposure to Aromatic Amines—Occupational Groups: *Producers of dye and antioxidant intermediates, and of dyes and antioxidants,* pharmaceuticals, rodenticides, industrial and biologic laboratory reagents, cosmetics, butter, margarine, baked goods, *repair and maintenance men, truckers, yard men, workers employed in fume zone of aromatic amine operations, rubber manufacturers,* rat catchers, textile, plastic, chinaware dyers and printers, laboratory technicians, security paper manufacturers and processers, airplane pilots, chemical workers, coal tar, patent fuel and crude anthracene producers and handlers, painters, pharmaceutical workers, chemical workers, leather dyers, citrus fruit dyers, fur dyers and furriers; marmalade, jelly and candy makers; soft drink manufacturers, ink makers, photographic chemical manufacturers, pharmaceutical manufacturers, colored wax goods makers, lithographers.

Nonoccupational Groups: Residents in vicinity of aromatic amine production and consumption plants, rubber factories, users of foodstuffs and cosmetics dyed with colors containing carcinogenic aromatic amine impurities, patients treated with carcinogenic amino compounds (pyridium, *o*-tolidin, fuschin, auramine, light Green SF, brilliant Blue, etc.), users of rubber goods containing carcinogenic antioxidants, users of detergents with carcinogenic whitening agents of aromatic amine nature, of polishes with similar-colored ingredients, users of brightening and whitening agents in household detergents of aminostilbene nature, consumers of the sweetener Dulcin (*p*-phenetylurea) and of bladder analgesic, phenylazo-α-α-diaminopyridien monohydrochloride.

Benzol

Sites of Benzol Cancers.—Recognized: blood-forming tissues (leukemias; lymphosarcomas?)

Exposure Stigmata.—Anemia, leukopenia, aplasia of bone marrow; erythrocytosis, leukocytosis, leukemoid reactions, hyperplasia and maturation arrest in bone marrow, allergic agranulocytosis of benzol-containing drugs, purpura.

Compounds of Economic Importance.—Benzol, benzol derivatives with hematotoxic properties or producing allergenic dyscrasias of the blood-forming tissues (drugs).

Operations and Products with Contact to Benzol for Producers, Processers, Users, Consumers, Residents.—Coal tar production and refining, petroleum processing, paraffin extraction and refining, *production of rubber and rubber goods,* production and *use of paints, paint removers,* lacquers, rubber cements; bronzing, silvering, and gilding liquids; artificial leather, resins, styrene, dry-cleaning fluids, leather enamel, waterproof fabrics, linoleum, motor and aviation fuel, industrial solvents, plastics; extraction of bones, fats, and oils; cleaning of machinery (degreasing); manufacture of chlorinated, sulfonated, nitrated, oxidated, alkylated, hydrogenated, and dehydrogenated benzol derivatives; production of explosives, pharmaceuticals, antiknock chemicals, detergents, photographic chemicals; *rotogravure printing;* coke oven operation; petrochemical production.

Occupational Groups: Coke oven workers, coal tar refiners and users, petrochemical manufacturers, service personnel of automobiles and airplanes, solvent manufacturers, paint and paint remover producers, *painters,* degreasers, painters, rubber workers, *rubber cementers,* dry cleaners, linoleum and plastic manufacturers, makers of organic chemicals, explosives, pharmaceuticals, detergents, *rotogravure printers, varnish manufacturers,* paraffin and wax refiners; oil, fat, and bone extraction workers; airplane dope workers, alcohol workers, aniline workers, artglass workers, asbestos-product impregnators, dry battery makers, beauty parlor operators, belt scourers, benzol purifiers, brake lining makers, bronzers, burnishers, rubber gasket makers and sealers in can industry, carbolic acid makers, chemists, chlorodiphenyl workers; cyclohexan-, maleic anhydrid-, ethylbenzol-, aniline-, nylon-, styrene-, isopropylbenzol-, diphenyl manufacturers; clutch-disk impregnators, coal tar still cleaners, mordanters, nitrobenzol workers, nitrocellulose workers, pencil makers, perfume makers, pharmaceutical workers, phenol producers, photographic chemical manufacturers, picric acid makers, plastic textile makers, polish producers, polishers, pottery decorators, putty makers, cobblers, compositors, dye makers, enamelers, engravers, flavoring extract makers, glue manufacturers, ink makers, lithographers, metal

washers, millinery workers, mirror silverers, pyroxylin plastic makers, rubber buffers, cement mixers, compounders and dippers, rubberized asbestos board manufacturers, rubber pressroom workers, rubber reclaimers and treaders, shade cloth workers, shellackers, shellac makers, shoe factory makers, shoe finishers, wooden shoe heel coverers, smokeless powder makers; tar, pitch, and oil tank cleaners; textile fullers, tobacco seedling treaters, trinitrotoluol makers, type cleaners, varnishers, varnish makers, war gas makers, waterproof fabric makers, wax makers, welders, wire insulators, window shade makers.

Nonoccupational Groups: Home users of paints; of paint, lacquer, and varnish removers, spot removers, dry cleaning fluids, rubber cements, hematotoxic drugs, polishes.

Isopropyl Oil

Sites of Isopropyl Oil Cancers.—Recognized: paranasal sinuses, larynx, lung.

Exposure Stigmata.—None.

Compounds of Economic Importance	Operations and Products with Contact to Isopropyl Oil for Producers, Processers, Users, Consumers, and Residents	Population Groups with Occupational and Environmental Exposure to Isopropyl Oil
Crude isopropyl alcohol liquor	*Production of isopropyl alcohol*	Occupational groups: *producers of isopropyl alcohol*

Mustard Gas (Bis (2-Chloroethyl) Sulfide)

Sites of Mustard Gas Cancers.—Recognized: lung, larynx.

Exposure Stigmata.—Chronic chemical bronchitis, bronchiectases, emphysema, chemical pneumonia.

Population Groups with Occupational and Environmental Exposure to Mustard Gas

Compounds of Economic Importance.	Operations and Products with Contact to Mustard Gas for Producers, Processers, Users, Consumers, and Residents	Population Groups with Occupational and Environmental Exposure to Mustard Gas
β-β'-dichlorodiethyl sulfide or Yperite or Lost; and related nitrogen mustards (tris(2-chloroethyl)amine)	*Production of sulfur- and nitrogen-mustards*, filling of gas ammunition, transportation of gas ammunition, handling of gas ammunition	Occupational Groups: *producers*, loaders and shippers of mustard gas and gas ammunition; users and *recipients of gas ammunition*, especially *military personnel*, also medical personnel (physicians, nurses, etc.) Nonoccupational Groups: civilians of areas exposed to war gas

Anthracene

Sites of Anthracene Cancers.—Recognized: skin of hands, forearms, scrotum.

Exposure Stigmata.—Chronic dermatitis, photosensitivity, comedones, melanoderma with greenish tint, hyperkeratoses, warts.

Compounds of Economic Importance	Operations and Products with Contact to Anthracene for Producers, Processers, Users, Consumers, and Residents	Population Groups with Occupational Exposure to Anthracene
Paranaphthalene, Anthracene Oil Green Oil Carbolineum	Coke oven and gas house coal tar distillation, manufacture of alizarin dyes and anthraquinone, *purification of anthracene oil, anthracene cake, grease manufacture* wood preservative, briquette making, lubricant of wire rope, diesel fuel, paint, lubricant of clay molds for brick making, waterproofing of lumber, stabilizer of gasoline, insecticide, fungicide, protective coating against ultraviolet radiation, manufacture of synthetic tanning agents, ingredient of printing inks	Occupational Groups: *anthracene plant workers*, brick manufacturers, dye workers, *grease factory workers*, lumber picklers, diesel engineers, mechanics, chemical workers

Coal Tar and Pitch

Sites of Coal Tar Cancers.— Recognized: skin, scrotum, lip, larynx, lung; suspected: bladder.

Exposure Stigmata.—Chronic dermatitis, melanoderma, hyperkeratoses, warts, papillomas, photosensitivity, loss of smell.

Compounds of Economic Importance.—Coal tar, pitch, refined tars, topped tar, gas house tar, coke oven tar, blast furnace tar, coal tar grease, coal tar light oil, coal tar acid oil, tar bases, pitch coke, Bergius oil tar, coal tar naphthalenes.

Operations and Products with Contact to Coal Tar and Pitch for Producers, Processers, Users, Consumers, and Residents.— Production of tar and pitch in illuminating gas manufacture, coke ovens, blast furnaces, tar distillation, enamel and coatings of iron and steel surfaces, oil and gas pipes, slips, docks, locks, water pipes, tanks, pilings, etc. industrial fuel, foundry mold and core binders, target pitch for clay pigeons, carbon electrode pitch, *roofing and water proofing tars* and pitches (roofs, decks, reservoirs, bridges, tunnels, foundations, dams, retaining walls, laminated felt and fabric), *impregnation of paper conduits and fiber pipes* for electrical conduits and drainage purposes, *coal tar paint, impregnation of fish nets, caulking material for boats,* rubber softener, reclaimer, and compounding materials, pitch coke, roofing paper, *medicinal ointments,* cosmetic products (soaps, hair lotions) manufacture of chemicals, battery boxes, manufacture of tiles, linoleum, printing inks, rubber composition, varnishes, solvents, disinfectants, pesticides, ore flotation reagents (cresylic acid), heavy-duty cleaners, degreasing agents of engines and machinery parts, manufacture of resins, plasticizers, synthetic tanning chemicals, drugs, explosives, quinoline derivatives (8-hydroxyquinolines), pickling inhibitors, production of phthalic acids, dye intermediates, chlorinated naphthalenes, vehicle for insecticide sprays, silicon-carbide production, animal dips, *patent fuel, briquettes, cork stone manufacture, insulation tape.*

Population Groups with Occupational and Environmental Exposure to Coal Tar and Pitch.—Occupational Groups: Artificial stone markers, asbestos goods workers, asphalt workers, *battery (dry) workers,* brick layers, *corkstone makers, carpenters, brush makers,* cement makers (plastic), *coke oven workers, chimney sweepers, coal tar workers and refiners,* cordage factory workers, electrode makers, electrometallurgical workers, *fishermen, boat builders, flue cleaners and gas house workers,* insulators, painters, pavers, *pitch workers, lens grinders, road repairers, roofers, roofing paper and shingle makers, rope makers,* shipyard workers, soap makers, *paper conduit manufacturers,* insulation board makers, *still (coal tar) cleaners,* water proofers, wood preservers, electrical equipment manufacturers, electrician cobblers, brickyard workers, wood picklers, rubber workers, pipe manufacturers and layers, *briquette and patent fuel makers, stokers, smokeless fuel producers,* chemical workers, impregnated felt makers, tar paint manufacturers, *glass-blowers, pitch-breakers, -wheelers, -shovellers, -filers, -grinders; fuel stowers, hostlers, briquette tippers,* railroad stokers, weather-proof stone makers, water-proof concrete manufacturers, and users, electricians, electric appliance and cable manufacturers, *paper conduit manufacturers,* cosmetic workers, insecticide bomb manufacturers, farmers.

Nonoccupational Groups: Residents living near tarred roads, steel plants, gas houses, railroad yards, power houses using coal fuel; users of insecticide bombs containing methylated naphthalenes made from coal tar, *cosmetics, medicines.*

Creosote

Sites of Creosote Cancers.—Recognized: skin (hands, forearms, scrotum, face, neck, penis); Suspected: lung.

Exposure Stigmata.—Chronic dermatitis of hands, forearms, face, and neck, melanoderma, papules, hyperkeratoses, warts, telangiectases.

