NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for TOBACCO SMOKING

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NTP Report on Carcinogens Listing for Tobacco Smoking

Carcinogenicity

Tobacco smoking is a *known to be a human carcinogen* based on studies in humans which indicate a causal relationship between tobacco smoking and human cancer (reviewed in IARC V.38, 1986; Burns et al., 1997a).

Tobacco smoking has been determined to cause cancer of the lung, urinary bladder, renal pelvis, oral cavity, pharynx, larynx, esophagus, lip, and pancreas in humans. Lung cancer deaths are associated with certain tobacco smoking patterns, increasing with increasing consumption of tobacco products and decreasing in certain groups as the amount smoked declines. Smoking cessation is associated with a decreased risk of developing cancer. The carcinogenic effects of tobacco smoke are increased in individuals with certain predisposing genetic polymorphisms.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Tobacco smoke has been demonstrated to be carcinogenic in several species of experimental animals. The evidence is most clearly established for the larynx in the hamster following inhalation of tobacco smoke, and for the skin of mice receiving dermal applications of tobacco smoke condensates. Tumors of the respiratory tract have also been reported in rats exposed to cigarette smoke. Individual chemical components of tobacco smoke have been shown to be carcinogenic to humans and/or experimental animals. Tobacco smoke or tobacco smoke condensates cause cell transformation and mutations or other genetic alterations in a variety of *in vitro* and *in vivo* assays. The urine of smokers has been found to be mutagenic and there is evidence of more chromosomal damage in the somatic cells of smokers than in nonsmokers.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL IDENTIFICATION

Nearly 4000 chemicals have been found in tobacco smoke (Vineis and Caporaso, 1995; Hoffmann and Hoffmann, 1995; IARC, 1986, pp. 86-87, 114-116), including acrolein, aromatic amines, benzene, formaldehyde, nitrosamines, polycyclic aromatic hydrocarbons, urethan (ethyl carbonate), radioactive elements (radium-226, radium-228, thorium-228, polonium-210), arsenic, nickel, chromium, and cadmium.

2.0 HUMAN EXPOSURE

2.1 Use

Currently, the primary source for tobacco smoking is cigarettes, the others being the use of pipes and cigars. The use of pipes and cigars was more prevalent in the 18th and 19th centuries, but there was a shift from these products to cigarettes after 1910, following mass marketing campaigns for cigarettes (IARC, 1986; Burns et. al., 1997b). Per capita consumption of cigarettes in the United States rose from 54 in 1900 (U.S. DHHS, 1989; cited by Burns et al., 1997b,c) to a peak of 4,345 in 1963 (Burns et al., 1997c).

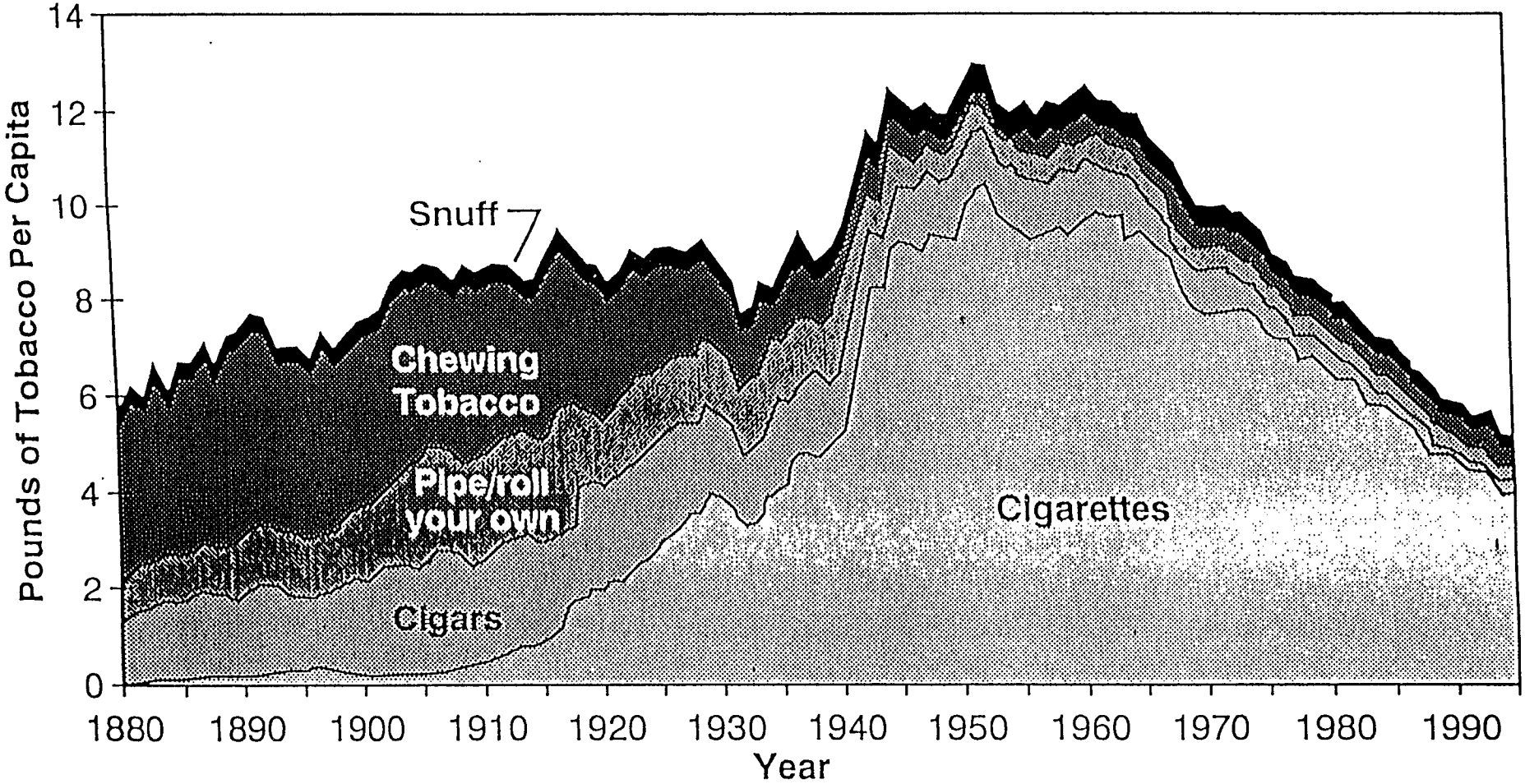
The use of tobacco products varies among racial, gender, and age groups. Currently, males have a higher prevalence of smoking than females (U.S. DHHS, 1980; cited by Burns et al., 1997c). Advertising campaigns began targeting the male population many years before targeting females, which may explain why men began smoking earlier in the century than women (U.S. DHHS, 1980; cited by Burns et al., 1997c). Smoking prevalence and cessation also vary with educational attainment (U.S. DHHS, 1989; Pierce et al., 1989; both cited by Burns et al., 1997c).

Figure 2-1 from Burns et al. (1997c) shows the trends in cigarette, pipe, chewing tobacco, and snuff consumption in the United States since 1880.

2.2 Production

Tobacco has been an important economic agricultural crop since the 1600s. North and Central America produced the highest quantity, with 1,158,506 tons harvested in 1982 (IARC, 1986). *Nicotiana tabacum* is the most common species of tobacco used in cigarettes, but *N. rustica* is also used in some areas (Garner, 1951; Wynder and Hoffmann, 1963; Tso, 1972; Akehurst, 1981; all cited by IARC, 1986). For smoking tobacco, the tobacco leaf material is manipulated by physical and chemical methods during the manufacturing process, some of which are intended to reduce the yields of toxic agents and tars in smoke. The tobacco is fine cut and wrapped in paper for consumption. Generally, cigarettes are a blend of different flue-cured grades, burley, Maryland, and oriental tobaccos (IARC, 1986).

