Genetic Differences in Chemical Carcinogenesis

Editor

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DEDICATION

To Pauline, whose patience I wish I possessed.

January, 1979

PREFACE

The process of chemically induced cancers involves a series of complex stages, each of which is capable of determining the rate of progression of this disease (see Stages in Carcinogenesis). At virtually every step, there are naturally-occurring variations among both individuals and groups of individuals which are controlled or regulated by host genes. It would seem that a specific genotype or, more likely, a certain set of gene combinations ultimately define which individuals are susceptible to chemically induced cancers.

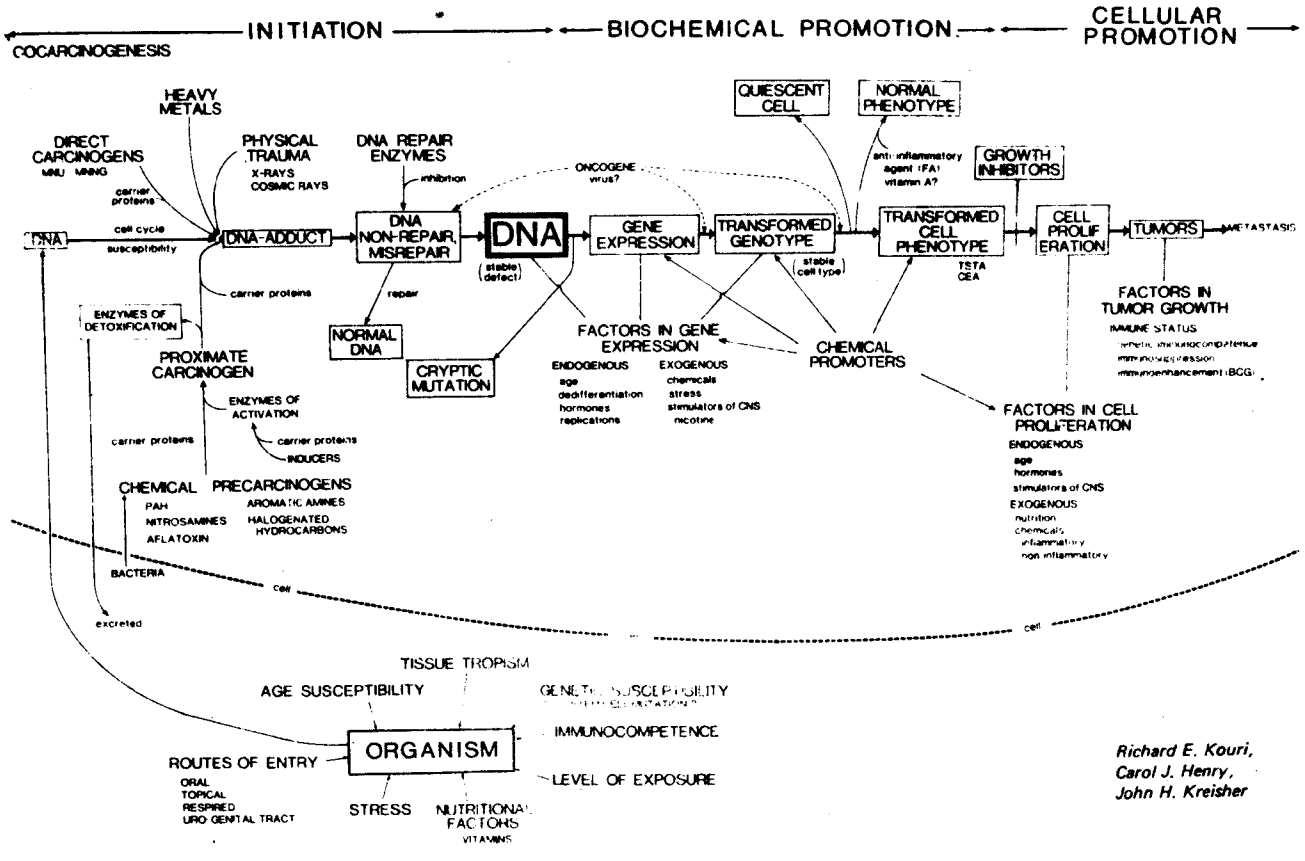
The first stage in the disease process entails exposure, uptake and distribution of chemical carcinogens within an individual (Chapter 1). Although exposure levels normally determine uptake, the assimilation and distribution of many chemical carcinogens seem to depend upon the presence of cytoplasmic receptor molecules. Moreover, the degree of expression of these receptor molecules may be regulated by host genes. Since most chemical carcinogens are relatively inert, they would remain within cells forever if not for specific enzyme systems that metabolize them to polar end products for bodily excretion. This metabolic process is highly complex, is host gene regulated, and controls not only this metabolic alteration to water-soluble forms, but also controls the production of intermediates that may be much more biologically active than the parent compounds (Chapter 2). These active intermediates can be detoxified and removed from cells; may bind to cellular macromolecules resulting in no appreciable damage; or can bind in a specific manner to macromolecular DNA, forming DNA adducts. DNA adducts, recognized as such by DNA repair enzymes, are either repaired, nonrepaired or misrepaired (Chapter 3). The latter two alternatives result in a stable DNA effect. Upon expression of this DNA sequence either naturally via normal endogenous factors, e.g., hormones or viruses (Chapters 4 and 5) or after exposure to exogenous chemicals (Chapter 6), this defect can be transformed into a stable cellular genotype. Proliferation of this stable genotype by exogenous promoters seems to be the major method by which transformation to the cancer cell phenotype occurs. These cancer cells may remain quiescent, may express a specific phenotype that is recognized by the immune system for removal from the body, or may proliferate into a palpable tumor (Chapter 6).