Compounds of Economic Importance	Operations and Products with Contact with Creosote for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Creosote
Wood and Peat Creosote Coal Creosote Creosote Oil Carbolineum	Distillation of wood, peat and coal, fractionation of blast furnace, coke oven and gas retort, coal tar, *creosoting lumber* (poles, pilings, boards, blocks, shingles, railroad	Occupational Groups: Distillers of wood, peat, coal tar; creosoters of lumber, telephone and electrical line workers, railroad track workers, carpenters, miners, farmers,

Middle Oil Heavy Oil	ties, mine props), diesel engine and industrial furnace fuels, *lubricant of brick molds,* tile and pipe molds, sheep dip, Lysol manufacture, skin and hair lotions, expectorants, tonics, emetics, germicides	brick, tile and pipe pressers, furnace men, diesel engine engineers, riveters, roofers, Lysol manufacturers Nonoccupational Groups: Consumers of medicinal preparations containing creosote, users of cosmetic preparations with creosote

Industrial, Commercial and Domestic Soots

Sites of Soot Cancers.—Recognized: skin, scrotum, lung.

Exposure Stigmata.—Chronic dermatitis, comedones, hyperkeratoses, warts, papillomas, bituminosis (anthracosis) of lung.

Compounds of Economic Importance	Operations and Products with Contact with Soots for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Soots
Soot, Carbon Black, Bone Black, Lamp Black, Oil Black, Incomplete Combustion Product of all kinds of carbonaceous matter, Acetylene Black, Furnace Black, Oil Furnace Black, Natural Gas Furnace Black, Channel Black	Industrial and *domestic furnaces* and power plants, ships, carbon black plants, oil field and oil refinery flares, smudge pots, coffee roasting plants, automobile and diesel engine exhausts, rubber manufacture, plastic-, paint-, ink-, black paper, carbon paper, and thermal dry cell manufacture; absorbent, explosive, phonograph record, shoe polish, confectionery, linoleum, leather coating, fertilizer, pesticide, colored concrete and grinding aid in cement industry, cosmetics, soot from railroad engines, incinerators, smoking and roasting of foodstuffs (meats, fish, coffee, etc.), dust from abraded automobile tires, coke ovens, smudge pots, curing of tobacco, charcoal broiling of meats and fish, printing, metal foundry, soot burning, charring of liquor casks, cosmetics, charcoal and turpentine making, lacquer	Occupational Groups: *Chimney sweeps,* cooks, meat and *fish smokers,* coffee roasters, *coke oven workers,* oil field and refinery workers, carbon black and other black manufacturers, soot burners, *furnace men,* garage employees, diesel truck drivers, bus drivers, taxi drivers, painters, ink and paint manufacturers, printers, rubber compounders, foundry workers, orchardists and farmers using smudge pots (burning used crank case oil and old rubber tires, etc.), tobacco farmers, railroad engineers and train personnel, roundhouse workers, eyebrow pencil manufacturers, plastic and explosive workers, carbon paper makers, lacquer and varnish manufacturers, farmers using diesel tractors, shoe polish manufacturers, linoleum and leather processers, liquid oxygen explosive makers, plastic manufacturers, concreters, plastic makers Nonoccupational Groups: Residents in areas near carbon black plants, railroad yards, harbors, oil refineries, power plants, along roads with heavy truck and automobile traffic (exhaust, rubber tire dust) roasting coffee or smoking and consuming smoked foodstuffs, drinking hard liquor aged in charred wooden caskets, or eating charcoal broiled and often burned meats or fish, using eyebrow pencils containing carbon black, operating home incinerators, smoking tobacco products especially those cured by fuel oil smoking, and holding burning end of cigars in the mouth (chutta), production of soot and tar in accidental burns of skin or in burns associated with use of kangri, kairo, or kang

Mineral Oils: Petroleum-, Shale-, and Lignite Oils, Greases, and Solvents

Sites of Cancer.—Recognized: skin, scrotum; suspected: larynx, lung.

Exposure Stigmata.—Chronic dermatitis, comedones, hyperkeratoses, warts, papillomas

Compounds of Economic Importance.—Crude petroleum oils, shale oils, lignite oils, Bergius hydrogenated coal oils, Fischer-Tropsch hydrogenated coal oils, crude thermo-cracked oils, crude steam-cracked oils, catalytically cracked oils, residual oils, industrial fuel oils, Bunker C fuel oils, home fuel oils, diesel oils, lubricating oils and greases, cooling and cutting oils, kerosene, light lubricating oils, gasoline, naphtha gas oil, petroleum spirits, engine distillate green oil, blue oil, polymerized and oxidized aliphatic and aromatic hydrocarbons and epoxides from volatilized gasoline exposed to ozonides, distilled and cracked native asphalts.

Operations and Products with Contact with Mineral Oils and Greases for Producers, Processers, Users, Consumers and Residents.—Production work in oil refineries, lignite oil-, shale oil-, Bergius oil-, and Fischer-Tropsch-oil *production plants* and their maintenance-, repair- and yard operations including pumping stations of pipe lines and trucking, furnaces of industrial and domestic oil power and heating plants, *textile* (cotton, wool, silk, synthetic fiber, asbestos) and *metallurgical factories,* greasing and *oiling of machinery,* degreasing of metal parts, *servicing of automobiles and trucks* and railroad cars and airplanes, repair work on such vehicles, production of rubber, ink, paint, carbon black, detergents, petrochemicals, plastics, linoleum; *oiling of roads, paving and repairing of roads, printing,* oiling of water surfaces in antimosquito work, spray painting, nebulizing and spraying of cutting oils and of pesticides with an oil or kerosene base, curing of tobacco leaves and servicing of smudge pots, production of medicinal and cosmetic preparations.

Population Groups with Occupational and Environmental Exposure to Mineral Oils.—Occupational Groups: *Workers in oil refineries, lignite oil and shale oil plants,* truckers, oil tanker employees, workers in oil storage facilities, oilers, garage men, *automobile service station employees,* painters, printers, insecticide sprayers, *textile workers,* rubber workers, *metallurgical workers,* machinists, *mechanics, gunsmiths, optical lens grinders, greasers,* oil furnace attendants, railroad engineers and roundhouse workers, ink, and paint manufacturers, road workers, carbon black producers, farmers and orchardists using smudge pots, tobacco farmers, repair and maintenance men in oil refineries, textile, metallurgical, and other plants, airplane pilots spraying insecticides or oil on water surfaces, detergent manufacturers, makers of medicines and cosmetics containing mineral oils.

Nonoccupational Groups: Residents of areas sprayed with insecticide mists, users of medicines (laxatives, ointments, sprays) and cosmetics (hair lotions, creams, etc.) containing mineral oils, consumers of drinking water polluted with mineral oil (naturally or artificially), or of foodstuffs from insecticide sprays, ship fuel oil dumped into bodies of water, home use of insecticide bombs, paint bombs, etc., urban population inhaling automobile and diesel engine exhaust containing noncombusted gasoline and oil.

Petroleum Asphalt, Bitumen, Tar, Coke, Pitch, Carbon: Lignite Tar, Shale Oil Tar, Synthetic Hydrogenated Coal, Bergius Oil Tars

Sites of Petroleum Asphalt Cancers.—Recognized: skin, scrotum; suspected: lung, larynx.

Exposure Stigmata.—Chronic dermatitis, melanoderma, hyperkeratoses, warts, papillomata.

Compounds of Economical Importance.—Petroleum distillation and cracking products, lignite and oil shale retorting products, hydrogenated coal, Bergius oil distillation products; bitumen, petroleum coke, petroleum carbon, petroleum pitch, blown asphalt, residual asphalt, sludge asphalt.

Operations and Products with Contact to Petroleum Asphalt and Petroleum-, Lignite-, and Shale-Oil Tars, Coke, and Pitch.—Petroleum refinery, shale oil refinery, lignite retorting plant, Bergius oil manufacturing plant, production and handling of asphalt paint, enamel, mastic, acid-resisting and water-proofing coatings, varnishes, acoustical compositions, acoustical and building and paving blocks, adhesives compositions for roofing, armature carbons and windings, fabrics, asbestos filler, artificial lumber, asbestos-cement panels, asbestos felt, calking compound, chewing gum, tiles, shingles, rubber, fuel, lacquers, disinfectants, floor coverings, medicine, paints, ointments, ornaments, pavements, pipe impregnating agents, paper impregnation, preservatives, sealing wax, stair treads, tree surgery compounds, vases, water-proofing agents, river bank protective coatings, *battery boxes,* brick sidings, road construction, roofing materials, casting molds, caving-bend protectives, cement, cork composition, dam-like and ditch protectives, depilatory, erosion preventive, fibrous roof coatings, pavement filler, carboids, concrete,

leather composition, mirror backing, mortar, putty, pipes, planks, felt impregnation, table tops, brake lining, clutch facings, cords, undercoating of automobile and railroad cars, insulating board, stucco, ropes, tubes, wall board, wrapping cloth, carpets, antifouling paint, briquette binder, foundry cores, electrodes, rubber ingredients, pipe coating, expansion joints, macadam material, japans, cattle sprays, burial vaults, dust laying material, phonograph records, friction elements, electrical appliances, knobs, insoles, pipe dips, plastics, rotogravure ink, shoe fillers, washers, frothing oils, linoleum tars, electrical insulation material.

Population Groups with Occupational and Environmental Exposure to Petroleum Asphalt and Petroleum-, Lignite-, and Shale-Oil Tars, Coke, and Pitch.—Occupational Groups: *Petroleum-, lignite- and shale-oil refinery workers*, truckers, painters, masons, carpenters, chemical workers, electrical workers, *electrometallurgical* workers, road construction workers, roofers, dam-dike-, levee-, revetment-, jetty-construction workers, felt-paper, shingle, and tile manufacturers, concrete workers, paper conduit manufacturers, pipe dippers, rubber workers, foundry workers, building material producers (blocks, felt, acoustical composition, wall boards, panels, fillers, calking compounds, cork), furnace attendants, tree surgeons, battery box manufacturers, artificial leather makers, automobile and railroad maintenance workers, *garage attendants*, pharmaceutical manufacturers, cosmetic manufacturers, farmers, *briquette makers* and users, brake lining manufacturers.

Nonoccupational Groups: Users of asphalt depilatories, shale oil tar ointments; residents near asphalted roads and high-traffic highways with dust from abraded rubber tires, and asphalt-petroleum tar oil coating, near oil refineries with effluents from catalytic cracking towers.

Paraffin and Petroleum Waxes

Sites of Paraffin or Wax Cancers.—Recognized: skin; suspected: lung stomach.

Exposure Stigmata.—Chronic dermatitis, wax boils, folliculitis, comedones, scleroderma, melanoderma, papules, warts, hyperkeratoses.

Compounds of Economic Importance.—Paraffins (crude, semirefined, fully refined), microcrystalline waxes, slop wax, slack wax, sweat wax, scale wax, tank-bottom wax, black wax, Foots oil, petrolatum (solid, jelly, liquid), synthetic Fischer-Tropsch hydrogenated coal waxes.