Figure 2-1. Per Capita Consumption of Different Forms of Tobacco in the United States, 1880-1995



Source: U.S. Department of Agriculture, 1996.

2.3 Regulations

Applicable regulations are given in detail in the Regulations table. Federal regulations related to tobacco products that concern taxation, customs duties, the potential for hand-to-mouth transfer of toxic substances when using tobacco in the workplace, warnings that smoking will exacerbate noncancer risks of certain drugs, and environmental tobacco smoke are not addressed in this section.

The U.S. Food and Drug Administration (FDA) regulates nicotine-containing cigarettes and smokeless tobacco products as nicotine-delivery medical devices under 21 CFR Part 897 "to reduce the number of children and adolescents who use these products and to reduce the life-threatening consequences associated with tobacco use." Measures to reduce the appeal of and access to cigarettes and smokeless tobacco products include numerous restrictions on advertising, including promotional items and event sponsorship. Tobacco-product-dispensing vending machines and self-service displays are prohibited except in adult establishments that do not allow children on the premises at any time. Retailers must request that persons up to the age of 27 present photographic identification bearing their birth date. Free distribution of tobacco products is prohibited. Each package and advertisement must bear the label "Nicotine-Delivery Device for Persons 18 or Older." Cigarettes may not be sold in packages of fewer than 20.

Analyses of FDA jurisdiction over tobacco products (cigarettes and smokeless tobacco products) have been published in the *Federal Register*, including 60 FR 41453-41787, August 11, 1995, with a correction at 60 FR 65349-65350; 61 FR 44615 ff., August 28, 1996; and 61 FR 45219-45222, August 28, 1996. FDA published Children and Tobacco Executive Summaries (U.S. FDA, 1996 a,b), which are available free on the Internet and by mail.

The Federal Trade Commission (FTC) of the Department of Commerce administers the Federal Cigarette Labeling and Advertising Act, Public Law 89-92 as amended through Public Law 98-474 (15 U.S. 1331) (FTC, 1998). Provisions include the ban of cigarette advertisements on radio and television, submission of annual reports to Congress on current practices and methods of cigarette advertising and promotion and recommendations for appropriate legislation, and requirement of rotation of four warning statements placed conspicuously on cigarette packages and advertisements. One of the warning statements is "SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy." The last four words may be omitted on billboards.

The Federal Communications Commission (FCC) shares responsibility with FTC for the ban of advertisements of cigarettes and smokeless tobacco on radio and television (FTC, 1998).

The Department of Health and Human Services (DHHS) also has responsibilities under the Federal Cigarette Labeling and Advertising Act, 15 U.S.C. Section 1341, Smoking, Research, Education, and Information. DHHS was given mandates to establish and carry out a program to inform the public of any human health dangers of cigarette smoking. All activities, including educational and research programs within DHHS shall be coordinated with similar activities of other Federal and private agencies via the Interagency Committee on Smoking and Health. DHHS shall collect, analyze, and disseminate information, studies, and other data associated with cigarette smoking that is relevant to human health. DHHS shall develop standards, criteria, and methodologies for improved information programs related to smoking and health. DHHS is to compile State and local laws relating to cigarette use and consumption. From January 1, 1986, and biennially thereafter, the Secretary of HHS shall transmit a report to Congress that contains an overview and assessment of educational efforts by Federal agencies and the extent of public knowledge regarding health consequences of smoking, a description of DHHS and Interagency

Committee activities, and a description of private sector activities in response to the effects of smoking and health. Regulations were not identified that corresponded to all of these mandates. However, CDC publications such as the Surgeon General's reports and the National Cancer Institute's monographs in the Smoking and Tobacco Control series appear to fulfill several of these mandates.

The Centers for Disease Control and Prevention's (CDC) Office on Smoking and Health (OSH) is the delegated authority to implement major components of the DHHS's tobacco and health program, which comprises programs of information, education, and research. CDC's authority includes collection of tobacco ingredients information to facilitate HHS's overall goal of reducing death and disability from use of tobacco products (CDC, 1997).

HHS, under 45 CFR Part 96—Subpart L—Substance Abuse Prevention and Treatment Block Grant, requires that to be eligible for Block Grants to support substance abuse prevention and treatment services, each State must have in effect and strictly enforce a law that prohibits sale or distribution of tobacco products to persons under age 18 by manufacturers, distributors, or retailers.

Federal agencies have issued regulations to implement Public Law 104-52, the Prohibition of Cigarette Sales to Minors in Federal Buildings and Lands. The General Services Administration (41 CFR), the Treasury Department (31 CFR), and the Railroad Retirement Board (20 CFR) prohibit the vending and free distribution of tobacco products on property under their jurisdictions.