Each of these stages can be, in certain instances, under host genetic control. Variations in the level of expression of these stages can determine susceptibility to chemically induced cancers. The determination of the cancer prone genotype(s) is a very viable approach to the understanding and eventual control of cancer in humans (Chapter 7).

This book is an attempt to present the state-of-the-art of genetic control of chemical carcinogenesis. The authors hope that this book will provide some insight into the intricacies of the chemical carcinogenic process and present some logical methods for the understanding and subsequent control of this disease.

Richard E. Kouri

STAGES IN CARCINOGENESIS



Richard E. Kouri,
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Dr. Kouri received his B.S. degree in Microbiology at Ohio State University in 1965, his M.S. and Ph.D. in 1968 and 1970 at the University of Tennessee in Radiation Biology. From 1970—1971 he was a postdoctoral fellow at the Roche Institute of Molecular Biology. Since 1971 he has been at Microbiological Associates, first as an Associate jinvestigator, 1971—1972; then Co-Project Director, 1972—1974; and to the present as Head, Department of Biochemical Oncology. He was made Director of Research in June 1977.

His research interests have included: in vivo and in vitro toxicological bioassays, carcinogen metabolism, genetic regulation of cancer susceptibility, and the molecular basis for chemically induced mutagenesis and carcinogenesis.

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Chapter 1

EXPOSURE, UPTAKE AND DISTRIBUTION OF CHEMICAL CARCINOGENS

Leonard M. Schechtman, Carol J. Henry, and Richard E. Kouri

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I. INTRODUCTION

Carcinogenesis is a multistep, highly complex process. Manifestation of the carcinogenic process is dependent upon the interaction of such factors as environmental exposure to carcinogens and/or adventitious agents, genetic susceptibility to carcinogenesis, host modifying factors (e.g., diet, metabolic capacity, hormonal effects, immune responses and age), co-carcinogenic interactions, as well as other intrinsic and extrinsic determinants.

Control of chemical carcinogenesis can hypothetically be excercised at any one of the many steps involved in the carcinogenic process. The role played by genetics in this process and the genetic regulation of carcinogenesis will be the subject of succeeding chapters in this book. The subject of this chapter will be human exposure to chemical carcinogens and control of this exposure to potentially carcinogenic environmental factors.

II. ENVIRONMENTAL EXPOSURE TO CHEMICAL CARCINOGENS

The first step that is amenable to control of carcinogenesis is at the level of exposure.[1] In its simplest sense, a decrease in the level of exposure to carcinogenic agents should result in a decreased risk. Whereas there is firm genetic influence on other steps in carcinogenesis (see ensuing chapters), few such obvious genetic controls exist at the level of exposure, uptake or distribution of chemical carcinogens.