Operations and Products with Contact to Paraffins and Waxes for Producers, Processers, Users, Consumers, and Residents.—Wax pressing, extracting and refining, wax blending, oil refining, adhesive for laminating paper, filler of meshed fabrics, saturant of cotton braid and jute, coating of wires and cables, water- and rot-proofing of textiles, tarpaulins, polish for shoes, furniture, automobiles, floors, etc.; waterproofing of brick walls, luster cleaner, coating of fruit and vegetable preserves, waterproofing of cellophane, impregnation of wrapping and building paper, rayon fiber lubricant, impregnation of cartridges, desensitizer of explosives, histologic impregnation material, absorbent of neutrons, oiling of wool yarns, of eggs, and of plastic beads, ethyl cellulose coating of metal in Cottrell precipitrons, artificial fruits and flowers, barrel lining, beater size for various paper stocks, belting impregnation, beer can lining, binding agents, blasting supplies, bottle cap liner coatings, Brewers' pitch composition, candles, capsules, carbon paper, cheese coatings, chewing gum ingredient, collapsible tube lining, cosmetic creams, hair dressings, cosmetic baths, crayons, dehydrated food packages, deicing compound, dental waxes, dressings for mechanical belts, drinking-cup impregnation, egg preservatives, electrical insulation, field ration packages, heat-sealing compounds, lipsticks, meat coating, metal drum lining, mildewproofing, ointments, ordnance packing, paperboard cartons and drums, paper milk bottles, fruit and vegetable coatings, printing inks ingredient, radio parts, rain clothing, rubber compositions, rust preventatives, sealing and luting compounds, ship launching grease, leather stuffings, depilating wax, feather remover of fowl, dielectric paper, transfer and photographic papers, lithographic papers, nonabsorbent creped cellulose, impregnation for sanitary napkins, waterproofing of insulating boards, molds for photoengraving and electrotyping, roofing paper, shrouds for goods and machinery, mulch paper, soda straws, sound records, stop-off for glass etching, tank tar treatment for wine, etc., galvanized iron coating, glass fabric impregnation, grease typewriter ribbon, wax acid bottles, wax emulsions and sizings, wax figures and toys, match sticks, manufacture of chlorinated paraffins, potting compounds, cosmetic surgical material, cutting and cooling oils, laxative preparations, horticultural wax, lining of acid pipelines.

Population Groups with Occupational and Environmental Exposure to Paraffins and Waxes.

Occupational Groups: *Wax pressers, petroleum refinery workers*, producers, users processers of the various products listed, *lignite and oil shale distillation.*

Nonoccupational Groups: *Persons parenterally injected for medical or cosmetic reasons* with paraffin and waxes, habitual users of paraffin oil laxatives, cosmetics containing paraffins and waxes of impure grade, consumers of foodstuffs coated with paraffins or waxes and packaged in paraffinized containers, users of chewing gum containing waxes, etc.

Ionizing Radiations: X-Radiation, α-, β-, γ-Radiations

Sites of Ionizing Radiation Cancers.—Recognized: skin, subcutaneous tissue, bones, hematopoietic tissues, lung, liver, larynx, thyroid, kidney; suspected: breast, uterus.

Exposure Stigmata.—Chronic radiation dermatitis, radiation ulcer of skin, melanoderma, leukoderma, atrophic foci, hyperkeratoses, chronic periostitis, leukopenia and hyperleukocytosis, telangiectases, loss of hair.

Devices and Compounds of Economic Importance.—Cosmic radiation, Ionizing radiation from earth crust and in water of ponds, springs, etc. due to presence of radioactive compounds, natural radioactive elements and their compounds of uranium-, thorium-, and actinouranium-series; artificial radioactive substances, radioactive isotopes, cathode tubes, roentgen-tubes, television tubes, radar tubes, radio tubes, electron-guns, synchrotrons and related accelerators of particles.

Operations and Products with Contact to Ionizing Radiations for Producers, Processers, Users Consumers, and Residents.—Cathode-ray and x-ray tube and apparatus manufacture, x-ray diffraction apparatus, production and use of television and radar equipment, *roentgenology, radiology,* atomic energy production and laboratory operations, *radiophysics, operation of industrially used x-ray* and cobalt bomb, photographic equipment, sterilization of foods, drugs and surgical dressings with ionizing radiations, electrostatic eliminators, *fluoroscopes, luminescent paint on dials,* watches, etc., *diagnostic* and *therapeutic use of ionizing radiation, cosmetic depilation,* ionization devices, resistance devices, delay devices, identification devices, arc measuring devices, weighing devices, radioactive thickness gauges, radiography of castings, forgings, paintings, chicken eggs, and welds; medical and industrial use of radioisotopes, ionizing energy use for chemical reactions (polymerization, etc.) *Mining of radioactive ores* or other minerals present in radioactively contaminated ores (coal, *cobalt,* etc.), *uranium ore smelters, and refineries.*

Population Groups with Occupational and Environmental Exposure to Ionizing Radiation.—Occupational Groups: Atomic energy plant and laboratory workers, military personnel handling such devices as well as fission and fusion bombs, biologists, chemists, chemical workers, gas mantle manufacturers, laboratory technicians and attendants including cleaning personnel and persons handling laboratory wastes, *luminous dial painters,* handlers and shippers of scrap metal with luminous paint, repair personnel of such devices and handling them, nurses, pharmaceutical workers using radioactive isotopes and tracer substances, *physicists, physicians,* pathologists, morticians, operators of electrostatic eliminators and persons working in rooms where such devices are used, (textile-paper-printing plants), *radiologists, radium laboratory workers, radium refinery workers,* research workers using radioactive material, *roentgen and cathode tube manufacturers,* television and radar tube makers and operators, *roentgenologists,* beauticians, shoe salesmen, uranium dye workers, ceramic workers, glass manufacturers, tile glazers, *uranium ore miners, miners in radioactive mines, uranium* paint makers.

Nonoccupational Groups: Patients receiving ionizing radiation for diagnostic or therapeutic reasons, *persons exposed to x-rays for removal of hair,* or for fitting shoes, persons consuming foodstuffs contaminated with radioactive fallout or *inhaling such material or having skin contact,* persons bathing in radioactive water or drinking such water, residents near radioactive plants.

Ultraviolet Radiation

Sites of Ultraviolet Radiation Cancers.—Recognized: skin (basal-cell and squamous-cell ca.); suspected: melanocarcinoma.

Exposure Stigmata.—Chronic actinic dermatitis, melanoderma, leukoderma, hyperkeratoses, papillomas.

Sources of Economic Importance	Operations and Products with Contact to Ultraviolet Radiation for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Ultraviolet Radiation
Sunlight, Radiation from Welding Arc, Mercury Arc &	*Outdoor occupations especially in dry, sunny climates and at high altitude or on large bodies of*	Occupational Groups: Agricultural laborers, boatmen, cattle men, construction workers, oil operators,

Carbon Arc Ultraviolet Lamps (Flame Arc), Fluorescent Lamps.

reater reflecting solar ultraviolet radiation, welding, administration of ultraviolet radiation for cosmetic and medicinal purposes, exposure to intense radiation from fluorescent lamps.

pharmaceutical manufacturers of vitamin D preparations, railroad engineers, cowboys, *drivers of trucks* and buses, *farmers, fishermen, gardeners, herders,* house painters, lumbermen, miners of surface mines, masons, nurserymen, oilfield workers, railroad track workers, *ranchers, road workers,* rural mail carriers, *sailors,* sportsmen, stockmen, vineyard workers, welders, barbers, beauty-shop operators, lifeguards, policemen.

Nonoccupational Groups: Residents of *dry-sunny regions,* of mountainous areas, of ocean shore areas, golfers, sunbathers, water sportsmen, tennis players, persons receiving ultraviolet radiation treatments for cosmetic or medical reasons (skin diseases, tuberculosis, rickets, etc.).

A critical analysis of the distribution of these established human carcinogens in the general environment of man demonstrates a widespread exposure to such agents. While for most of these agents a conclusive proof of their cancer-producing action, and thus the existence of an actual cancer hazard from contact with these agents, is limited to occupational exposures, general experience with carcinogenic agents indicates that without any doubt, many of the nonoccupational exposures to the modern industrial carcinogens by the general population must constitute a cancer hazard, at present quantitatively undetermined, which in some persons causes or contributes to the causation of cancers.

The evidence on hand, when critically and competently evaluated, in fact strongly suggests that the majority of cancers affecting the following organs are attributable to exposures to environmental carcinogens: skin, mouth, paranasal sinuses, larynx, lung, esophagus, stomach, intestine, liver, blood-forming organs, bone, bladder, kidney and thyroid. The probable existence of similar causal relations can be suspected, moreover, for at least a part of the cancers affecting the brain, breast, and uterus.

The important role which environmental agents evidently play in the production of cancers receives weighty additional support from the following facts:

(*a*) Striking quantitative and qualitative differences which cannot be attributed to racial factors exist in the epidemiologic cancer panorama in different parts of the world. The general cancer panorama as to different organs affected and to incidence rates for various sites involved among inhabitants of countries of the Western World, for instance, differs fundamentally from that present among natives of Africa.

(*b*) Cancer incidence rates for males and females in different parts of the world show marked fluctuations, which in part can be traced to the influence of definite environmental factors active in only some but not all regions and population groups to different degrees upon the members of the 2 sexes.

(*c*) The recent changes in the incidence rates of several cancers, especially lung cancer, cannot be attributed to alterations in the biologic composition of the human population, i.e., endogenous factors, but must be related to rather recent and important changes in the quantitative and qualitative composition of the carcinogenic spectrum in most industrialized countries.

(*d*) Similar causal factors must underlie the observed higher frequency of cancers

of various organs among inhabitants of urban areas over that found among those of rural ones.

Educated guesses concerning the possible or probable causes of some of these observations are justified by applying the evidence existing on recognized human carcinogens to these developments. However, in most instances such tentative conclusions prove to be either insufficient or totally inadequate for providing satisfactory explanations for all aspects of the epidemiologic phenomena cited. It becomes quite obvious that additional environmental causal factors of so-far-unknown nature must be active in the production of human cancers and their epidemiologic fluctuations in different population groups and during various periods. It is likely that some such factors may be represented by the numerous chemical agents which were found capable of producing cancers in experimental animals and which have become an integral part of the human economy (Table 2).

TABLE 2.—*Potential Human Carcinogens, Their Origin and Distribution in the Human Environment, and the Cancers Caused by Them**

Aliphatic and Aromatic Epoxides

Sites of Epoxide Cancers.—Suspected: skin, lung, blood-forming tissues.

Compounds of Economic Importance	Operations and Products with Contact to Aliphatic and Aromatic Epoxides for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Aliphatic & Aromatic Epoxides
Aliphatic and aromatic epoxide monomers and polymers, Vinycyclohexene dioxide, Ethylene oxide, Propylene oxide	Production of aliphatic and aromatic epoxides and epoxide resins, plastics and polymers, atmospheric oxidation products of aliphatic and aromatic constituents of volatilized gasoline by ozone and ozonides, sterilization of instruments and dressings, food preservative, fumigant, polymerization products of ethylene oxide and propylene oxide used as lubricants, vehicles, solvents, binders, intermediates in production of rubber and in food, pharmaceutical, cosmetic, agricultural, textile, paper, petroleum and other industries: ointment bases for open dressings, vehicles in suppositories, carriers of drugs, (antibiotics, sulfonamides), cosmetic creams, lipsticks, hair dressings, assistants in rayon spinning, dispersants of dyes and lakes, sizing and finishing components of textiles, demulsifier of crude petroleum oil emulsions, selective solvents for aromatic fractions, additives to tin- and copper-plating baths, solutions for electropolishing aluminum, ingredients of buffing compounds, impregnation of electrical contacts, film former on silver conductors, intermediates of plastic and resin production, solubilizing and spreading agents in agricultural sprays, binders in detergent soaps, inter-	Occupational Groups: Worker groups producing, processing, using, handling the various items listed Nonoccupational Groups: Residents of urban areas inhaling volatilized gasoline oxidized and polymerized by ozone and ozonides formed by photochemical action of intense solar radiation; users of consumer goods containing epoxides (monomers or polymers).

* Table 2 continued thru page 37/259

mediates in antistaling agents of bread and stabilizers of ice cream, softeners of leather, intermediates of household detergents and dispersants of household cleaners coatings of drums, barrels, cans, structural plastics for castings, lamination of glass, encapsulation of electrical parts, aircraft parts, tanks, pipes, solder.

β-Propiolactone

Sites of β-Propiolactone Cancers.—Suspected: skin, connective tissue.