Under 32 CFR 85.6, health promotion efforts in each military service should include smoking prevention and cessation programs. Health care providers are encouraged to take the opportunity at routine medical and dental examinations to apprise service personnel of tobacco use risks (including smokeless tobacco) and how to get help to quit.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F C C	47 CFR—TITLE 47—TELECOMMUNICATION. CHAPTER I—FEDERAL COMMUNICATIONS COMMISSION. PART 73—RADIO BROADCAST SERVICES. Subpart H—Rules Applicable to All Broadcast Stations. 47 CFR 73.4055—Sec. 73.4055 Cigarette advertising. Promulgated: 44 FR 36388, June 22, 1979. U.S. Code: 15 U.S.C. 1335.	15 U.S.C. Sec. 1335 banned after January 1, 1971, advertising of cigarettes and little cigars on any medium of electronic communication subject to FCC jurisdiction.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 801—PART 801—LABELING. SUBPART D—Exemptions From Adequate Directions for Use.	Subchapter H covers 21 CFR parts 800-898 and governs medical devices. Cigarettes and smokeless tobacco as defined in 21 CFR 897 are exempt from section 502(f)(1) of the FFD&C Act.
	21 CFR 801.126—Sec. 801.126 Exemptions for cigarettes and smokeless tobacco. Promulgated: 61 FR 44615, Aug. 28, 1996.	
	21 CFR 803.19—Sec. 803.19 Exemptions, variances, and alternative reporting requirements. Promulgated: 60 FR 63597, Dec. 11, 1995, as amended at 61 FR 44615, Aug. 28, 1996.	Manufacturers of cigarettes and smokeless tobacco products are required to submit medical device reports for serious adverse effects that are not well known or well documented by the scientific community.
	21 CFR 897—PART 897—CIGARETTES AND SMOKELESS TOBACCO. Promulgated: 61 FR 44615, Aug. 28, 1996, unless otherwise noted. U.S. Code: 21 U.S.C. 352, 360, 360h, 360i, 360j, 371, 374, 393.	Part 897 regulates nicotine-containing cigarettes and smokeless tobacco as medical devices.
	21 CFR 897.1—Sec. 897.1 Scope.	Failure to comply with any applicable provision in this part in the sale, distribution, and use of cigarettes and smokeless tobacco renders the product misbranded under the FFD&C Act.
	21 CFR 897.2—Sec. 897.2 Purpose.	Restrictions on the sale, distribution, and use of cigarettes and smokeless tobacco are established "to reduce the number of children and adolescents who use these products and to reduce the life-threatening consequences associated with tobacco use.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 897.3—Sec. 897.3 Definitions.	This section defines cigarettes, smokeless tobacco, manufacturers, distributors (common carriers excluded), and packages. Retailers are any persons who sell cigarettes or smokeless tobacco to individuals for personal consumption or who operate a facility where vending machines or self-service displays are permitted (see 21 CFR 897.16).
	21 CFR 897—Subpart B—Prohibition of Sale and Distribution to Persons Younger Than 18 Years of Age.	
	21 CFR 897.10—Sec. 897.10 General responsibilities of manufacturers, distributors, and retailers.	Each manufacturer, distributor, and retailer must ensure that the cigarettes and smokeless tobacco products it manufactures, labels, advertises, packages, distributes, sells or otherwise holds for sale comply with all applicable requirements under this part.
	21 CFR 897.12—Sec. 897.12 Additional responsibilities of manufacturers.	Manufacturers shall remove self-service displays, advertising, labeling, and other items that do not comply.
	21 CFR 897.14—Sec. 897.14 Additional responsibilities of retailers.	Except as allowed under Sec. 897.16(c)(2)(ii), a retailer may sell cigarettes and smokeless tobacco only in direct, face-to-face exchange. A retailer may not sell cigarettes or smokeless tobacco to any person younger than 18 years of age and must verify age for persons under the age of 26 by photographic identification containing the bearer's date of birth. Retailers may not offer for sale these products in units smaller than the smallest package distributed by the manufacturer for individual customer use. Self-service displays, etc., that do not comply with requirements must be removed or brought into compliance.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 897.16—Sec. 897.16 Conditions of manufacture, sale, and distribution.	Brand or trade names of new cigarette or smokeless tobacco products introduced after January 1, 1995, may no longer use the name of a nontobacco product. The minimum number of cigarettes allowed per package is 20. Vending machines and self-service displays are permitted only when located in establishments that do not allow entry at any time of persons under 18 years of age. Mail-order sales are permitted except for redemption of coupons. Free sample distribution is not permitted.
	21 CFR 897—Subpart C—Labels.	
	21 CFR 897.24—Sec. 897.24 Established names for cigarettes and smokeless tobacco.	Appropriate names for cigarette products as provided in Section 502 of the act are cigarette and cigarette tobacco.
	21 CFR 897.25—Sec. 897.25 Statement of intended use and age restriction.	Each package shall bear the statement "Nicotine-Delivery Device for Persons 18 or Older."
	21 CFR 897—Subpart D—Labeling and Advertising.	
	21 CFR 897.30—Sec. 897.30 Scope of permissible forms of labeling and advertising.	Manufacturers, distributors, and retailers who advertise and label media other than those specified must provide 30-days' notice to FDA, giving the medium and discussing the extent to which persons younger than 18 years of age may see the advertisement or label. Outdoor advertising, including billboards, must not be placed within 1000 feet of any elementary or secondary school, public playground, or playground area (including baseball diamonds and basketball courts) in a public park.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 897.32—Sec. 897.32 Format and content requirements for labeling and advertising.	This section excludes print advertising inside retail establishments where vending machines and self-service displays are permitted and in adult publications such as newspapers, magazines, and periodicals of limited distribution to persons younger than 18 years of age (fewer than 2 million or less than 15% of the total readership). Audio and video formats exclude music and sound effects. Video formats must be static black text on a white background. The advertisement must append the statement "Nicotine-Delivery Device for Persons 18 or Older" after the appropriate product name as specified in 21 CFR 897.24.
	21 CFR 897.34—Sec. 897.34 Sale and distribution of nontobacco items and services, gifts, and sponsorship of events. Effective Date Note: At 61 FR 44617, Aug. 28, 1996, in Sec. 897.34, paragraph (c) [regarding event sponsorship] was added, effective Feb. 28, 1998. At 61 FR 47550, Sept. 9, 1996, the effective date was corrected to Aug. 28, 1998.	"No manufacturer and no distributor of imported cigarettes and smokeless tobacco may market, license, distribute, or sell items or services" (or cause these actions by others) that bear the brand name, logo, symbol, motto, selling message, recognizable color or pattern of colors, or other indicia of product identification associated with any brand of cigarettes or smokeless tobacco. These product-associated restrictions also apply to sponsorship of any athletic, musical, artistic, or other social or cultural event or any entry or team in any event by any manufacturer, distributor, or retailer. (The sponsor may use the name of the company if the corporate name and corporation were registered before January 1, 1995, and does not include the brand name, etc.) Manufacturers, distributors, and retailers may not offer or cause to be offered gift or redemption items other than cigarettes or smokeless tobacco.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F T C	16 CFR CHAPTER I—FEDERAL TRADE COMMISSION.	FTC administers the Federal Cigarette Labeling and Advertising Act. One of the purposes is to inform the public adequately about any adverse health effects of cigarette smoking by use of warning labels on cigarette packages and advertisements. Because applicable FTC regulations were not found in the CFR, selected portions of the U.S. Code are presented in this table. Public Law 91-222 Sec. 1 may be cited as the Public Health Cigarette Smoking Act of 1969. Public Law 98-474 Sec. 1 may be cited as the Comprehensive Smoking Education Act.
	16 CFR 0—PART 0—LAWS ADMINISTERED. Authority: Public Law 89-92, Sec. 2, July 25, 1965, 79 Stat. 282 and subsequent amendments: Public Law 91-222, Sec. 2, Apr. 1, 1970, 84 Stat. 87; Public Law 98-474, Sec. 6(a), Oct. 12, 1984, 98 Stat. 2204). U.S. Code: 15 U.S.C. Sec. 1331.	
	16 CFR 408—PART 408—UNFAIR OR DECEPTIVE ADVERTISING AND LABELING OF CIGARETTES IN RELATION TO HEALTH HAZARDS OF SMOKING.	Content for 16 CFR 408 was not located, but it would appear to pertain to Public Law 89-92 and subsequent laws.
	15 U.S.C. Sec. 1333 Labeling; requirements; conspicuous statement.	Labels on cigarette packages and advertisements other than billboards must bear in rotation one of four warning statements, including: "SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy" and "SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health." The messages may be slightly reduced in billboard advertising. Cigarette manufacturers and importers must submit a plan to FTC detailing how the messages will be rotated.
	15 U.S.C. Sec. 1334a Preemption.	Cigarette packages are not required to bear any other health statement than that required by 15 U.S.C. sec. 1333.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F T C	15 U.S.C. Sec. 1335 Unlawful advertisements on medium of electronic communication [subject to the jurisdiction of the FCC].	See FCC in this table. Cigarette manufacturers were banned from cigarette advertising on television and radio in 1969 (FTC, 1998).
	15 U.S.C. Sec. 1337 Reports to Congress by the Secretary [of Health and Human Services] and Federal Trade Commission.	FTC shall transmit annually to Congress a report on current practices and methods of cigarette advertising and promotion and recommendations for appropriate legislation.
H H S	45 CFR—TITLE 45—PUBLIC WELFARE. SUBTITLE A—DEPARTMENT OF HEALTH AND HUMAN RESOURCES.	
	45 CFR 96—PART 96—BLOCK GRANTS. Subpart L—Substance abuse prevention and treatment. Promulgated: 58 FR 17070, March 31, 1993 with tobacco-related amendments 61 FR 1491-1509, January 19, 1996. U.S. Code: 42 U.S.C. 300x-21 to 300x-35 and 300x-51 to 300x-64.	The amendments promulgated January 19, 1996, implement section 1926 of the Public Health Service (PHS) Act regarding the sale and distribution of nicotine-containing tobacco products to minors by requiring, as a condition of eligibility for Block Grants, that individual States have in effect and enforce a law that prohibits such sales and distribution to minors.
	45 CFR 96.122—Sec. 96.122 Application content and procedures.	This section requires States applying for Block Grants to provide a copy of the state law described in Sec. 96.130 and a description of enforcement strategies.
	45 CFR 96.123—Sec. 96.123 Assurances.	Applications for Block Grants must include Assurances that the State has a law in effect that makes it unlawful to sell or distribute tobacco products to minors and enforces the law in a manner reasonably expected to reduce the extent to which tobacco products are available to persons younger than age 18.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
H H S	45 CFR 96.130—Sec. 96.130 State law regarding the sale of tobacco products to individuals under age of 18.	Since fiscal year 1994 (in some cases fiscal year 1995), for States to be eligible for Block Grants to assist State programs providing substance-abuse prevention and treatment services, they must have in effect a law making it unlawful for manufacturers, distributors, or retailers to sell or distribute tobacco products to minors. Prohibitions include over-the-counter and vending-machine sales. States must conduct annual, random, unannounced inspections to ensure compliance. The report to the HHS Secretary must include descriptions of enforcement activities, including inspection methodology and overall success. Annual reports should include a plan for improving enforcement and should document progress in reducing availability to minors.
	15 U.S.C. Sec. 1335a List of cigarette ingredients; annual submission to Secretary; transmittal to Congress; confidentiality.	Cigarette manufacturers, packagers, and importers are required to report a list of ingredients added to tobacco in cigarette manufacture to the Secretary of HHS. Brands and companies do not need to be identified. The Secretary shall give reports to Congress that summarize ongoing and planned research activities on the health effects of tobacco additives and provide any information pertinent to the health risk of an ingredient.
	15 U.S.C. Sec. 1337 Reports to Congress by the Secretary [of Health and Human Services] and Federal Trade Commission.	The Secretary of HHS shall transmit to Congress annually, beginning ca. January 1971, a report to Congress on health consequences of smoking and recommendations for appropriate legislation.
	15 U.S.C. Sec. 1341 Smoking, research, education, and information.	The Secretary of HHS shall establish and carry out a program to inform the public of any dangers to human health presented by cigarette smoking. [See text for details.]