Exposure to chemical carcinogens is itself not a genetically controlled occurrence and should be at random. However, there is some evidence which suggests that cellular uptake of chemical agents is under genetic control and that this genetic control occurs via the binding of chemicals to macromolecules in mammalian cells. Poland et al.[2] have examined the binding affinity of various halogenated dibenzo-p-dioxins, dibenzofurans and polycyclic hydrocarbons by hepatic cytosol and have proposed that hepatic uptake of such agents may be genetically regulated. Wilding et al.[3] have also shown that drug binding may be under genetic control in man.

Genetics could also play other more subtle roles in certain aspects related to exposure, uptake, and distribution of chemical carcinogens through such factors as ethnic background, personal preferences, and some psychological and physiological influences such as alcoholism and/or smoking.[4] However, the genetic factors that control, regulate, or influence these characteristics have not as yet been thoroughly defined, due mainly to the limitation of good model systems by which to study such characteristics. Thus, in view of such limitations, it is difficult to discriminate genetic from nongenetic influences.

It has been estimated that approximately 85% of all human cancers result directly or indirectly from environmental influences.[5] Evidence in support of this contention has evolved slowly over roughly the last 200 years, which were marked initially by the discovery of Sir Percivall Pott in 1775 that scrotal cancer among chimney sweeps was attributable to occupational exposure to soot.[6]

One of the prime evidences in support of the major role played by the environment in the incidence of human cancers is that cancer morbidity and mortality in the human population show marked geographical pattern differences.[7-13] The examination of the wide variety of cancers and their incidences relative to geographical distribution has provided information regarding the role of both the environment and genetic determinants in the etiology of cancer. The National Cancer Institute has compiled a publication tabulating the cancer mortality rates by individual county in the continental United States for the period 1950-1969,[11] as well as an atlas depicting the geographical

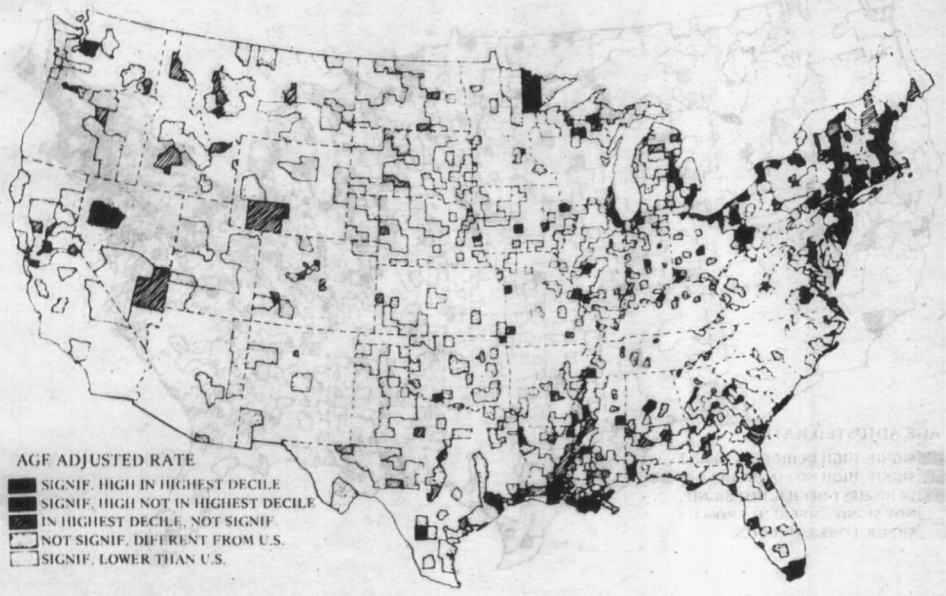

FIGURE 1. Cancer Mortality, 1950—1969, by county, all sites combined white males. Symbols shown on figure. (Taken from Mason, T. J., McKay, F. W., Hoover, R., Blot, W. J., and Fraumeni, J. F., Jr., Atlas of Cancer Mortality for U.S. Counties: 1950—1969, DHEW Publ. No. (NIH) 75-780, U.S. Government Printing Office, Washington, D.C., 1975. With permission.)