Compounds of Economic Importance	Operations and Products with Contact to Beta-Propiolactone for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to β-Propiolactone
Hydracrylic acid β-lactone hydrolyses under formation of polymeric acrylic ester acids	Production from formaldehyde and ketene, acrylic polymerization agent, chemical intermediate for propionic compounds, virucide for biologic products, air disinfectant.	Occupational Groups: Producers and industrial users of β-propiolactone, producers of virus vaccines (poliomyelitis, hydrophobia) and of human tissue implants, plasma; plastic manufacturers. Nonoccupational Groups: Recipients of biologic preparations sterilized with β-propiolactone, persons inhaling air sterilized with this virucide.

Carbamates

Sites of Carbamate Cancers.—Suspected: lung, hematopoietic organs.

Exposure Stigmata.—Leukopenia, transplacental penetration with effect on fetus(?)

Compounds of Economic Importance	Operations and Products with Contact to Carbamates for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Carbamates
Urethan (Ethyl Carbamate), Urethan aldehyde condensate, Thiourethans, Alkyl-*N*-phenyl carbamates, Isopropyl-*N*-(chlorophenyl) carbamate, Polyurethans	Production of urea from ammonium carbamate, production of carbamates and polyurethan plastics, fungicides, weed killers, insecticides, insecticide repellents, snailicides, sedative for fish, rubber vulcanizers, accelerators, plastic stabilizers, antioxidants, diesel fuel additives, corrosion inhibitors, selective solvent of chemicals and drugs, surface active agents, resins, plastics, adhesives, rubber (solid and foam), water-resistant textile, bristles, fibers, casting and potting compounds, coating materials for wire, glass, wood, metals, etc., plasticisers, hypnotic, sedative, anesthetic, antispasmodic, anticonvulsive, antileukemic, antipyretic, diuretic, antiseptic, anthelmintic, enzyme inhibitor, miotic, trypanocidal, ingredient of quinine sclerosing agent, ingredient of cosmetic astringent, latent flavor developer in packaged food, dye intermediate, ingredient of nonluminous candles.	Occupational Groups: Producers of carbamates and urea, farmers, railroad track workers, employees of fish nurseries, road workers, pharmaceutical manufacturers, rubber and plastic manufacturers, dye workers, cosmetic workers. Nonoccupational Groups: Persons treated with carbamate medicinal preparations and possibly the offspring of pregnant women given such preparations; residents of areas in which carbamate pesticides are dusted or sprayed; users of cosmetics containing urethan; consumers of foodstuffs containing carbamates as latent flavor developers.

Chlorinated Hydrocarbons: Carbon Tetrachloride, Chloroform, DDT, Aramite, Chlorinated Naphthalenes

Sites of Chlorinated Hydrocarbon Cancers.—Suspected: liver, lung, skin.

Exposure Stigmata.—Jaundice, liver degeneration and cirrhosis, dermatitis.

Compounds of Economic Importance	Operations and Products with Contact to Chlorinated Hydrocarbons for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Chlorinated Hydrocarbons
Carbon tetrachloride-tetrachlormethane, Chloroform-trichlormethane DDT-dichlorodiphenyltrichloroethane; Aramite-2-(tert-butylphenoxy)-isopropyl-2-chloroethyl sulfite Chlorinated Naphthalenes (Halowaxes)	Carbon Tetrachloride-Chloroform: Manufacture of chlorinated hydrocarbons, of benzophenone and carbon disulfide, dry cleaning agent, spot remover, paint remover, degreasing agent, organic solvent, extractant of fats and oils (fat waste, essential oils, alkaloids), solvent for gums, resins, waxes, and rubber, fumigant, fire extinguisher fluid, production of Freon refrigerants, hair shampoo preparations, anthelmintics, anesthetic, pharmaceuticals DDT-Aramite: Insecticide-miticide, livestock dip, moth repellent for woolens and furs, soil poisoner Chlorinated Naphthalenes: Solvents, plasticizers, crankcase oil additive, upper cylinder oil, cutting oil ingredients, contact insecticide, ovicide, soil poisoner, wood impregnating agent (for shuttles in weaving), impregnating of paper capacitors, wood preservative, sealing compounds, coatings, ingredients of fire-retarding paints	Occupational Groups: Workers producing, processing, using, and handling the various items listed. Nonoccupational Groups: Persons using carbon tetrachloride and chloroform as cleaners or as fire-extinguishing fluids at home or as paint removers; persons consuming foodstuffs containing DDT and Aramite as residues or inhaling such materials following spraying or dusting of these agents for reasons of personal sanitation or of pest control; persons using chlorinated naphthalenes around the house or around the farm as greases of machinery or as impregnation agent of lumber

Estrogens (Natural and Synthetic)

Sites of Estrogen Cancers.—Suspected: uterus, breast, prostate(?), blood-forming tissues, bladder(?).

Exposure Stigmata.—Glandular endometrial hyperplasia, gynecomastia, feminizing symptoms in the male, cirrhosis of liver(?).

Compounds of Economic Importance	Operations and Products with Contact to Estrogens for Producers, Processers, Users, Consumers and Residents	Population Groups with Occupational and Environmental Exposure to Estrogens
Estradiol, Estrone, Estriol, Equilin, *d*-Equilin, Diethylstilbestrol, Hexestrol, etc.	Production of estrogenic chemicals, manufacture of estrogenic preparations for medicinal, cosmetic, and agricultural uses, handling of estrogenic animal feed and implantation of estrogenic pellets into fowl, cosmetic lotions and creams.	Occupational Groups: Chemical and pharmaceutical manufacturers of estrogens, producers of estrogenic cosmetic preparations, farmers using estrogens in feeds; for the chemical caponization for fowl and for the artificial induction of lactation in dairy stock and for stimulation production of eggs. Nonoccupational Groups: Infants and adults receiving estrogenic treatment for a great variety of ailments (menopausal

		symptoms, hypogenitalism, dysmenorrhea, arrest of lactation, arteriosclerosis, carcinoma of the prostate and breast, gonorrhea of vagina in infants, etc.; users of estrogenic cosmetic preparations; consumers of meat from animals given estrogenic feed or estrogen implants.

Diethylene Glycol

Sites of Diethylene Glycol Cancers.—Suspected: bladder.

Compounds of Economic Importance	Operations and Products with Contact to Diethylene Glycol for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Diethylene Glycol
Diglycol, 2,2'-oxydiethanol,	Production of diethylene glycol and of derivatives (ethers), antifreeze, plasticizer of polyvinyl alcohol, solvent of phenolic resins, dyestuffs, and in toluene manufacture, textile fiber sizing and finishing agent, hygroscopic conditioner of synthetic fibers, coupling agent in lubrication, soaking, knitting and similar textile operations, humectant of tobacco in cigarettes, leak preventive applied to jute packing of gas mains, dehydrating and desulfurizing agent of natural gas, softener of glue, plasticizer of cork, resin binders, book binding adhesives, solvent in alkyd resins in steam-set inks, inhibitor in magnesium foundry sand mold mixes, additive of oils used for metal cutting, agricultural sprays and polishes, diluent of brake fluids.	Occupational Groups: Producers, processers, users of the various items listed. Nonoccupational Groups: Smokers of cigarette tobacco treated with diethylene glycol humectant.

8-Hydroxyquinoline

Sites of 8-Hydroxyquinoline Cancers.—Suspected: uterus, rectum, brain, bladder.

Compounds of Economic Importance	Operations and Products with Contact to 8-Hydroxyquinoline for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to 8-Hydroxyquinoline
8-oxyquinoline, 8-quinolinol, its copper and zinc chelate complex, its benzoate and sulfate and its iodochloro and diiodo compounds; phenyl-mercury-8-hydroxyquinoline	Production from quinolines in coal tar, its use in chemical analyses as a precipitant of metal ions (chelate former), as a stabilizer of hydrogen peroxide (employed as a bleaching agent in cosmetics as a rocket propellant), as an anticatalyst in chemical reactions, as a fungicide in ointments and powders (athlete's foot, Dutch Elm disease, textiles, paints, in adhesive of paraffinized milk containers), in fluoroscopic screens,	Occupational Groups: Manufacturers and industrial users of the various products, gardeners, military personnel, pharmaceutical manufacturers, cosmetic manufacturers, tobacco growers, food processers, chemical workers and chemists, fluorescent screen manufacturers, adhesive producers, chemists. Nonoccupational Groups: Users of cosmetics, rectal suppositories, contraceptives, fungicidal powders and

	in baby powders, as an amebacide, antiseptic, antiperspirant, deodorant, bactericidal agent in rectal suppositories and spermicidal agent in contraceptives, food preservative, fungicide for tobacco leaves, emulsion paints, separation reagent of beryllium from aluminum.	ointments, amebacidal drugs, baby powders, processed foods containing additives with 8-hydroxyquinoline or packaged in containers using this chemical in adhesive, smokers of tobacco treated with it.

Surfactants-Detergents

Sites of Surfactant Cancers.—Suspected: skin, lung, alimentary tract, bladder.

Compounds of Economic Importance	Operations and Products with Contact to Surfactants for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Surfactants
Dodecylbenzol derivatives, Polyoxyalkylene sorbitant alkylates (Tweens) (Tween 20-Tris (polyoxyethylene) sorbitan monolaurate) (Tween 80-Tris (polyoxyethylene) sorbitan monooleate) Polyoxyethylene (8)stearate	Production of dodecylbenzol petroleum or petroleum products (kerosene), production of detergents (household and industrial) from the basic chemicals, packaging and shipping and subsequent handling of detergent powders and liquids, for production of soap substitutes, soap additives, dentrifices, additives to lubricating oils, drycleaning liquids, ore flotation agents, rubber latex fabrication, as cleaners of metal surfaces (electroplating), degumming of silk and scouring of wool, as car washes, additive to foodstuffs.	Occupational Groups: Worker groups producing, processing, using, and handling the various items listed (petrochemical workers, detergent manufacturers, handlers, and shippers, manufacturers of soaps, dentrifices, lubricating oils, rubber latex, ore flotation materials; electroplaters, garage men, silk and wool manufacturers, bakers, processed food manufacturers, dry cleaners. Nonoccupational Groups: Users of certain household detergents and dinnerware contaminated with detergent residues, consumers of foodstuffs containing certain emulsifiers, fat substitutes, stabilizers, or dentrifices with such additives

Tannic Acid

Sites of Tannic Acid Cancers.—Suspected: liver

Exposure Stigmata.—Jaundice, liver necroses.

Compounds of Economic Importance	Operations and Products with Contact to Tannic Acid for Producers, Processers, Users, Consumers, Residents	Population Groups With Occupational and Environmental Exposure to Tannic Acid
Tannic acid, Tannin	Producers of tannic acid and tannin from vegetable products (tree bark, nut shells), leather tanning, slime depressant in ore flotation agent, cotton and rayon dye mordant, thinner of drilling mud, protein fiber curing agent, antioxidant, solutizer process for removal of mercaptans from gasoline, manufacture of water-repellent fabrics, pyrogallol manufacture, weighting of silk, fur dye, clarification agent of fruit juices, precipitant of gelatin, cosmetic astringent, astringent of mucous membranes (intestine) in diarrhea, cutaneous burn remedy, ingredient of red wine, tea, nuts, fruits, hop, etc.	Occupational Groups: Workers producing, processing, handling and using the various items listed Nonoccupational Groups: Patients with third-degree cutaneous burns treated with tannic acid preparations or taking orally tannic acid preparations for intestinal disorders with or without ulcerations, consumers of tannic acid-containing foodstuffs.

Thiourea, Thiouracil, Thioacetamide, Acetamide and Derivatives

Sites of Thiourea, etc. Cancers.—Suspected: liver, thyroid
Exposure Stigmata.—Hypothyroidism.