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
OTHER	41 CFR—TITLE 41—PUBLIC CONTRACTS AND PROPERTY MANAGEMENT. SUBTITLE C—FEDERAL PROPERTY MANAGEMENT REGULATIONS.	
	41 CFR 101-20—MANAGEMENT OF BUILDINGS AND GROUNDS. Promulgated: 61 FR 2121-2122, Jan. 25, 1996. U.S. Code: 40 U.S.C. 486nt. Public Law 104-52, Sec. 636 (Prohibition of Cigarette Sales to Minors in Federal Buildings and Lands Act).	The General Services Administration (GSA) prohibited the sale of tobacco products in vending machines and the distribution of free samples in federal government-owned and -leased space. When promulgated, GSA intended to remove vending machines selling tobacco products from government property.
	31 CFR—TITLE 31—MONEY AND FINANCE: TREASURY.	
	31 CFR 12—PART 12—RESTRICTION OF SALE AND DISTRIBUTION OF TOBACCO PRODUCTS. Promulgated: 61 FR 25396, May 21, 1996. Public Law 104-52.	To implement Public Law 104-52, tobacco products sales from vending machines and free distribution are prohibited in federal buildings under the jurisdiction of the Secretary of the Treasury.
	20 CFR—TITLE 20—EMPLOYEES' BENEFITS.	
	20 CFR 368—PART 368—PROHIBITION OF CIGARETTE SALES TO MINORS. Promulgated: final rule 61 FR 54732-54733, Oct. 22, 1996. Public Law 104-52.	The Railroad Retirement Board, which conducts its business in GSA-owned or GSA-leased facilities, issued these regulations to comply with public Law 104-52 (see GSA entry).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
OTHER	32 CFR—TITLE 32—NATIONAL DEFENSE. CHAPTER I—OFFICE OF THE SECRETARY OF DEFENSE. PART 85—HEALTH PROMOTION.	
	32 CFR 85.6—Sec. 85.6 Procedures.	Health promotion efforts in each military service should include smoking prevention and cessation programs. Military personnel at initial entry and permanent transfer should be informed about smoking's health consequences as well as those of alcohol and drug abuse. During routine physical and dental examinations, health care providers are encouraged to advise of risks of tobacco use, including smokeless tobacco; advise of the health benefits of abstinence; and advise how to get help to quit.

[a]Regulations considered for inclusion in the table and discussion were examined in the 1998 editions of titles 16, 19-21, 29, 31, 32, 40, and 41 and in the 1997 editions of titles 42, 45, and 47 of the *Code of Federal Regulations* and in 1997, 1998, and 1999 issues of the *Federal Register* through January 31, 1999.

3.0 HUMAN STUDIES

Cigarette smoking has been known to cause cancer in humans for many years, and is now considered to be the leading preventable cause of cancer in developed countries (Burns et al., 1997b, see Appendix B). This report focuses on mainstream smoke, not sidestream or environmental tobacco smoke.

3.1 Historical Review

Around 1900, vital statisticians noted an increase in lung cancer. Definite trends in mortality and disease incidence became more conspicuous by 1930, and since that date numerous studies on the effects of smoking have been conducted. Several notable studies linking cigarette smoking to cancer of the lung brought widespread attention to the topic in 1952 to 1956. From 1950 to 1960, statements based on the accumulated evidence were made by the cancer societies of Denmark, Norway, Sweden, Finland, and the Netherlands, the American Cancer Society, and the Canadian National Department of Health and Welfare. These groups agreed that lung cancer due to smoking was an important health hazard (U.S. DHEW, 1964).

In 1956 the U.S. Public Health Service first became officially involved in reviewing the available data on smoking and its effects. At that time, the Surgeon General recommended the formation of a scientific study group on the subject, and one was established jointly by the National Cancer Institute, the National Heart Institute, the American Cancer Society, and the

American Heart Association. The group concluded that there is a causal relationship between excessive smoking of cigarettes and lung cancer. In 1957 and 1959 the Surgeon General made public statements stating the causal link between smoking and lung cancer (U.S. DHEW, 1964). The 1964 Report of the Advisory Committee to the Surgeon General of the Public Health Service concluded that there is a causal relationship between smoking and lung cancer, cancer of the lip, and laryngeal cancer (U.S. DHEW, 1964). In the 1979 Report of the Surgeon General, the causal relationship between cigarette smoking and cancer of the esophagus was added to those mentioned in the 1964 Report (U.S. DHEW, 1979).

In 1980, the U.S. Department of Health and Human Services (U.S. DHHS, 1980; cited by Burns et al., 1997c) produced a report entitled *The Health Consequences of Smoking for Women.* In 1989 and 1990 the U.S. DHHS produced two more reports, *Reducing the Health Consequences of Smoking: 25 Years of Progress* (U.S. DHHS, 1989; cited by Burns et al., 1997b,c) and *The Health Benefits of Smoking Cessation* (U.S. DHHS, 1990, cited by Burns et al., 1997b,c).

3.2 Target Organs

An IARC Working Group (IARC, 1986, pp.127-308; see Appendix A) reviewed studies on the carcinogenicity of tobacco smoke in humans and came to the following conclusions: cigarette smoking causes cancer of the lung, and the risk of squamous-cell (epidermoid) and small-cell carcinomas of the lung is higher than the risk of adenocarcinoma of the lung. Bladder and renal pelvis cancers are also caused by tobacco smoking (particularly cigarettes), although the risk of these two cancers is lower than the risk of lung cancer. Tobacco smoking causes oral, oropharyngeal, hypopharyngeal, laryngeal, esophageal, and lip cancers, as well as pancreatic cancer. Some data also suggested a causal relationship between tobacco smoking and stomach and liver cancers, but the data were not conclusive. There was also no conclusive evidence of a causal link between tobacco smoking and cervical cancer, although there is an increased risk in smokers.

3.3 Trends Associated with Smoking and Cancer Risk

In 1997, the National Cancer Institute published Monograph 8, entitled *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control.* This volume provided detailed presentations of the disease risks caused by smoking, using data from five recent prospective epidemiological studies and more extensive follow-up data on the American Cancer Society (ACS) Cancer Prevention Studies I (CPS-I) and II (CPS-II) (Burns et al., 1997a). The following summarizes general trends from the Monograph.