patterns of these cancer mortalities per county over the same 20 year period.[12] Two cancer mortality maps from the atlas depicting age-adjusted rates for 35 anatomic sites of cancer for white males and females are presented in Figures 1 and 2, respectively. A similar analysis was performed for The Danish Cancer Registry for the period 1943-1972.[13] Such analyses serve to identify locales with elevated cancer death rates, geographical clustering of specific kinds of cancers, and high-risk communities; they serve to provide information regarding ethnic influences, and contributory effects of occupational and other environmental factors; and they serve to provide a means for relating the cancer mortality patterns with human risk factors. Epidemiologic evaluations of this kind have also furnished data regarding the influence of such parameters as sex, age, urbanization, socioeconomic status, cultural factors, air pollution levels, and geographic relocation of migrant workers. For example, it has been determined that cancer incidences in the offspring of migrants more often reflect those of the new environs rather than those of the geographical locale from which they originated.[14]

Today human contact with physical and chemical carcinogenic agents through occupational exposure is considered to be one of, if not the major, environmental factor(s) which contribute to the high incidence of this enigmatic and ubiquitous disorder.[15] A comprehensive list of environmental agents which have been associated with occupational, iatrogenic, and other environmental cancers has been tabulated by R. Doll,[16] reproduced here (Tables 1, 2, and 3) with permission. From these and other data it becomes obvious that the influential role of physical agents, industrial products and by-products, drugs, diet, cigarette smoking, and adventitious agents take on a great deal of importance in terms of their total impact on human cancer.

By-products of cigarette smoking have been recognized as important environmental factors which play a role in human carcinogenesis. Cigarette smoke and specific subfractions of tobacco smoke condensate have been implicated as both mutagens and

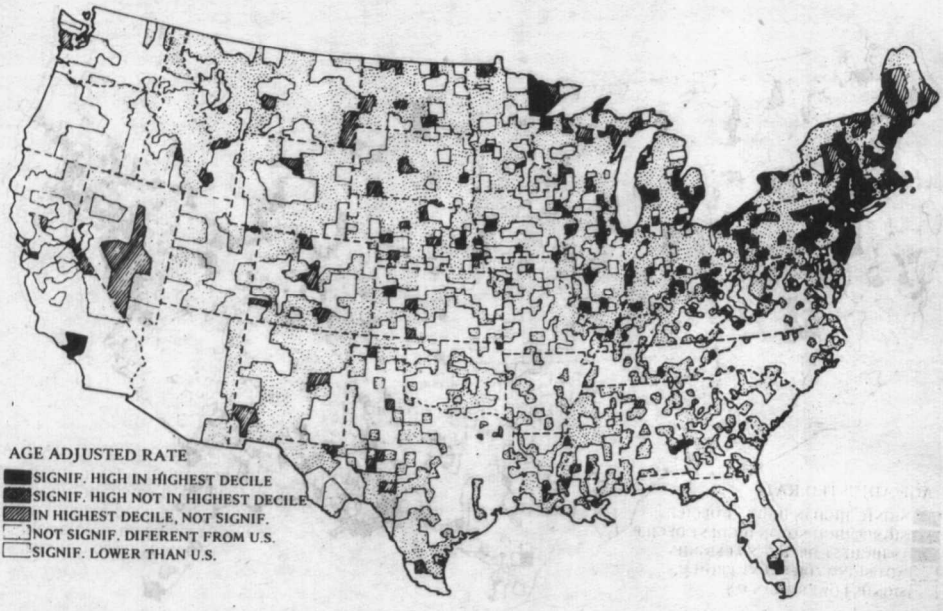

FIGURE 2. Cancer Mortality, 1950—1969, by county, all sites combined white females. Symbols shown on figure. Taken from Mason, T. J., McKay, F. W., Hoover, R., Blot, W. J., and Fraumeni, J. F., Jr., Mortality for U.S. Counties: 1950—1969, DHEW Publ. No. (NIH) 75-780, U.S. Government Printing Office, Washington, D.C., 1975. With permission.)

carcinogens, and are currently being examined as potential initiators and/or promoters of pulmonary carcinogenesis see Reference 17 for review). It has been reported that cigarette smoking is a major factor contributing to cancer in the United States, with lung cancer accounting for >25% of all cancer deaths in the U.S. in 1975, and approximately 25% of the total cancer mortality in the United Kingdom.[18]

It is not within the scope of this chapter to discuss the individual roles of cigarette smoke, adventitious agents (such as viruses), diet, metabolism, genetic factors (such as genetic predisposition, familial incidence, race, sex, etc.), and systemic factors (such as humoral influences, immunosurveillance, aging, etc.). Some of these will be dealt with further in this volume as they relate to chemically-induced carcinogenesis; others have been discussed previously elsewhere (see Reference 19 for review).