Compounds of Economic Importance	Operations and Products with Contact to Thiourea, Thiouracil, Thioacetamide, Acetamide for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Thioura, Thiouracil, Thioacetamide, Acetamide
Thiourea of Thiocarbamide, 2-Thiouracil, 6-Methyl-2-thiouracil, 6-Propyl-2-thiouracil, Thioacetamide, Acetamide or Ethanamide	Thiourea: Inhibitor of thyroid function (medicinal antithyroid agent), fungicide, accelerator of sprouting in dormant tubers, pesticide, flame proofing agent of nylon, weighting agent of silk, dye bath adjuvant of textiles, gold or sepia toning agent in photography, urea substitute in urea-formaldehyde resins, pickling inhibitor and ingredient in cleaning and plating of metals, preparation of nonglare mirrors, synthesis of sulfathiazole Thiouracil: Antithyroid agent Thioacetamide: Organic solvent in leather, textile, and paper industries, accelerator of vulcanizing of Buna rubber, stabilizer of motor fuel containing tetraethyl lead, combined with mercury a mordant of seed grain, solubilizer of riboflavin Acetamide: Solvent of organic and inorganic chemicals, soldering flux, dye solvent in textile industry, ingredient of urea molding compound, activator in bleaching liquor, wetting agent, accelerator in dyeing, raw product for pharmaceutical manufacture, nutrient for mold growth, humectant for paper, antiacid in lacquer, explosives, and cosmetics, plasticizer in leather, cloths, films, and coatings	Occupational Groups: Producers, processers, and users of these compounds in the different industries and occupations Nonoccupational Groups: Consumers of foodstuffs contaminated with these substances; persons receiving thiourea and thiouracil preparations for medical reasons

Thermic and Oxidation Products of Oils and Fats of Vegetable and Animal Derivation: Waxes and Greases

Sites of Vegetable and Animal Fat Cancers.—Suspected: lung, alimentary system, bladder

Compounds of Economic Importance	Operations and Products with Contact to Processed Oils and Fats to Producers, Processers, Users, Consumers, and Residents	Population Groups with Occupational and Environmental Exposure to Processed Vegetable and Animal Fats and Oils
Lard, Vegetable Oils and Fats, Shortenings, Candle Pitch, Bone Pitch, Rubber Pitch, Margarine Emulsifier, Glycerin Pitch, Wool Fat, Sperm Oil, Fish	Dairy products, margarine, salad dressing, shortenings, coatings, paint ingredients, varnishes, linoleum, inks, soaps, detergents, surface active agents, degreasing agents, emulsifiers, lubricants, plasticizers, refining and rendering of oils and fats, hydrogenation of oils and fats, deep-fat frying of fish, meat, baked goods, resin	Occupational Groups: Deep-fat-frying cooks (restaurants, "ready to eat" food industry), margarine manufacturers, processers and refiners of oils and fats, soap-, varnish-, ink-, linoleum-, paint-, detergent manufacturers, makers of shortenings and salad dressings Nonoccupational Groups: Domestic cooks, consumers of poly-

Oils, Polymerized & oxidized fatty acid emulsifiers and contaminants of heated fats & oils, or of chromic-acid-treated fats and oils (bleached), polyoxyethylene (8) stearic acid	production, core binders, japans, production of candle and soap stocks, refining of vegetable oils with alkalies, refining of refuse greases (packing house, grease, bone grease, garbage and sewage greases, woolen mill wastes), lacquers, lubricant for borings	merized and oxidized fatty acid products from deep-fat frying or as emulsifiers in margarine and salad dressings or shortenings; consumers of breads and rolls prepared with the emulsifier polyoxyethylene (8) stearic acid

Water-Insoluble Carbon and Silicon Macromolecular Polymers: Cellophane, Polyethylene, Polyvinyl Chloride, Polyacrylic Plastics, Polystyrene, Polyamides; Polyphenol-Formaldehyde Plastics, Polysilicones Polytetrafluoromethylene

Sites of Polymer Cancers.—Suspected: site of implantation and mucosal contact

Compounds of Economic Importance	Operations and Products with Contact to the Various Hydrophobic Carbon and Silicon Polymers for Producers, Processers, Users, Consumers, and Residents	Population Groups with Occupational and Environmental Exposure to Hydrophobic Carbon and Silicon Macromolecular Polymers
Monomers and polymers of the various polymers listed as well as their different copolymers and related polymers	Carbon Polymers: Production, processing, use and consumption films, packaging materials, impregnation of containers including food containers, bottles, tubes, flasks, boxes for foodstuffs, medicines, cosmetics, chemicals, lining of cans, barrels, etc., coating of textiles, paper, etc., sheets, plates, rods, tubing, pipes, structural material, glass substitute, water proofing, textiles, yarn, thread, optical goods, furniture, household and garden supplies, wax blends, electric appliances, leather substitute, rubber substitute, bristles, surgical prostheses, materials, sprays for mothballing of machinery and ships, etc., sausage skins, textile finishes, dental prostheses, cosmetic surgical implants	Occupational Groups: Workers engaged in production, processing, use, and consumption of items listed Nonoccupational Groups: Users of medical and dental protheses, of cosmetic surgical implants, of cosmetic, sanitary, and medicinal preparations containing these polymers as ingredients; persons using consumer and household goods containing these polymers
Methyl-ethyl- and phenylchloro-silicones and their polymers	Polysiloxanes: Water repellent, lubricants, anticaking and antifoaming agents, grease and oil repellents, polishes, rubber-, metal-, and plastic-mold cast releasing agents, slippage improvers for textiles, hydraulic fluids, waterproofing agents for leather, masonry impregnation agent, stopcock grease, filler for high-voltage conductor in aircraft, moisture-proof sealing compounds, resins, rubber, foam rubber, hand lotion ingredient, antifoam mist in treatment of pneumonia and pulmonary edema, ingredient of antibiotic paste, surgical prostheses	

Water-Soluble Carbon Macromolecular Polymers: Sodium Carboxymethyl Cellulose, Dextran, Polyvinyl Pyrrolidone, Polyvinyl Alcohol

Sites of Polymer Cancers.—Suspected: soft tissues around implants, lung, mucosal contact areas, organs and tissue of retention and deposition.

Compounds of Economic Importance.—Sodium carboxymethyl cellulose (NaCMC)-sodium cellulose glycolate (CMC); dextran; polyvinyl pyrrolidone (Periston, Plasmosan, Plasdone, Subtosan, Kollidon); polyvinyl alcohol, iodine polyvinyl pyrrolidone.

Operations and Products with Contact to Hydrophilic Carbon Polymers for Producers, Processers, Users, Consumers, and Residents.—Production and processing of monomers and polymers, packing and shipping, industrial use and application; *sodium carboxymethyl cellulose:* adhesive, detergent additive (soil antiredeposition agent), whitener retention agent in household detergents, filtration reducing agent in drilling mud, emulsifier of oils in water base drilling fluids, ingredient of printing paste for textiles, emulsion agent for paints, ceramics, creaming rubber latex; antistick compound, preparation of grease-proof paper, size of paper and textiles, filtration agent of uranium ores, paint thickener, thickener of polyvinyl acetate emulsions, nylon sizing, emulsifier and stabilizer of ice cream, cheese, thickener of foodstuffs.

Dextran: Plasma expander, size of paper and textile, thickener, adjunct to oil well drilling mud.

Polyvinyl Pyrrolidone: Hydrogen peroxide stabilizer, germicide for topical oral and intravenous use, plasma expander, adsorbent of toxins and dyes, hair lacquer, drug dispersant, retardant of drugs, suspending agent of cosmetics and foodstuffs, clearing agent of beer and fruit juices, copolymer of plastics, film former, substitute for shellac and other natural gums in lithography and printing processes, redeposition of soil preventive for household detergents,

Polyvinyl Alcohol: Ingredient of cosmetics, emulsifier and gelatin substitute in foodstuffs (ice cream), coating of candies and confectionery, medicated films, bacterial culture medium, adhesive, pharmaceutical preparations (sutures, dressings), sausage casings, size for felt and straws, improver of ceramic clays, coating of paper, size of nylon, cotton fabrics, stencil screens, tape, boiler scale inhibitor, release agent of molds, of plastic compounds, semipermeable membranes, polarizing films, gaskets, belts, ingredient of ink, photographic and screen printing emulsions, gasoline hose, solvent-resistant gloves, heat-seal coatings, electrical and acoustical insulation, additive to paraffin wax-aluminum salt waterproofing compound, bonding material of synthetic nonwoven fabrics, surgical prosthetic material for filling tissue defects

Population Groups with Occupational and Environmental Exposure to Hydrophilic Carbon Polymers.—Occupational Groups: Producers, processers, users and consumers of the various items listed.

Nonoccupational Groups: Users of hair sprays, cosmetic preparations, and foodstuffs containing these polymers, recipients of medicinal preparations by various routes containing these polymers; users of household detergents inhaling dust or mist.

Beryllium

Sites of Beryllium Cancers.—Suspected: lung, bones.

Exposure Stigmata:—Acute and chronic berylliosis, demonstration of berryllium in biologic materials, granulomas of skin and other tissues.

Compounds of Economic Importance	Operations and Products with Contact to Beryllium for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Beryllium
Glucinium, beryl beryllium alloys of copper, aluminum, magnesium, nickel, steel, emerald, aquamarine, beryllium chloride,	Ore mining and milling, production and processing of alloys for cylinder heads of motors, springs, metal parts in precision instruments, watches, cog wheels, ball bearings, screws, electrodes for welding, electrical contacts, surgical instruments and needles, high-tempera-	Occupational Gorups: Workers producing and processing the various items listed and becoming exposed (lung, skin, etc.) to beryllium-containing dust, fumes, fragments Nonoccupational Groups: Exposure to phosphors from broken fluo-

beryllium oxide, sodium beryllium fluoride, beryllium nitrate, beryllium bromide, beryllium borocarbide, beryllium sulfate, beryllium zinc silicate, beryllium stearate, beryllium silicate	ture membranes, parts of pumps; beryllium glass for windows in x-ray tubes, crucibles, refractories, phosphors in fluorescent light tubes, ceramic glazes, dental cements, high-temperature resistance tools, pipes, green glass, cosmetic and medical powders, artificial emeralds, shielding in atomic energy operations, gas mantles, electric arc carbons, grinding agents, soldering and welding additives, metallurgic electrolysis	rescent light tubes, residents of vicinity of beryllium smelters and fluorescent-tube plants

Cobalt

Sites of Cobalt Cancers.—Suspected: connective tissue, lung.

Compounds of Economic Importance	Operations and Products with Contact to Cobalt for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Cobalt
Cobalt ore, cobalt alloys, cobaltous acetate, cobaltous carbonate, cobaltous carbonyl; cobaltous chloride, cobaltous nitrate, cobaltous oxide, cobaltous hydroxide, cobaltous phosphate, cobaltous sulfate, cobalt naphthenate	Mining and smelting of cobalt ore, deactivator of gum formation in gasoline, convection loop in nuclear reactors, carbide cermets, catalyst in Fischer-Tropsch synthesis, pigment and colors in glazes, glass, paints, enamels, plating, alloys in various types of steel (high-speed, die and valve, tool), wool dye, ingredient of vitamin B_{12}, accelerator of drying of paints and varnishes	Occupational Groups: workers engaged in production and processing of products listed, and their users Nonoccupational Groups: Consumers of vitamin B_{12}

Selenium

Sites of Selenium Cancers.—Suspected: liver, thyroid.
Exposure Stigmata.—Cirrhosis of liver, jaundice.