3.3.1 Smoking Prevalence

Cigarette smoking has been mostly a phenomenon of the 20th century. Mass marketing efforts of cigarette companies launched the trend for smoking in 1913, although at that time, most smokers were men. Women began smoking after being targeted by advertising later in the 1930s (Burns et al., 1997b).

Lung cancer deaths were rare at the turn of the century, but rose rapidly among males in the 1930s and then began to decline in the late 1980s, reflecting the decline in smoking prevalence among white males that had begun in the late 1950s. For women, lung cancer rates began to rise sharply only in the 1960s, since their initiation to smoking occurred later (Burns et al., 1997b).

3.3.2 Disease Consequences

Burns et al. (1997b) refers to reports of the Surgeon General (U.S. DHHS, 1989, 1990) and a previous NCI Monograph (Haenszel, 1966; cited by Burns et al., 1997b) that document the disease consequences associated with smoking. The excess rates of cancer from smoking vary by the smoker's age, number of cigarettes smoked per day, and the duration of smoking. Even though early age of initiation results in a longer duration of smoking at any given age, there is little evidence from the CPS-I 12-year follow-up study that early initiation results in an increase in lung cancer risk, other than its contribution to smoking duration.

The death rates for lung cancer in the United States have varied drastically over time (40 years) and between males and females. In the CPS-I study, lung cancer rates were lower among white females than white males, even when analyzed by number of cigarettes smoked per day and duration of smoking. Other factors, such as differences in pattern of inhalation or type of cigarette smoked, may have contributed to the difference in rates (Burns et al., 1997b).

Age-adjusted death rates for lung cancer increased among smokers (male and female) from the CPS-I study (1959 to 1965) to the CPS-II study (1982 to 1988). Among never-smokers the lung cancer rates changed little. Since white females began smoking later in the century than white men, the increase in death rates for women from lung cancer was expected. Differences in smoking behavior over time were offered as an explanation for the increase in death rates among the white males. However, when specific groups based on age, duration of smoking, and cigarettes per day were compared, lung cancer rates for white male smokers of 20 cigarettes per day who smoked for longer than 40 years were still higher in CPS-II than in CPS-I (Burns et al., 1997b).

3.3.3 Cessation

New data have supported the previous knowledge that cessation of smoking dramatically reduces the risk of lung cancer in comparison with the risks of continuing to smoke (Burns et al., 1997b). The relative risk of lung cancer death does not decrease until the smoker has quit smoking for five years. While the risks decline steadily from 5 to 20 years following cessation, the risk of lung cancer remains slightly higher for former smokers than for never-smokers (Burns et al., 1997b).

3.3.4 Annotated Bibliography

The following recent studies confirm the causal relationship between smoking and increased cancer risks. Some add new information on the health effects and trends associated with smoking.

Colditz, G., W. DeJong, D. Hunter, D. Trichopoulos, and W. Willett, Eds. 1996. Smoking. In: Harvard report on cancer prevention, vol. 1: Causes of human cancer. Cancer Causes Control 7:S5-S6.

High consumption of fruits and vegetables seems to reduce the adverse effects of smoking in numerous studies. However, the greatest reduction in risk can be achieved through avoiding or preventing smoking and smoking cessation.

Doll, R. 1996. Cancers weakly related to smoking. Br. Med. Bull. 52(1):35-49.

The author refers to IARC (1986), which found a causal relationship between smoking and cancers of the lung, larynx, oro- and hypo-pharynx, esophagus, bladder, renal pelvis, and pancreas. Doll added that this review now justifies the conclusion that cigarette smoking causes cancers of the stomach, renal body, liver, and nose, and has been implicated in myeloid leukemia.

Friedman, G. D., I. Tekawa, M. Sadler, and S. Sidney. 1997. Smoking and mortality: The Kaiser Permanente experience. In: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Burns, D. M., L. Garfinkel, and J. M. Samet, Eds. NIH publication no. 97-4213. (Smoking and tobacco control monographs: no. 8.) U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; Bethesda, MD; pp. 477-499.

The study found that the relative risk (RR) of dying from lung cancer among women was highest for blacks and whites and only moderately high in Asians. Among men, the RR was highest in whites, next highest in blacks, and lowest in Asians.

The RR of lung cancer was more than twentyfold higher for women who smoked at least 20 cigarettes per day than for women who never smoked (among age categories 35 to 49 years; 65 to 74 years; and 75 years and older). The risk was also more than twentyfold higher for women in the 65 to 74 age category who smoked fewer than 20 cigarettes per day. For men, a dose-response relationship showed an increasing RR of lung cancer with increasing numbers of cigarettes smoked.

The relative risk of lung cancer generally increased with increased duration of smoking in women. Duration was also found to be strongly related to lung cancer risk in men (among age category 50 to 64 years).

A decline in RR of lung cancer with increasing duration of quitting was observed among women in the 50 to 64 and 75 or older age categories. The same decline in lung cancer risk with increased cessation of smoking was found among men in the 50 to 64 age category.

In addition to finding significant increases in RR of dying from lung cancer as a result of smoking, the study found statistically significant increases in cancer of the pancreas in women and cancer of the stomach in men who smoke.

Giovannucci, E., E. B. Rimm, M. J. Stampfer, et al. 1994. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J. Natl. Cancer Inst. 86:183-191.

The study examined the association between cigarette smoking and risk of colorectal adenoma and colorectal cancer in men. Men who smoked in the 20-year time span examined had an increased incidence of small colorectal adenomas and those who smoked for 20 years or more had an increased incidence of larger adenomas. The induction period for colorectal cancers was at least 35 years.

Hrubec, Z., and J. K. McLaughlin. 1997. Former cigarette smoking and mortality among U.S. veterans: a 26-year followup, 1954 to 1980. In: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Burns, D. M., L. Garfinkel, and J. M. Samet, Eds. NIH publication no. 97-4213. (Smoking and tobacco control monographs: no. 8.) U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; Bethesda, MD; pp. 501-530.

Former cigarette smokers had higher relative risks for larynx cancer than for lung cancer. However, the lung cancer risk involved more deaths. Lung cancer mortality was much reduced after 40 or more years of cessation, but the risk still remained 50% higher than for never-smokers.

Kawachi, I., G. A. Colditz, M. J. Stampfer, W. C. Willett, J. E. Manson, B. Rosner, D. J. Hunter, C. H. Hennekens, and F. E. Speizer. 1997. Smoking cessation and decreased risks of total mortality, stroke, and coronary heart disease incidence among women: a prospective cohort study. In: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Burns, D. M., L. Garfinkel, and J. M. Samet, Eds. NIH publication no. 97-4213. (Smoking and tobacco control monographs: no. 8.) U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; Bethesda, MD; pp. 531-565.

The overall relative risk of dying from cancer was higher for smokers compared with nonsmokers, and the risk increased with the number of cigarettes smoked per day. When the data were analyzed excluding lung cancer, a weak association was found between smoking and mortality from cancers of the buccal cavity, pharynx, esophagus, and pancreas. Additionally, risk of total cancer was greater in the first two years after cessation of smoking, but the relative risk fell to the level of never-smokers after 10 to 14 years of cessation.

Lumey, L. H. 1996. Prostate cancer and smoking: A review of case-control and cohort studies. Prostate (NY) 29:249-260.

In the review of case-control and cohort studies, a significant association was not found between smoking and prostate cancer. Additionally, the association of other risk factors and prostate cancer is not likely to be confounded by smoking since smoking does not seem to be causally related to prostate cancer.

Stellman, S. D., J. E. Muscat, S. Thompson, D. Hoggmann, and E. L. Wynder. 1997. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. Cancer (Philadelphia) 80:382-388.

An 18-year study of lung carcinoma patients and hospital controls indicated that filter cigarettes may not reduce the risk of cancer from lifetime cigarette smoking because many smokers inhale more deeply to compensate. The deposition pattern of particulate matter in the lungs appears to have shifted from more lodged in the bifurcation zone of the tracheobronchial tree to more lodged in the alveoli. Adenocarcinoma may be increasing over

squamous cell carcinoma in women (and further study in men is needed) because of deeper inhalation and higher concentrations of nitrosamines in modern cigarettes.