III. SOURCES AND ROUTES OF EXPOSURE IN HUMAN CARCINOGENESIS

A. Carcinogenesis by Physical Agents

The major routes of exposure to carcinogenic agents to which humans are subjected include dermal exposure, exposure through inhalation, and exposure by ingestion. Epidermal exposures to carcinogens are mainly attributed to physical agents such as ultraviolet (UV) radiation and ionizing radiation (X- and gamma rays, alpha and beta particles, neutrons and protons). Data to date suggest that changes in the levels of exposure to UV radiation as a function of geographical locale (e.g., degrees north latitude), time, weather patterns, etc., influence the incidence of skin cancer in man.[20] A similar correlation has been found with respect to ionizing radiation. Differences in exposure levels to ionizing radiation from naturally occurring sources are also dependent upon geographical locale (radioactivity differences in different parts of the earth's

TABLE I

Occupational Cancers

Agent	Occupation	Site of cancer
Ionizing radiations		
Radon	Certain underground miners (uranium, fluorspar, hematite)	Bronchus
X-rays, radium	Radiologists, radiographers	Skin
Radium	Luminous dial painters	Bone
Ultraviolet light	Farmers, sailors	Skin
Polycyclic hydrocarbons in soot, tar, oil	Chimney sweepers	Scrotum
	Manufacturers of coal gas	Skin
	Many other groups of exposed industrial workers	Bronchus
2-Naphthylamine; 1-naphthylamine	Chemical workers; rubber workers; manufacturers of coal gas	Bladder
Benzidine; 4-aminobiphenyl	Chemical workers	Bladder
Asbestos	Asbestos workers; shipyard and insulation workers	Bronchus pleura and peritoneum
Arsenic	Sheep dip manufacturers; gold miners, some vineyard workers and ore smelters	Skin and bronchus
Bis(chloromethyl)ether	Makers of ion-exchange resins	Bronchus
Benzene	Workers with glues, varnishes, etc.	Marrow (leukemia)
Mustard gas	Poison gas makers	Bronchus; larynx; nasal sinuses
Vinyl chloride	PVC manufacturers	Liver (angiosarcoma)
(Chrome ores)	Chromate manufacturers	Bronchus
(Nickel ore)	Nickel refiners	Bronchus; nasal sinuses
(Isopropyl oil)	Isopropylene manufacturers	Nasal sinuses
Specific agent not identified	Hardwood furniture makers	Nasal sinuses
Specific agent not identified	Leather workers	Nasal sinuses

surface, exposure to cosmic rays as a function of altitude).[20] Upton has suggested that cancers attributable to low-level ionizing radiation may follow a "linear, nonthreshold dose-incidence relationship" and in this respect, could account for up to 1% of naturally occurring induced cancer.[20] On the other hand, medical technological sources of radiation (e.g., medical X-ray and fluoroscopy equipment, in vivo deposition of radioisotopic tracers) account for only a fractional amount of total physically-induced cancers.[20, 21] That UV radiation is a prime cause of skin cancer in man is supported by a multiplicity of facts relating the incidence of skin cancer to (1) the amount and intensity of UV radiation from the sun, (2) the levels of pigmentation among races, (3) the extent of exposure of various body parts, (4) exposure of laboratory animals to UV radiation, and (5) the capacity to repair UV-damaged DNA.[22]

B. Chemically Induced Carcinogenesis

Carcinogenesis attributable to ingestive exposures result mainly from food, water, and drug consumption, while cancers attributable to inhalation exposure result mainly from polluted air, aerosolized environmental and occupationally related carcinogens, and cigarette smoking. The passive consumption of materials other than proximate or ultimate carcinogens associated with these products is generally not considered the direct cause of human cancers, but generally results from an interaction of these with