Compounds of Economic Importance	Operations and Products with Contact to Selenium for Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Selenium
Copper ore, sulfuric acid sludge, seliniferous plants, alloys with copper, stainless steel, cadmium, selenium dioxide, selenium oxychloride, selenium diethyldithiocarbamate, sodium selenate, cadmium sulfoselenide	Copper refining, sulfuric acid production both giving selenium as by-product, rubber vulcanizing accelerator, pigment for glass, paint, plastic (red, brown, amber), electronic rectifier, photoelectric cell, pigment in ceramic, paper, leather, printing ink, etc. decolorizer of glass, stainless steel additive, soil additive for insect repelling and poisoning in greenhouses and citrus fruit, chemical oxidizing catalyst, toner in photography, film in xerographic plates for electrophotographic printing, cosmetic and medicinal agent (hair lotion against dandruff)	Occupational Groups: workers engaged in the production, processing, and use of the items listed Nonoccupational Groups: Persons using selenium-containing cosmetics, eating foodstuffs naturally contaminated with selenium (seleniferous plants grown in seleniferous soil [grain] and meat from food animals eating such plants)

Iron

Sites of Iron Cancers.—Suspected; lung, liver.

Exposure Stigmata.—Siderosis of the lung, siderocirrhosis of the liver.

Compounds of Economic Importance	Operations and Products with Contact to Iron and Iron Oxide Dust to Producers, Processers, Users, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Iron and Iron Oxide
Hematite, iron metal, iron oxide pigment	*Hematite Mining*, iron ore transportation and shipping, iron and steel production, grinding and polishing of *iron casts in foundries*, polishing of glass, mirrors, optical glass, metal parts (watches), diamonds; production and use of iron oxide as pigment in paints (iron work, ship hulls, etc.), rubber, linoleum, paper, ceramics	Occupational Groups: *Hematite miners, foundry workers, watch makers*, mirror polishers, paint manufacturers, painters.

Since the experiences with experimental animals by the administration of known human carcinogens, particularly those of occupational type, have amply demonstrated that under proper experimental conditions these agents elicit cancers of the same or other organs in one or several animal species, it seems scientifically sound to assume that among the large number of experimental carcinogens some will be found which are carcinogenic also to man. For this reason, all experimental carcinogens must be looked upon for the time being as "potential human carcinogens" until evidence to the contrary becomes available. Their presence in consumer goods, such as especially foodstuffs, cosmetics, home remedies, sanitary goods, household goods, and other articles of general and uncontrolled consumption and exposure appears to be objectionable since these agents may create cancer hazards which are difficult or impossible to demonstrate with the at-present-available epidemiologic methods and therefore may escape discovery.

The available factual and circumstantial evidence on environmental human carcinogens and cancers thus indicates that exogenous factors may account for many and diverse cancers afflicting mankind.

The following statements of two internationally prominent medical scientists support this interpretation of the evidence:

(*a*) Folke Henschen, Professor of Pathology, Karolinska Institutet, Stockholm, Sweden: "I think it is practically the most urgent problem to investigate in finest details the exogenous causes of cancer. This problem seems to me to be easier and more fruitful than the researches on cellular changes in beginning cancer, of course very important too." (May 9, 1955).

(*b*) Austin M. Brues, Director, Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Ill.: "But if there is an increase in lung cancer, and if this is due to an extrinsic factor, then something in our environment has been permitted to go well above the allowable level according to the criteria used in our probably best-regulated business. . . . The question of environmental carcinogenesis is quite properly attracting increasing attention, and one can foresee that it is likely to become a source of financial importance in cancer research." (Presidential address, 46th Annual Meeting of the American Association for Cancer Research, 1955).

Once an adequate amount of reliable and valid causal data on environmental carcinogens becomes available, the control of many human cancers by recognized and proven public health methods of a preventive nature should offer the same prospects as those successfully applied in the past for the control of infectious diseases, because of the existence of many similarities in the behavior of the causal agents of these 2 classes of pathogens and of the disease manifestations elicited by them (Table 3).

TABLE 3.—*Similarities in Epidemiologic and Symptomatic Patterns of Environmental Cancers and Infectious Diseases*

1. Carcinogenic spectrum is as wide and varied as pathogenic spectrum of infectious diseases.
2. Shift in main target organ dependent on route of introduction of causal agent occurs in both groups of diseases.
3. Carcinogens, like infectious pathogens, may display definite tissue and organ affinities.
4. Minor changes in chemical structure of carcinogens may cause change in target organ similar to that seen sometimes with different strains of micro-organisms.
5. Carcinogens vary among each other as markedly in potency as infectious pathogens do in virulence.
6. Differences in individual susceptibility to the action of causal agents are found in cancerous as well as infectious diseases.
7. Carcinogens are as species-specific as infectious pathogens.
8. Successive changes in the reaction status of the host and in the character of the reaction products characterize not only the cancerization process but also some chronic infectious conditions.
9. Cancers and infectious diseases have a centrifugal distribution pattern.

II. Characteristics of Environmental Carcinogens

1. *Definition.*—While there is no entirely scientifically satisfactory definition of carcinogens, the following definition may be adequate for all practical purposes: A carcinogen is a chemical, physical, or parasitic agent which when coming in contact with and introduced into animals, including man, under proper conditions elicits cancerous reactions in one or several organs and tissues regardless of the route of exposure and the dose or physical state of the agent used. Carcinogens are capable as a rule of producing cancers in one or several species but not in all species and in one or several tissues, but not in all tissues. The target organ of the carcinogen may, moreover, vary with the species. The carcinomatous reaction, moreover, may appear in an organ or tissue which is remote from the site of primary contact. It follows from these statements that a carcinogen which is capable of producing cancers in experimental animals may or may not exert the same action in man or not at the same site. For this reason, every effort should be made to obtain evidence on members of population groups which become exposed to any agent capable of causing cancers in animals. The population groups most suitable for such purposes are usually industrial producers or users of such agents. As long as human evidence is not on hand, experimental carcinogens remain merely suspect of exerting a cancerous action on man, i.e., they remain "potential human carcinogens." Any restrictive and precautionary measure which may be applied as a matter of common sense to such agents for the protection of the population, therefore, cannot be based on conclusive scientific facts but on incriminating circumstantial evidence. It would indeed be foolish and irresponsible, on the other hand, to lightly dispose of such potential cancer hazards as being "calculated risks" which must be tolerated as unavoidable by-products of normal living in an industrial economy.

The acceptability of a chemical or physical agent as a noncarcinogen depends on the adequacy of the test procedures, i.e., dose, routes of introduction, frequency, intensity, and duration of exposure, length of observation time, number and species of animals, and type of vehicle including solvent and dispersing agent. Unless chemically variable and ill-defined mixtures are tested, the agent investigated should be chemically identified and pure, and the instruments, vehicles, etc., used in the test procedures should be free from other carcinogenic agents, including contaminations from carcinogenic air pollutants.

Likewise, final recognition of a physical and chemical agent as a carcinogen should not be granted on the basis of observations reported by one investigator, or group of investigators, only. This acceptance should depend on the reproducibility of the results

TABLE 3A.—*Dose Variations for Different Carcinogens at a 50% Tumor Yield Level for Treated Animals* *

Carcinogen	Amt., μg.
1, 2, 5, 6-Dibenzanthracene	20
20-Methylcholanthene	20
3, 4-Benzpyrene	80
4-Dimethylaminostilbene	100
4-Dimethylaminoazobenzene	500

* R. Boyland.

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Tumor Yield
Animals *

Amt., μg.
20
20
50
100
500

Vol. 71, Mar., 1961

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by at least two, better even more, independent parties of investigators. However, the demonstration of carcinogenic properties for a particular agent by investigators of recognized competence in experimental carcinogenesis should be regarded from a practical viewpoint as adequate evidence of the probable carcinogenic qualities of such an agent until this conclusion is either substantiated or refuted by the results of investigations by other competent experimental cancerologists. This attitude should be adopted to guard against any loose and irresponsible positive or negative claims which might be advanced on the basis of ill-planned and incompetently interpreted results of experiments by insufficiently experienced investigators or planted by parties with special interests. Reports on the alleged carcinogenicity of chemicals, therefore, should contain detailed information on the experimental procedures used before they should be given serious consideration as scientifically acceptable evidence.

2. *Classification of Carcinogens.*—Carcinogens may be classified according to several principles.

(*a*) Chemical Classification: In the extensive listing of experimental carcinogens prepared by Hartwell, carcinogens are arranged on the basis of their chemical characteristics. This grouping is useful for demonstrating the distinct scatter pattern of carcinogens upon numerous classes of chemicals and our present lack of definite factual knowledge concerning the special chemical characteristics which convey carcinogenic properties to some but as a rule, not most of the member compounds of any particular class. The concept of "chemical group carcinogens" thus has only restricted applicability and is generally valid at present for only two classes of carcinogens: radioactive chemicals and chemicals possessing estrogenic properties.

Even in chemicals which may contain intramolecularly the active carcinogenic component, carcinogenic activity depends upon the biologic availability of this component to the tissues of contact. If the component cannot be released by the metabolic forces of the body from its inactive state, the carcinogenic component remains carcinogenically ineffective. Thus, most of the various food dyes which contain β-naphthylamine or α-naphthylamine in their molecules have been carcinogenically inactive when tested on rats, although 2 have shown carcinogenic properties for mice (Orange SS, Oil Yellow HA). Experiences made with various chromates differing in the degree of their water solubility have been of similar nature. The highly water-soluble and corrosive chromates as well as the almost water-insoluble chromates have proved, when tested on rats and mice, to be carcinogenically little or ineffective, while chromates of medium solubility have proved to be highly potent carcinogens. It is likely that similar differences in solubility or biologic availability of certain inorganic and organic arsenic compounds may account for the contrasting statements made concerning the occurrence of arsenic cancers among members of population groups exposed to various arsenicals.

(*b*) Target Organ Classification: Carcinogens have been classified according to the specific organ or tissue in which they elicit cancers, i.e., skin, lung, liver, bladder, etc. This classification has some practical merit, if one is interested to know the various carcinogens which have been shown to elicit cancers in a certain organ or tissue regardless of the route of administration. However, in many instances the site of the target organ depends upon the route of introduction and for this reason may change when the route of introduction is altered. It may be mentioned, moreover, that minor chemical changes in some members of the hepatocarcinogenic azo-dye group shift the target organ from the liver to the bladder.

The following 4 classes may be established on this principle used in a modified form:

I. Cancers at the site of primary contact (arsenic, asbestos, chromium, nickel, soot, tar, petroleum oils, x-rays, etc.: skin, lung, nasal sinuses, bone, leukemia)

II. Cancers at the site of excretion (aromatic amines, arsenic: bladder, skin)

III. Cancers at the site of secondary retention and storage (radium, benzol, arsenic, thorium X, azo dyes, etc.: bone, bone marrow, liver, skin, etc.)

IV. Cancers at the site of special affinity (hormones, organotropic chemicals: thyroid, liver, genital organs, blood-forming organs) (estrogenic chemicals, goitrogenic chemicals, hepatotoxins, myelotoxins).

(*c*) Human Carcinogenicity Classification or Species Specificity Classification: Carcinogens may be grouped according to their species-specific activity, i.e., according to the various species in which any particular carcinogen may be capable of eliciting cancers. Of main importance in this respect is a classification in which the relative significance of carcinogens concerning their carcinogenicity to man represents the guiding principle. The following groups may be established when this principle is applied.

I. Recognized human carcinogens (mainly occupational carcinogens and a few environmental ones [solar radiation, ionizing radiation from natural sources, arsenicals, soot, schistosomiasis])

II. Suspected human carcinogens for which the total available evidence (experimental and human) is not completely conclusive as to their carcinogenicity to man (estrogens, iron, tobacco extractives)

III. Potential human carcinogens for which the available evidence is restricted to observations on experimental animals and which represent constituents of the human economy, i.e., with which man has frequent and intimate contact in the form of consumer goods, industrial activities, industrial or industry-related environmental pollutants

IV. Experimental carcinogens, which are chemicals shown to cause cancers in experimental animals but which are not constituents of any part of the human economy or human environment and which, therefore, are entirely at present of scientific significance.