Thun, M. J., C. Day-Lally, D. G. Myers, E. E. Calle, W. D. Flanders, B.-P. Zhu, M. M. Namboodiri, and C. W. Heath, Jr. 1997. Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II (1982 through 1988). In: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control, Burns, D. M., L. Garfinkel, and J. M. Samet, Eds. NIH publication no. 97-4213. (Smoking and tobacco control monographs: no. 8.) U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; Bethesda, MD; pp. 305-382.

The study analyzed time trends in disease risks associated with smoking. From the first (1959-1965) to the second study (1982-1988), lung cancer death rates nearly doubled in men and increased almost sixfold in women. For never-smokers, lung cancer rates remained essentially the same. In 1982, lung cancer became the largest single contributor to accelerated mortality among smokers.

When comparisons were made between lung cancer death rates and the cigarettes per day-, age-, and duration of smoking- strata, modest increases in lung cancer death rates from CPS-I to CPS-II were found for black and white males who smoked 40 cigarettes per day. No differences between the death rates and the stratifying factors were found between the two studies for white males who smoked 20 cigarettes per day until they had smoked greater than 40 years. In CPS-II, the lung cancer death rates for black and white males who smoked 20 cigarettes per day for 40 to 49 years were substantially higher than those in CPS-I.

Lastly, the evolution of cigarettes, such as low tar cigarettes, has not protected smokers from lung cancer. Potential benefits of smoking reduced-tar cigarettes (as measured by machine smoking) seem to be overwhelmed by the changes in smoking practices and other unidentified factors.

4.0 EXPERIMENTAL CARCINOGENESIS

Carcinogenicity studies conducted on animals have been reviewed by IARC (1986) and Vineis (1995). Evidence for the experimental carcinogenesis of inhaled tobacco smoke in mice, rats, hamsters, rabbits, and dogs and of dermally applied tobacco smoke condensates on mice, rats, hamsters, and rabbits is covered in the IARC Monograph, Volume 38 (1986, pp. 139-161; see Appendix A). The evidence for carcinogenicity in experimental animals is best established for laryngeal cancer in hamsters exposed to tobacco smoke by inhalation and for skin tumors in mice exposed dermally to various cigarette smoke condensates. One study reported tumor induction in the respiratory tract of rats exposed to cigarette smoke.

5.0 GENOTOXICITY

The genotoxicity of tobacco smoke has been reviewed by IARC (1986), Vineis and Caporaso (1995), and Vineis (1995). Evidence for the genetic toxicity of fresh tobacco smoke and tobacco smoke condensates in prokaryotes, lower eukaryotes, plants, mammalian systems *in vitro,* and rodents *in vivo* is covered in the IARC Monograph, Volume 38 (1986, pp. 153-163; see Appendix A).

Both direct and sidestream tobacco smoke were mutagenic in various strains of *Salmonella typhimurium*. In other tests on *S. typhimurium*, all tobacco smoke condensates were

found to be mutagenic except those obtained from nitrate-treated cigarettes. The activity was seen only when an exogenous metabolic system was present. Most mutagenic activity occurred in basic fractions. Less activity was seen in acidic fractions and almost no mutagenic activity was found in neutral fractions. High, medium and low-tar cigarettes were tested and found to be equivalent in mutagenic activity. Testing of various filters only marginally reduced mutagenicity. Cigars, cigarettes, and pipes had decreasing specific mutagenic activity, respectively. In addition, the urine of rats and baboons exposed to cigarette smoke showed mutagenic activity in *S. typhimurium*.

Fresh tobacco smoke and, in most cases, tobacco smoke condensates have also been shown to induce gene mutations in *Saccharomyces cerevisiae* and mouse lymphoma cells, mitotic recombination and gene conversion in *S. cerevisiae*, chromosomal aberrations in *Allium cepa*, sex-linked recessive lethal mutations in *Drosophila melanogaster*, sister chromatid exchanges (SCE) in Chinese hamster lung V79 cells, Chinese hamster ovary cells, and human lymphocytes *in vitro*, and cell transformation in mouse L-cells, hamster lung fibroblasts, Syrian hamster embryo cells, mouse C3H 10 T1/2 embryo cells, and human fetal lung cells *in vitro*. Cigarette smoke condensates were negative only for gene mutations in *S. cerevisiae*.

In vivo, exposure to fresh tobacco smoke inhibited DNA repair capacity in the mouse liver and induced SCE in mouse bone marrow, but not in Chinese hamsters and Wistar rats. Both fresh tobacco smoke and cigarette smoke condensates were negative for chromosomal aberrations in Chinese hamsters.

6.0 OTHER RELEVANT BIOLOGICAL DATA

IARC (1986) reviewed experimental studies on the toxicity of tobacco smoke in animals including cellular and chemical responses, histopathological manifestations following subchronic exposure, and immunotoxicity (pp. 140-148) and on the metabolic effects of tobacco smoke (pp. 149-153). Please refer to Appendix A.

7.0 MECHANISMS OF CARCINOGENESIS

A recent review by Vineis (1995) on tobacco and cancer included a discussion of the mechanisms of carcinogenesis caused by tobacco smoking. His review is summarized below.

7.1 Mutations in Oncogenes or Tumor Suppressor Genes

The involvement of proto-oncogenes and tumor suppressor genes has been repeatedly proposed in chemical carcinogenesis. Epidemiological investigations specific to tobacco smoke have considered the association between lung cancer and tobacco smoking with regards to the *ras* oncogenes. K-*ras* mutations have been found in the DNA isolated from some human non-small cell lung carcinoma (NSCLC). These mutations appear to occur more frequently in adenocarcinoma from smokers than those from nonsmokers. All K-*ras* mutations in a study comparing smokers with nonsmokers were in codon 12 with mostly G-T transversions (Vineis, 1995).

Other studies have focused on the expression of the *p*53 gene as detected by immunostaining of sections of cancers of the head and neck. Smokers were much more likely to exhibit overexpression of the *p*53 gene in tumor tissue than nonsmokers. Tumors studied from a group of patients who had given up smoking more than 5 years previously also showed overexpression of the *p*53 gene (Vineis, 1995). Overexpression of the *p*53 gene often indicates the presence of a mutation leading to inactivation of the tumor suppressor function.

Vineis (1995) stated that it is most likely premature to conclude that *ras* or *p*53 genes are causally involved in the mechanism of tobacco carcinogenesis. Although the observations summarized are highly relevant, longitudinal evidence on the time sequence of tobacco smoking, gene mutations, and cancer onset is lacking.

7.2 Genetic-Environmental Interactions

A case-control study of lung cancer mortality among relatives of lung cancer patients and other investigations using twins have found that, overall, smoking, not genetic makeup, is the determinant of lung cancer (Vineis, 1995).

However, certain metabolic polymorphisms seem to confer a higher risk of developing cancer from smoking. Individuals exhibiting high CYP1A1 and low glutathione *S*-transferase activity polymorphisms have been found to have a higher lung cancer risk at certain levels of cigarette smoking than individuals not exhibiting the genetic pattern. For example, Japanese patients with these genotypes appeared to contract lung cancer after fewer cigarettes than other genotypes (Nakachi et al., 1993; cited by Vineis, 1995).