TABLE 2

Iatrogenic Cancers

Agent	Site of cancer
Diagnostic or therapeutic X-rays	All sites
Thorium	Bone
Thorotrast	R.E. system (liver, spleen)
Polycyclic hydrocarbons	
In coal tar ointments	Skin
In liquid paraffin (?)	Stomach, colon, rectum
Alkylating agents	
Melphalan, cyclophosphamide	Myeloid leukemia
Estrogens	Corpus uteri, breast ♀ (?)
Stilbestrol	Vagina, breast ♂
Steroid contraceptives	Liver
Androgens (anabolic steroids)	Liver
Arsenic	Skin, lung
Chlornaphazine	Bladder
Phenacetin	Renal pelvis
Immunosuppressive drugs	Reticulosarcoma
SV40 virus contaminating polio vaccine (transplacental) (?)	Central nervous system

TABLE 3

Other Environmental Cancers

Agent	Site of cancer
Sunlight	Exposed skin (rodent ulcer, squamous carcinoma, melanoma [?])
Use of "kangri" and "dhoti"	Skin of abdomen and thigh
Chewing betel, tobacco, lime	Mouth
Reverse smoking	Palate
Smoking	Mouth, pharynx, larnyx, bronchus, esophagus, bladder
Alcoholic drinks	Mouth, pharnyx, larynx, esophagus
Aspect of sexual intercourse (? virus)	Cervix uteri
Infectious mononucleosis (?)	Hodgkin's disease
Aflatoxin	Liver
Shistosomiasis	Bladder

such factors as flora associated with the gastro-intestinal tract and endogenous cellular enzymes which can metabolically activate (and inactivate) procarcinogens.

The role that nutritional factors play in human cancers has been reviewed elsewhere.[23-26] Aside from the possibility that certain foods may be carcinogenic, it has been suggested that foods, food components, and food additives can alter the levels of enzymes which metabolize carcinogens in vivo.[27,28] These alterations can be manifest as enzyme induction or repression and can ultimately affect activation, inactivation and endogenous metabolic generation of carcinogenic metabolites. Dietary constituents have been implicated in most forms of gastro-intestinal and peripherally associated organ cancers, such as stomach, colonic, esophageal, hepatic, and pancreatic cancers, and have been associated with certain cancers of organs and tissues under

endocrine control, such as breast, ovarian, endometrial, and prostatic cancers (see Reference 25 for review). In addition, approximately 20 organic chemical carcinogens which are naturally occurring have been identified in foods, mainly as metabolites of fungi and green plants.[29-31] Some of those associated with green plants include cycasin (methylazoxymethanol-β-glucoxide), nitrosamines and nitrosamides, pyrrolizidine alkaloids, allyl and propenyl benzene derivatives (e.g., safrole), brachen fern, trace amounts of polycyclic aromatic hydrocarbons and thiourea.[29] Some carcinogens associated with fungi include aflatoxins, sterigmatocystin, yellow rice toxins (eg., the fungal metabolites luteoskyrin and cyclochlorotine), and griseofulvin.[29] Other carcinogenic substances of biological origin have been associated with *Streptomyces* bacteria (e.g., actinomycin D, mitomycin C, streptozotocin and elaiomycin), *Escherichia coli* (e.g., ethionine), and other bacteria (e.g., nitrosamines).[29]

Exposure to carcinogens by ingestion is further complicated by the contribution of marine and fresh water foods exposed to aquatic pollutants. These pollutants are derived from effluents from industry and sewage, erosion of land treated with pesticides, insecticides and other agricultural chemicals, dumping and discharges by ships at sea, offshore crude oil drilling sites, exchange of pollutants between the atmosphere and waterways, seepage of oil and polycyclic aromatic hydrocarbons from the ocean floor, and introduction of chlorinated hydrocarbons and chlorinated phenols through attempts to disinfect water via chlorination.[32,33] That contamination of the aquatic environment is not an oversimplification is emphasized by the current estimates of marine polycyclic hydrocarbon pollution which amount to $0.2—6 \times 10^6$ metric tons per year,[32] and of chlorinated organic contaminants from sewage treatment plants approximating >1000 tons per year.[34] As of 1975, 423 organic chemicals had been identified in the aquatic environment; of these, 325 were determined to be present in treated drinking water, a significant proportion of which are potentially carcinogenic or toxic.[34] Aquatic animals exhibit neoplasms as a result of exposure to chemical pollutants in their environment,[35,36] but in addition, as a major part of the food chain, marine and fresh water life can serve as carriers of carcinogenic pollutants.[37,38] Industrial wastes expelled into municipal and coastal waterways which find their way to more widespread bodies of water including lakes, streams, estuaries, and the sea can thus be consumed by humans via consumption of marine and fresh water plants and animals, as well as consumption of drinking water (see Reference 35 for review).