(*d*) Carcinogenic Potency Classification: An attempt has recently been made to distinguish between strong and weak carcinogens and to use such distinctions for the establishment of screening methods of food additives and contaminants for carcinogenic properties and potency (Table 3.4).* In practice the establishment of such a classification is bound to encounter distinct difficulties for several reasons. Existing experience with a large number of carcinogenic tests performed on numerous carcinogens has shown that even when strictly standardized test conditions are employed the potency rating for any particular carcinogen may vary considerably with the different strains of the same species, with the sex as well as with different species. The potency rating is also subject to marked fluctuations depending upon the particular type of test conditions used, i.e., the route of introduction, the type of vehicle, the use of single or repeated administrations, the length of the observation period, mortality rate from other causes among animals in test series, etc. Quite apart from the considerable difficulties encountered in defining in generally acceptable terms, local and general tumor yield, length of latent period, metastatic spread, growth rate, and accurately what are the criteria of a strong carcinogen in contrast to a weak carcinogen, there exists at present no reliable method for measuring in absolute terms carcinogenic potency of a chemical for any particular species, much less for several or all species.

The marked discrepancies in "carcinogenic potency" between different species for a particular carcinogen are well illustrated by observations made on several aromatic amines. Benzidine is doubtlessly highly carcinogenic for man, but seems to be rather weakly carcinogenic for dogs, since it took some 7 years for demonstrating the presence of bladder tumors in 2 of 6 dogs fed benzidine for many years (Spitz et al.). Similar observations exist for 2-acetylaminofluorene, which is evidently a most potent carcinogen for rats, causing cancers in many organs in this species. Dogs, on the other hand, reacted only after 7 to 8 years of exposure to relatively massive doses of this chemical with the development of bladder cancers (Morris et al.).

The almost universal inability to produce cancers of the lung in experimental animals by the inhalation of carcinogens which un-

* Table 3.4—Boyland, Berenblum; Fieser; Bryan and Shimkin.

doubtedly at least in part are responsible for cancers of the human lung is one example for the existing methodologic shortcomings. Similar deficiencies exist for many carcinogens in regard to determining their carcinogenic potency to parts of the alimentary tract.

Experiments with carcinogenic polycyclic aromatic hydrocarbons adsorbed to the surface of carbon particles (soot, carbon black) suggest that the carcinogenic potency of these carcinogenic compounds is reduced when these agents are administered in this form, especially when the carbon particles are of very small size, because the adsorbed hydrocarbons are not readily eluted and released for action from such particles by substances of the host organism, i.e., they have become biologically unavailable.

When using carcinogens belonging to different chemical classes there is often no common quantitative denominator between them for the establishment of comparative potency rates. Likewise, species-specific absorption or removal rates of carcinogenic preparations subcutaneously injected influence critically tumor yield at the site of introduction as well as the appearance and distribution of cancers in remote organs. All systems proposed to classify or grade carcinogens on the basis of presumptive carcinogenic potency have been applied to polycyclic aromatic hydrocarbons. Little has been done in this respect in regard to aromatic amino- and azo-compounds, none for metals or radiations.

(*c*) Classification by Carcinogenic Completeness: Recent observations on cocarcinogenesis have given rise to the concept of a multistage mechanism in the cancerization process, i.e., the separate action of "initiating" and "promoting" factors in the processes of cancerization and cancerigenesis (Berenblum; Shubik; Foulds; Setälä; Graffi; Salaman, etc.). Walpole in analyzing these data recently proposed to distinguish between "initiating carcinogens," "promoting carcinogens," and "complete carcinogens," i.e., carcinogens which combine initiating and promoting properties. It is remarkable, however, that under certain circumstances even carcinogens of the initiating as well as of the promoting type may elicit tumors without the coaction of the other complementary carcinogenic factor, i.e., that they behave like complete carcinogens. Among the known initiators this is true of urethan, triethylenemelamine, and β-propiolactone, while among promoters this has been observed for croton oil, phenol, and Tween 60 and may be present also for dodecanol. Poel, because of these findings and his own observations with the cocarcinogenic, or promoting, basic fraction of creosote oil, proposed that all promoting carcinogens were in fact weak carcinogens, i.e., they exert an effect synergistic with that produced by the "carcinogens" tested. Setälä, on the other hand, has recently stated that in his opinion all promoting agents exerted a purely nonspecific, cell-proliferation(hyperplasia)-stimulating action, and thus they did not constitute a factor essential for carcinogenesis.

Saffiotti and Shubik, in contrast, have argued from their observations on the effects of low concentrations of carcinogens given in single doses alone or followed by repeated doses of the same carcinogen or of croton oil, that a clear distinction can be made between an additive action of carcinogenic effects and a promoting action of a cocarcinogen on a carcinogenically sensitized tissue. It is also certain that not all cell-proliferation-stimulating agents act as "cocarcinogens" or are "weak carcinogens." On the other hand, experiences with certain hyperplasia-producing chemicals administered in combination with "complete carcinogens" indicate that such effects upon certain organs may be essential for "promoting" cancer development in organs which would not occur if the carcinogen would be administered alone. Carcinomas of the thyroid, for instance, result in rats by the combined administration of a goitrogen (thiouracil) with 2-acetylaminofluorene, which when given alone does not cause cancers of the thyroid. Cancers of the

breasts in mice are observed when methylcholanthrene administrations are combined with that of estrogens (Jull). Estrogenic treatments in combination with administrations of acetylaminofluorene are ineffective in rats for increasing the incidence of breast tumors, while this effect is obtained when in the experimental management estrogens are replaced by progesterone (Cantarow, Stasney and Paschkis).

It remains an open question whether or not the various properties (promoting, hyperplastic, carcinogenic, or tumorigenic) ascribed to promoting agents are in all cases identical and thus perhaps different phase effects of the same property or represent possibly separate biologic qualities inherent in the same chemical. At any rate, in view of the highly fragmentary and controversial evidence available on these interesting and provocative aspects of carcinogenesis, there appears to be at present insufficient evidence on hand for the development of a useful and rational classification of carcinogens on the principle of initiating, promoting, and complete carcinogens as proposed by Walpole.

There exists apparently a second group of possibly "incomplete" carcinogens. These are agents which need to become active the co-action of some endogenous or hereditary factor, or of some exogenous factor or factors of exogenous (dietary) nature, which are totally unrelated to the chemical cocarcinogens. Urethan, for instance, will elicit pulmonary tumors in certain hereditarily predisposed strains of mice or will cause the development of skin tumors when its intraperitoneal introduction is combined with cutaneous applications of croton oil. A number of azo dyes, of the butter yellow type (dimethylaminoazobenzene) are most prone to cause the development of liver cancers in rats, if these animals receive a diet deficient in riboflavin. Such carcinogens appear to be conditional carcinogens which need the complementary action of another factor for realizing their carcinogenic properties.

The amount of available information on conditional carcinogens is very scanty and little understood as to the actual role which "complementary factors" play in such types of carcinogenesis. It is, moreover, obvious that with a few exceptions "carcinogens" are complete carcinogens which need neither cocarcinogens nor complementary factors for the production of cancers. It is felt, therefore, that at least at the present time the available data on complementary or conditional carcinogenesis do not lend themselves to the development of a useful and scientifically sound classification of carcinogens.

3. *Action Mechanism of Carcinogens.*—The carcinogenic effects of chemicals upon cells and tissues differ in one fundamental aspect from their toxic effects. While cells and tissues will recover anatomically and functionally from toxic effects, unless they are killed by them, and may at times even acquire after recovery an increased resistance to a repeated toxic action of a particular chemical, the biologic effects of carcinogens are definitely long-lasting, if not permanent, and for this reason make once carcinogenically exposed cells more susceptible to repeated exposures. For making the carcinogenic effect of chemicals on cells more readily understood, one may compare the action of carcinogens on cells with that exerted by light rays upon the emulsion of a photographic film. In both instances the activating agents act upon certain specific elements present in the exposed medium. This action does not need to be continuous or prolonged; it may be rather brief or intermittent. The degree of the biologic and photochemical effects produced on the tissues and the emulsion, respectively, has a direct relation to the total dose of the activating agent administered.

While right from the start the carcinogenic as well as photochemical effects produced are indelible and permanent and result in additive and cumulative changes in the exposed medium upon repeated exposures, they are initially not demonstrable in either medium unless additional factors

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come into play, i.e., factors which are either generated in the host organism or applied as developers and fixatives to the photographic film. Under the influence of such factors there occurs a gradual development of demonstrable and visible alterations which represent the cancerous growth or the photographic image, respectively. The length of time required for visualizing the end-product of the interaction between the activating carcinogenic or actinic agent and the medium, i.e., the host organism and the photographic emulsion, depends upon the intensity of exposure as well as on the relative reactivity of the exposed medium, i.e., the relative degree of constitutional or acquired sensitivity and susceptibility of the person and the degree of sensitivity of the emulsion, respectively. The developmental period in the cancerization process is known as "latent period."

It may vary, depending upon the specific exposure conditions prevailing and the reactivity of the host organism, between 6 months and 50 years, according to experiences made in man with occupational carcinogens. If the action of a carcinogen is weak and the resistance of the host organism is high, the development of the cancerous response in the tissues may be so slow that it never reaches a manifest stage during the lifetime of such a person but remains in some intermediary "precancerous" stage. Under corresponding circumstances the photographic image may not be visualized at all by the application of developing chemicals, or only a faint and indistinct image appears on the film.

For making a photographic image on a film permanent, fixatives have to be employed, because without their action, even a well-developed image will ultimately fade and disappear. Somewhat similar phenomena have been observed in human and experimental cancerous reactions. Lesions which were clinically and/or histologically cancers have regressed spontaneously, i.e., they were not biologically cancers. Such reversible cancerous reactions have been found, for instance, in the skin of workers exposed to the carcinogenic action of coal tar as well as in the mucosa of the urinary bladder in dye workers having occupational contact with carcinogenic aromatic amines. Such phenomena are known as "false positives" in industrial medicine. In fact, this course of events is the rule for the histologically "cancerous" lesions of the skin in monkeys appearing after repeated paintings with coal tar, because these reactions tend to regress and heal despite continued applications of the cancerous material.

The permanence or irreversibility of a cancerous response thus depends upon the action of some biologic "fixating" mechanism probably provided by the host organism.

4. *"Safe Dose."*—It is technically possible to determine a "minimal" effective dose of a well-defined carcinogen under specific experimental conditions applied to experimental animals of an established strain belonging to a certain species. Such information has obviously more scientific than practical value in assessing even crudely the relative degree of cancer hazard to human beings from contact with such agents because of the well-known species-specificity in the qualitative and quantitative reactivity of different species to environmental chemical and physical carcinogens. The limited value which this type of information possesses under the prevailing circumstances is even more restricted by the fact that in the great majority of experiments the number of animals used is insufficient for adjudging the presence of weak carcinogenic effects among members of the species used. For obtaining any information possibly applicable and valuable to the human problem many hundreds of animals would have to be employed in such tests, as apparent from the following considerations.

Observations made in occupational carcinogenesis in man and in experimental carcinogenesis in animals have demonstrated that the degree of carcinogenic response, i.e., the incidence rate of cancers among the population at risk, decreases with the intensity and duration of exposure. Carcinogens

thus behave in regard to dose response like chemicals when tested for toxic and pharmacologic properties. It may be mentioned in this connection that the toxic and pharmacologic responses of animals to chemicals are quantitatively as well as qualitatively as species-specific as those obtained with carcinogens. The results of such tests have nevertheless generally been accepted and have profitably been used for many years in science and industry despite their limitations concerning their direct applicability to man. The available pharmacologic and toxicologic methods make it relatively easy to determine in animals minimal effective toxic and pharmacologic doses, which permit the setting of rather reliable safety standards for man. The test methods available for such a purpose in experimental chemical carcinogenesis, on the other hand, are at present inadequate for this purpose.