In regard to bladder cancer, *N*-acetyltransferase is a non-inducible enzyme that deactivates carcinogenic aromatic amines, and more than 50% of the Caucasian populations have been found to be slow acetylators. A study of smokers and nonsmokers found that slow acetylators had higher levels of 4-aminobiphenyl-hemoglobin adduct in the blood than fast acetylators. Metabolic polymorphism, amount of smoking, and the type of tobacco smoked exert separate influences on the level of carcinogen-hemoglobin adducts (Hecht and Hoffmann, 1991; cited by Vineis, 1995). Bladder cancer rates have been shown to be higher in smokers who exhibit a double deletion of alleles coding for glutathione-*S*-transferase M1 than in smokers or nonsmokers who have one or two functional alleles for this enzyme thought responsible for detoxifying certain carcinogens (Bell et al., 1993).

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 38 (Tobacco Smoking) 1986 pp. 15-34, 47-81, 86-87, 127-375

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IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS[1]

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Following the recommendations of an ad-hoc Working Group, which met in Lyon in 1979 to prepare criteria to select chemicals for *IARC Monographs*(1), the *Monographs* programme was expanded to include consideration of exposures to complex mixtures which may occur, for example, in many occupations or as a result of human habits.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs* series. This preamble reflects subsequent re-evaluation of those criteria by working groups which met in 1977(2), 1978(3), 1982(4) and 1983(5).

2. OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals, groups of chemicals, industrial processes and other complex mixtures to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts, and to indicate where additional research efforts are needed. These evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendation is given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or other international agencies.

[1]This project is supported by PHS Grant No. 1 U01 CA33193-03 awarded by the US National Cancer Institute, Department of Health and Human Services.

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental and other chemicals. A users' survey, made in 1984, indicated that the monographs are consulted by various agencies in 45 countries. As of March 1986, 38 volumes of the *Monographs* had been published or were in press. Five supplements have been published: two summaries of evaluations of chemicals associated with human cancer, an evaluation of screening assays for carcinogens, and two cross indexes of synonyms and trade names of chemicals evaluated in the series(6).

3. SELECTION OF CHEMICALS AND COMPLEX EXPOSURES FOR MONOGRAPHS

The chemicals (natural and synthetic including those which occur as mixtures and in manufacturing processes) and complex exposures are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues are also considered. The scientific literature is surveyed for published data relevant to the *Monographs* programme; and the IARC *Survey of Chemicals Being Tested for Carcinogenicity* (7) often indicates those chemicals that may be scheduled for future meetings.

As new data on chemicals for which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances or complex exposures to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; recognized sources of information on chemical carcinogenesis and on-line systems such as CANCERLINE, MEDLINE and TOXLINE are used in conjunction with US Public Health Service Publication No. 149(8). Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, TN, USA.

The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production and use, on occurrence, and on analysis are carried out by Tracor Jitco, Inc., and its subcontractor, Technical Resources, Inc., both in Rockville, MD, USA, under a separate contract with the US National Cancer Institute. Most of the data so obtained refer to the USA and Japan; IARC attempts to supplement this information with that from other sources in Europe. Representatives from industrial associations may assist in the preparation of sections describing industrial processes.

Six months before the meeting, articles containing relevant biological data are sent to an expert(s), or are used by IARC staff, to prepare first drafts of the sections on biological effects. The complete drafts are then compiled by IARC staff and sent, prior to the meeting,

to all participants of the Working Group for their comments.

The Working Group meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited by a professional editor and prepared for reproduction. The aim is to publish monographs within nine months of the Working Group meeting. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. The monographs are also available *via* the WHO Distribution and Sales Service.

These procedures are followed for the preparation of most volumes of monographs, which cover chemicals and groups of chemicals; however, they may vary when the subject matter is an industry or life-style factor.

5. DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few exceptions have been made: in certain instances, reports from government agencies that have undergone peer review and are widely available are considered. The monographs do not cite all of the literature on a particular chemical or complex exposure: only those data considered by the Working Group to be relevant to the evaluation of carcinogenic risk to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals or complex exposures for which monographs have appeared is asked to make them available to the Unit of Carcinogen Identification and Evaluation, Division of Environmental Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

6. THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the Working Group; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to make an evaluation of the carcinogenicity of the chemical or complex exposure.

Working Group participants who contributed to the consideration and evaluation of chemicals or complex exposures within a particular volume are listed, with their addresses, at the beginning of each publication. Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies and industrial associations.

7. GENERAL PRINCIPLES APPLIED BY THE WORKING GROUP IN EVALUATING CARCINOGENIC RISK OF CHEMICALS OR COMPLEX MIXTURES

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals (or complex mixtures of chemicals) of

neoplasms that are not usually observed, the earlier induction of neoplasms that are commonly observed, and/or the induction of more neoplasms than are usually found —although fundamentally different mechanisms may be involved in these three situations. Etymologically, the term 'carcinogenesis' means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours. In the monographs, the words 'tumour' and 'neoplasm' are used interchangeably. (In the scientific literature, the terms 'tumorigen', 'oncogen' and 'blastomogen' have all been used synonymously with 'carcinogen', although occasionally 'tumorigen' has been used specifically to denote a substance that induces benign tumours.)

(a) Experimental Evidence

(i) *Evidence for carcinogenicity in experimental animals*

The Working Group considers various aspects of the experimental evidence reported in the literature and formulates an evaluation of that evidence.

Qualitative aspects: Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical (or complex mixture) involve several considerations of qualitative importance, including: (a) the experimental parameters under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.; (b) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which target organ(s); (c) the spectrum of neoplastic response, from benign neoplasm to multiple malignant tumours; (d) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others may have promoting activity only; and (e) the possible role of modifying factors.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities are also considered in the interpretation of data.

Many chemicals induce both benign and malignant tumours. Among chemicals that have been studied extensively, there are few instances in which the only neoplasms induced are benign. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end-points' that do not readily undergo transition to malignancy. If a substance is found to induce only benign tumours in experimental animals, it should nevertheless be suspected of being a carcinogen, and it requires further investigation.

Hormonal carcinogenesis: Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both endogenously and exogenously; in many instances, long exposure is required; and tumours occur in the target tissue in association with a stimulation of non-neoplastic growth, although in some cases hormones promote the proliferation of tumour cells in a target organ. For hormones that occur in excessive amounts, for hormone-mimetic agents and for agents that cause hyperactivity or imbalance in the endocrine system, evaluative methods comparable with those used to identify chemical carcinogens may be required; particular emphasis must be laid on quantitative

aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

Complex mixtures: There is an increasing amount of data from long-term carcinogenicity studies on complex mixtures and on crude materials obtained by sampling in occupational environments. The representativity of such samples must be considered carefully.

Quantitative aspects: Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age) and route and schedule of administration; often, the target organs at which a cancer occurs and its histological type may vary with these parameters. Nevertheless, indices of carcinogenic potency in particular experimental systems (for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless(9)) have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other species, including humans.

Chemical carcinogens share many common biological properties, which include metabolism to reactive (electrophilic(10-11)) intermediates capable of interacting with DNA. However, they may differ widely in the dose required to produce a given level of tumour induction. The reason for this variation in dose-response is not understood, but it may be due to differences in metabolic activation and detoxification processes, in different DNA repair capacities among various organs and species or to the operation of qualitatively distinct mechanisms.

Statistical analysis of animal studies: It is possible that an animal may die prematurely from unrelated causes, so that tumours that would have arisen had the animal lived longer may not be observed; this possibility must be allowed for. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates(9), with associated significance tests(12), have been recommended. For internal neoplasms that are discovered 'incidentally'(12) at autopsy but that did not cause the death of the host, different estimates(13) and significance tests(12) may be necessary for the unbiased study of the numbers of tumour-bearing animals.

The design and statistical analysis of long-term carcinogenicity experiments were reviewed in Supplement 2 to the *Monographs* series(14). That review outlined the way in

which the context of observation of a given tumour (fatal or incidental) could be included in an analysis yielding a single combined result. This method requires information on time to death for each animal and is therefore comparable to only a limited extent with analyses which include global proportions of tumour-bearing animals.