Drugs, such as certain immunosuppressive agents,[39] estrogens,[40] oral contraceptives,[41] antineoplastic agents,[42] schistosomicides,[43] trichomonicides,[44] diethylstilbestrol,[45] and other commonly used drugs[46] have also been associated with the development of human cancer. It is estimated that drug-induced cancers amount to less than 1% of all human cancers;[46] however, this figure may rise with the current increased rate of introduction of new drugs if not prescreened through the available in vitro and in vivo bioassays for their mutagenic and carcinogenic potentials.

Human exposure to chemical carcinogens by inhalation originates mainly from three major sources, i.e., tobacco smoke, air pollution, and occupational exposure. Among those cancers associated with cigarette smoking are cancers of the lung, lip, mouth, tongue, esophagus, pharynx, larynx, and urinary bladder.[47] Of these, the incidence of lung cancer surpasses the others by a wide margin. Similarly, lung cancer is one of the most prevalent neoplasms associated with job-related exposure and air pollution exposure to carcinogens. Nearly 13% of all deaths among individuals >45 years old are attributable to lung cancer,[48] although statistics vary with geographical locale, sex, and (possibly) genetic predisposition. Sawicki[49] has tabulated the constituents of the gaseous, vapor and particulate phases of ambient air in terms of background levels, urban levels and levels of high pollution, and has indicated the presence of a wide variety of

TABLE 4

Influence of Occupational and Other Factors Upon BaP Intake

Factor	BaP intake (μg/day)	Cigarette equivalents (packs/day)
Smoking one pack of cigarettes each day	0.4	1.0
Coke oven workers		
Top side exposures	180.0	450.0
Side and bench exposure	70.0	175.0
Coal tar pitch worker	750.0	1875.0
Airplane pilots		
Transatlantic flights	0.93	2.3
Domestic cross country	1.38	3.5
Employee in restaurant	0.8	2.0
Person living near expressway 24 hr/day (adverse meteorology)	0.02	0.05
Commuter on an expressway 2 hr/day (adverse meteorology)	0.04	0.10
Exposure to ambient BaP levels 8 hr/day	0.02	0.05

From Bridbord, K., Finklea, J. F., Wagoner, J. K., Moran, J. B., and Caplan, P., in *Carcinogenesis, Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis*, Vol. 1, Freudenthal, R. I. and Jones, P. W., Eds., Raven Press, New York, 1976, 319. With permission.

known carcinogens, co-carcinogens, carcinogen precursors, and potential carcinogens. These include nitrous compounds, alkenes, alkeneoxides, sulfur dioxide, ozone, formaldehyde and other aldehydes, halocarbon compounds (e.g., fluorinated gases, vinyl chloride), hydrocarbons, phenols, nitrosamines and their precursors, chloroalkylethers, para-dioxane and aza arenes, sulfates, aromatic amines, sulfites, unsaturated compounds (e.g., olefinic hydrocarbons), polycyclic aromatic hydrocarbons, and asbestos.[49]

Among these chemical agents, polycyclic aromatic hydrocarbons (PAH) have been studied quite extensively. PAH are combustion products of compounds composed of carbon and hydrogen and generally result from the incomplete combustion of organic matter. They are omnipresent in the environment (aquatic and atmospheric)[35, 50] and are derived from a number of sources including cigarette smoke, heat and power generation, fossil fuel combustion, refuse burning, motor vehicle emissions, coke production, and industrial contaminants.[25, 49, 51-58] Gross[54] reported on the identification of more than 40 PAH associated with auto exhaust emissions; a number of these are probable human carcinogens. At least as many PAH are likely to be associated with the other environmental sources.