In an assessment of the potency of a carcinogen, proper consideration must be given to the fact that marked variations exist in the relative carcinogenic potency of chemical and physical carcinogens for different species as well as for the same tissue or tissues in different species. The target organ or organs of different species for the carcinogenic action of an environmental agent also may vary. Under no circumstances should a carcinogen be considered safe for human consumption because it does not elicit any cancers when given by mouth to mice or rats, while it produces cancers when introduced by some other route (subcutaneous, cutaneous, etc.), since some of the most potent human carcinogens would have to be included in the class of chemicals (β-naphthylamine; 3, 4-benzpyrene; arsenicals) which can safely be incorporated in foodstuffs. Any chemical which is capable of producing cancers of any type in any tissue or organ of any species when introduced by any route and in any dose should be considered as a potential human carcinogen until its innocuousness for man has definitely been established. Screening tests for carcinogenic properties of chemicals entering consumer goods are particularly indicated for those chemicals displaying some chemical and physical similarities with known carcinogens (Table 4) or producing in man or animals biologic effects often found with carcinogens and suggesting therefore a possible carcinogenic action (Table 5) (Hueper).

The following calculation conveys a general impression concerning the potency range which must be explored in screening operations for giving practically valuable information.

We have in the United States a cancer morbidity rate of about 5 living cancer cases of all types and causes among 1,000 persons per year. This same attack rate would be present in a series of experimental animals exposed to one single carcinogen if only one cancer would appear during a given year among 200 animals tested. The carcinogen thus would display a potency equivalent to that exerted by the entire group of exogenous and endogenous carcinogens active in the general population. It is apparent that the establishment of safety

TABLE 4.—*Chemical and Physical Similarities with Known Carcinogenic Chemicals*

(1) Chemical composition, structure, spatial configuration, electronic density
(2) Polymerizing and cross-linking tendencies
(3) Protein complex formation
(4) Sulfhydryl binding or inactivation
(5) Enzyme action (inhibition or activation) (fermentative metabolism stimulation, coenzyme I and catalase depression, etc.)
(6) Potential carcinogenic metabolite formation, particularly compounds having a hydroxyl and an amino group ortho to each other in an aromatic system of 2 or more rings.
(7) Refractivity, fluorescence, infrared and ultraviolet absorption spectrum

TABLE 5.—*Biologic Stigmata for Carcinogenically Suspect Chemicals*

(1) Anatomical reactions (atypical cellular hyperplasias, hyperkeratoses, carcinomatoid, sarcomatoid and leukemoid reactions, mucosal polyps, papillomas, adenomatoid proliferations, adenomas)
(2) Radiomimetic and mutagenic effects (mitotic poisons)
(3) Hepatotoxic, myelotoxic, carcinolytic and carcinostatic effects
(4) Estrogenic effects
(5) Sensitization phenomena (chemoallergies, photosensitization)
(6) Congenital abnormalities in offspring after introduction into pregnant maternal organism

limits on the basis of such experimental observations would be improper because (*a*) the human population often becomes exposed to the same agent from several sources; (*b*) it has contact with numerous environmental carcinogens which may exert a synergistic action, and (*c*) it sustains a degree of contact with these agents which neither can quantitatively or qualitatively be determined nor can be controlled effectively as long as it is present. The recently published rather unrealistic and arbitrary recommendations made on this subject by the Food Protection Committee (Publication 749, *National Academy of Sciences*, December, 1959) are in need of critical examination and modification before they are suitable for practical adoption because they do not provide sufficient protection to the consuming public against cancer hazards from food additives and contaminants.

Since a so-called "safe dose" of a carcinogen for man cannot be determined with the existing methods, wisdom and reason decrees that under such circumstances only a "zero dose" is a "safe dose" for all known, suspected, and potential human carcinogens wherever such a level of exposure can be attained. It is obvious that the existence of a number of natural carcinogens (ultraviolet radiation in sunlight, arsenical impurities in many environmental agents, ionizing radiations, etc.) prevents such a goal from being attained in all instances. However, this fact is scarcely a valid excuse for minimizing the additional cancer hazards which may be imposed upon the general population if such unavoidable exposures to carcinogens are reinforced by avoidable exposures to the same agents when incorporated indiscriminately and injudiciously into consumer goods (arsenical pesticide and feed additive residues in foodstuffs, estrogen in meat, radioactive materials in foods, drinking water, etc.), medicinal preparations, and environmental pollutants.

Such additional but avoidable exposures may indeed increase the carcinogenic load, especially in sensitized or hypersensitive, metabolically abnormal persons, to a level at which the development of a cancer may ensue. Practical industrial experiences with a certain highly potent occupational carcinogen, namely, β-naphthylamine, recently demonstrated as an impurity in 2 former food dyes and still permitted as cosmetic dyes (yellow OB and yellow AB) indicate that exposures to a few micrograms per day are sufficient to create a definite bladder cancer hazard in man. Daily contact with minute doses of certain carcinogens sustained over a long period of time thus may be sufficient for producing cancers in those persons of the total population at risk who are for constitutional or other reasons most susceptible.

Table 6.—*Tumor Yield from Graduated Doses of 3,4-Benzpyrene, Subcutaneously Injected into C-57 Black Mice as Single Dose and as 12 Monthly Refracted Doses* *

Dose, Mg.	No. Mice	No. of Tumors Within 18 Months	
		After Single Dose	After Refracted Dose
0.025	72	6	2
0.05	72	7	6
0.10	72	16	17
0.25	72	20	43
0.50	72	17	51
Total number of tumors		66	119

* W. C. Hueper and Wm. W. Payne.

Experimental information recently obtained on this aspect strengthens this view. The total cancer yield of graduated doses of 3, 4-benzpyrene administered subcutaneously to series of mice either as a single dose or in 12 monthly refracted doses was studied. It was found that the total cancer yield was much higher when certain amounts of benzpyrene were administered in 12 equal fractions than when the total amount was given by a single injection (Table 6). Since almost all exposures of man to environmental carcinogens are of long duration and of the often-repeated type, the cited experimental observations are of distinct significance in adjudging the seriousness of environmental cancer hazards even in the presence of contact with apparently small or minute amounts of carcinogens.

To Be Concluded.

Congenital Defects Due to Thalidomide

SIR,—We were interested to read Dr. M. A. Lécutier's case report (December 1, p. 1447) of a baby with multiple congenital deformities which were attributed to thalidomide. Similar features were observed at a necropsy recently performed on a baby born in this hospital. In this case, however, the date of prescription of thalidomide has been checked from the original prescription.

Case History.—A woman aged 29 was delivered normally of a 5½ lb. (2.9 kg.) female infant at 41 weeks' gestation. She has one other live normal child aged 8. The mother was prescribed "triptizol" (amitriptyline) 25 mg. t.d.s. on September 14, 1961, for depression, and thalidomide ("distaval") was added on October 10, 1961, 25 mg. daily. One hundred tablets were prescribed. She returned to her general practitioner on January 11, 1962, and reported that she was pregnant (L.M.P. November 26, 1961). Pregnancy was normal throughout. At birth the baby was noted to have gross upper limb deformities and an abnormal, flattened face. On the tenth day of life a systolic murmur was heard for the first time. Her general condition was otherwise good and she was discharged. She returned to the routine follow-up clinic aged 6 weeks in cardiac failure and was admitted to the Royal Hospital for Sick Children, where she died on November 19.

Necropsy.—There was gross shortening of both forearms with absence of ulnar bones and flexural deformities of both wrists. There were only four fusiform digits on both hands and a vestigial thumb had been amputated from the left hand on September 19. The heart was enlarged and showed truncus arteriosus and a high interventricular septal defect. The lungs showed terminal congestion but were otherwise normal. There was a deficiency of the left diaphragm. The gut was normal apart from the absence of the appendix. The left kidney was absent and the right kidney 1½ times normal size. The uterus was unicornuate, the one horn on the right side. All other organs were examined but found normal.

It appears that this woman became pregnant whilst taking thalidomide and continued to take it for four to five weeks after conception. In a recent article in this journal (October 13, p. 944) Drs. C. Lutwak-Mann and M. F. Hay, working on rats, suggest that thalidomide affects the preimplantation embryo, in addition to the toxic effect on limb buds. The generalized abnormalities in this baby are in keeping with this suggestion, and this case re-emphasizes the potential dangers of prescribing any drugs to females of child-bearing age whether pregnant or not.

I am grateful to Dr. J. W. Farquhar for permission to report this case.

—I am, etc.,

ANNE STEWART.

Elsie Inglis Memorial Maternity Hospital, Edinburgh 8.

Exposure to Asbestos Dust and Diffuse Pleural Mesotheliomas

SIR,—The letters of Dr. W. J. Smithers and his colleagues (November 3, p. 1194) and of Dr. W. T. E. McCaughey and his colleagues (November 24, p. 1397) draw attention to the association between malignant mesothelioma of the pleura and exposure to asbestos dust. In the first letter it is mentioned that the degree of pulmonary asbestosis in these cases of pleural mesothelioma may be variable, and in the second that the duration of the exposure to asbestos dust may be intermittent. It would appear that they have not noticed a recent article in which I describe a new pulmonary condition, basal asbestosis, and stress its association not only with malignant mesothelioma of the pleura but also of the peritoneum.[1]

Briefly, the following points were made:

(1) There is a condition, limited or basal asbestosis, where the lesion is more or less confined to the lung bases, presumably due to the downward movement of the sharp asbestos fibres, before they become asbestos bodies. This produces no pulmonary signs or symptoms, is not evident clinically, and is usually overlooked at necropsy. It will be missed even microscopically, unless sections are examined from the lung bases.

(2) While this basal asbestosis is unlike classical asbestosis in most particulars, it appears to attain locally a carcinogenic concentration, and as this lesion does not shorten the patient's life the carcinogenic action of asbestos can presumably act for a longer period. Indeed, this basal asbestosis may be found later to produce more malignant tumours than classical asbestosis.

(3) In three years in the necropsy service of a teaching hospital six cases of malignant mesothelioma were encountered, three pleural and three peritoneal, and in five of these the basal asbestosis was demonstrated. The lung bases are only a few millimetres distant from the peritoneum over the diaphragm, and the occurrence of peritoneal mesothelioma in basal asbestosis is not unexpected.

(4) In 1961 in four centres in the United States I found nine examples of basal asbestosis out of 15 cases of pleural and peritoneal mesotheliomas in which adequate lung was available for study. In all but two of them the basal asbestosis had been overlooked.

(5) In very few of these cases was an industrial or occupational exposure to asbestos mentioned, but this is of no significance unless direct questions are put to patients or their relatives. What is more important is that the world's annual consumption of asbestos has increased from 500,000 tons in 1942 to 2,400,000 tons in 1961, and that asbestos is to-day used in such a wide variety of manufactured products that, theoretically at least, the number of people who may be exposed to asbestos is enormous, and few of those thus exposed work in factories which are designated asbestos factories.

In January, 1963, will appear an article[2] in which I draw attention to asbestos as a modern urban hazard. Asbestos is virtually indestructible, and while strontium-90 has a half-life of 28 years asbestos has a half-life of an infinity of years. The article demonstrates on evidence from necropsies that a large and increasing percentage of the population are inhaling asbestos fibres. As these tend to gravitate to the lung bases there will be a cumulative effect, and one wonders if in 20 years' time asbestos-induced mesothelioma may not be as common as cancer of the lung is to-day.—I am, etc.,

J. G. THOMSON.

Department of Pathology, University of Capetown Medical School, Observatory, C.P., South Africa.

REFERENCES

1 Thomson, J. G., *S. Afr. med. J.*, 1962, 36, 759.
2 —— Kaschula, R. O. C., and MacDonald, R. R., *ibid.*, in press.

Risks of Primary Vaccination

SIR,—Professor G. W. A. Dick (November 17, p. 1275) reprints a table (I) on "Mortality per Million Primary Vaccinations"[1] which seems to me to mislead. There is no mention of the number at risk in each separate age