Generally, benzo(a)pyrene (BaP) is accepted as the model PAH. To date, more is known about BaP than that of all other PAH. BaP has been identified as an atmospheric pollutant, comprising 3 to 5% of motor vehicle emissions, as a by-product of char-broiling foods, as an occupational risk factor (e.g., in coal for pitch, in sidewalk and roofing tar), and as a constitutent of cigarette smoke.[51] Measurements of human exposure to PAH generally employ BaP as an index compound.[51] Bridbord et al.[51] have tabulated the relative daily BaP intake of various ambient and occupational exposures and have related these to the number of cigarettes that would have to be consumed per day to obtain an equivalent exposure to BaP by smoking; the data is reproduced here (Table 4). From these data the authors concluded that (1) PAH levels can

TABLE 5

Analysis of the Evaluations Made by Working Groups for Substances Included in *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*

Number of chemicals evaluated	222
Number of chemicals carcinogenic to man	19
Number of chemicals definitely carcinogenic in experimental animals only	111
Number of chemicals producing some carcinogenic effect in experimental animals	42
Number of chemicals for which the data were inadequate for evaluation	32
Number of chemicals for which the available data did not reveal a carcinogenic effect	18

From Preussmann, R., *Oncology*, 33, 51, 1976. With permission.

TABLE 6

Chemicals for Which There Is Unquestionable Evidence of Carcinogenicity in Experimental Animals

Number of chemicals carcinogenic in experimental animals only	111
Human exposure known for	106
Occupational exposure known for	95*
Medicinal exposure known for	29
General environmental exposure known for	52*

* Including 11 to 15 polycyclic aromatic hydrocarbons which occur in soot and tars.

From Preussmann, R., *Oncology*, 33, 51, 1976. With permission.

be attributed to both outdoor as well as indoor exposure with the latter source surprisingly high, (2) the greatest exposure to BaP for smokers is cigarettes, (3) occupational exposure to BaP can amount to exposure levels several orders of magnitude higher than that for tobacco smokers, and (4) motor vehicle emissions are an important source of BaP, although relatively small compared to other sources listed.

Many of the identified job-related carcinogens have yet to be defined with respect to their biologically relevant routes of exposure, although cutaneous, ingestion, and inhalation constitute the main routes and the latter is most likely the primary entry route of many such agents. Occupationally related chemical carcinogens and potential carcinogens include (among others) vinyl chloride,[59-61] bis(chloromethyl)ether,[62-64] certain inhalation anesthetics[65] such as trichloroethylene (which is structurally similar to vinyl chloride, which itself at one time was considered for possible use as an anesthetic for humans), and isoflurane (which is structurally similar to the carcinogenic halogenated ethers bis[chloromethyl]ether and chloromethyl methyl ether), benzoyl chloride,[66] chloroprene (a monomer in manufacture of synthetic rubber),[67,68] and other ingredients employed in rubber manufacture (e.g., β-napthylamine, benzene, asbestos, and certain nitrosamines),[69] coke by-products,[70] BaP,[51,71] benzene,[72] metals (such as copper, aluminum, nickel, lead, cadmium, uranium, arsenic, beryllium, and chromium),[73-79] agricultural chemicals such as certain chlorinated hydrocarbon pesticides[80] (e.g., DDT, aldrin, dieldrin, chlordane, heptachlor, and kepone), and various industrial compounds such as polychlorinated biphenyls,[81] asbestos,[82-86] and fibrous glass.[87]

A number of agents, including several of those discussed above, have been evaluated for carcinogenic risk under the auspices of the International Agency for Research on Cancer (IARC). For summarial purposes, the information available up through 1975 published by IARC[88] is shown in Tables 5, 6, and 7, as presented by Preussmann.[57] In addition, a further detailed breakdown of 94 of the chemical agents examined under the IARC program has been presented by Tomatis[89] and are reproduced here (Tables 8, 9, and 10). It should be noted that some of the studies to date have reported equivocal results and are therefore subject to various interpretations. As time progresses and the data base increases more of these problems should be resolved.