Evaluation of carcinogenicity studies in experimental animals: The evidence of carcinogenicity in experimental animals is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

(1) *Sufficient evidence* of carcinogenicity is provided when there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects.

(2) *Limited evidence* of carcinogenicity is available when the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung adenomas and adenocarcinomas and liver tumours in certain strains of mice).

(3) *Inadequate evidence* of carcinogenicity is available when, because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

(4) *No evidence* of carcinogenicity applies when several adequate studies are available which show that, within the limits of the tests used, the chemical or complex mixture is not carcinogenic.

It should be noted that the categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals or complex mixtures are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

(ii) *Evidence for activity in short-term tests*[1]

Many short-term tests bearing on postulated mechanisms of carcinogenesis or on the properties of known carcinogens have been developed in recent years. The induction of cancer is thought to proceed by a series of steps, some of which have been distinguished experimentally (15-19). The first step — initiation — is thought to involve damage to DNA, resulting in heritable alterations in or rearrangements of genetic information. Most short-term tests in common use today are designed to evaluate the genetic activity of a substance.

[1]Based on the recommendations of a working group which met in 1983(5).

Data from these assays are useful for identifying potential carcinogenic hazards, in identifying active metabolites of known carcinogens in human or animal body fluids, and in helping to elucidate mechanisms of carcinogenesis. Short-term tests to detect agents with tumour-promoting activity are, at this time, insufficiently developed.

Because of the large number of short-term tests, it is difficult to establish rigid criteria for adequacy that would be applicable to all studies. General considerations relevant to all tests, however, include (a) that the test system be valid with respect to known animal carcinogens and noncarcinogens; (b) that the experimental parameters under which the chemical (or complex mixture) is tested include a sufficiently wide dose range and duration of exposure to the agent and an appropriate metabolic system; (c) that appropriate controls be used; and (d) that the purity of the compound or, in the case of complex mixtures, that the source and representativity of the sample being tested be specified. Confidence in positive results is increased if a dose-response relationship is demonstrated and if this effect has been reported in two or more independent studies.

Most established short-term tests employ as end-points well-defined genetic markers in prokaryotes and lower eukaryotes and in mammalian cell lines. The tests can be grouped according to the end-point detected:

Tests of *DNA damage*. These include tests for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria and differential survival of DNA repair-proficient/-deficient strains of bacteria.

Tests of *mutation* (measurement of heritable alterations in phenotype and/or genotype). These include tests for detection of the loss or alteration of a gene product, and change of function through forward or reverse mutation, recombination and gene conversion; they may involve the nuclear genome, the mitochondrial genome and resident viral or plasmid genomes.

Tests of *chromosomal effects*. These include tests for detection of changes in chromosome number (aneuploidy), structural chromosomal aberrations, sister chromatid exchanges, micronuclei and dominant-lethal events. This classification does not imply that some chromosomal effects are not mutational events.

Tests for *cell transformation*, which monitor the production of preneoplastic or neoplastic cells in culture, are also of importance because they attempt to simulate essential steps in cellular carcinogenesis. These assays are not grouped with those listed above since the mechanisms by which chemicals induce cell transformation may not necessarily be the result of genetic change.

The selection of specific tests and end-points for consideration remains flexible and should reflect the most advanced state of knowledge in this field.

The data from short-term tests are summarized by the Working Group and the test results tabulated according to the end-points detected and the biological complexities of the test systems. The format of the table used is shown below. In these tables, a '+' indicates that the compound was judged by the Working Group to be significantly positive in one or more assays for the specific end-point and level of biological complexity; '-' indicates that it was judged to be negative in one or more assays; and '?' indicates that there were contradictory

results from different laboratories or in different biological systems, or that the result was judged to be equivocal. These judgements reflect the assessment by the Working Group of the quality of the data (including such factors as the purity of the test compound, problems of metabolic activation and appropriateness of the test system) and the relative significance of the component tests.

Overall assessment of data from short-term tests

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes				
Fungi/ Green plants				
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				

An overall assessment of the evidence for *genetic activity* is then made on the basis of the entries in the table, and the evidence is judged to fall into one of four categories, defined as follows:

(1) *Sufficient evidence* is provided by at least three positive entries, one of which must involve mammalian cells *in vitro* or *in vivo* and which must include at least two of three end-points — DNA damage, mutation and chromosomal effects.

(2) *Limited evidence* is provided by at least two positive entries.

(3) *Inadequate evidence* is available when there is only one positive entry or when there are too few data to permit an evaluation of an absence of genetic activity or when there are unexplained, inconsistent findings in different test systems.

(4) *No evidence* applies when there are only negative entries; these must include entries for at least two end-points and two levels of biological complexity, one of which must involve mammalian cells *in vitro* or *in vivo*.

It is emphasized that the above definitions are operational, and that the assignment of a chemical or complex mixture into one of these categories is thus arbitrary.

In general, emphasis is placed on positive results; however, in view of the limitations of current knowledge about mechanisms of carcinogenesis, certain cautions should be respected: (i) At present, short-term tests should not be used by themselves to conclude whether or not an agent is carcinogenic nor can they predict reliably the relative potencies of compounds as carcinogens in intact animals. (ii) Since the currently available tests do not detect all classes of agents that are active in the carcinogenic process (e.g., hormones), one must be cautious in utilizing these tests as the sole criterion for setting priorities in carcinogenesis research and in selecting compounds for animal bioassays. (iii) Negative results from short-term tests cannot be considered as evidence to rule out carcinogenicity, nor does lack of demonstrable genetic activity attribute an epigenetic or any other property to a substance (5).

(b) Evaluation of Carcinogenicity in Humans

Evidence of carcinogenicity can be derived from case reports, descriptive epidemiological studies and analytical epidemiological studies.

An analytical study that shows a positive association between an exposure and a cancer may be interpreted as implying causality to a greater or lesser extent, on the basis of the following criteria: (a) There is no identifiable positive bias. (By 'positive bias' is meant the operation of factors in study design or execution that lead erroneously to a more strongly positive association between an exposure and disease than in fact exists. Examples of positive bias include, in case-control studies, better documentation of the exposure for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in exposed individuals than in individuals not exposed.) (b) The possibility of positive confounding has been considered. (By 'positive confounding' is meant a situation in which the relationship between an exposure and a disease is rendered more strongly positive than it truly is as a result of an association between that exposure and another exposure which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking.) (c) The association is unlikely to be due to chance alone. (d) The association is strong. (e) There is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship; however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an exposure and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias; (b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of

exposure or outcome have been weighed. In addition, it must be recognized that the probability that a given study can detect a certain effect is limited by its size. This can be perceived from the confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above the upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement. Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

The evidence for carcinogenicity from studies in humans is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

(1) *Sufficient evidence* of carcinogenicity indicates that there is a causal relationship between the exposure and human cancer.

(2) *Limited evidence* of carcinogenicity indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.

(3) *Inadequate evidence* of carcinogenicity, which applies to both positive and negative evidence, indicates that one of two conditions prevailed: (a) there are few pertinent data; or (b) the available studies, while showing evidence of association, do not exclude chance, bias or confounding.

(4) *No evidence* of carcinogenicity applies when several adequate studies are available which do not show evidence of carcinogenicity.

(c) Relevance of Experimental Data to the Evaluation of Carcinogenic Risk to Humans

Information compiled from the first 38 volumes of the *IARC Monographs* shows that, of the chemicals or groups of chemicals now generally accepted to cause or probably to cause cancer in humans, all of those that have been tested appropriately produce cancer in at least one animal species. For several of the chemicals (e.g., aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

For many of the chemicals (or complex mixtures) evaluated in the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. **In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.** The use of the expressions 'for practical purposes' and 'as if they presented a

carcinogenic risk' indicates that, at the present time, a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatic correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw per day) of a particular chemical required to produce cancer in test animals and the dose that would produce a similar incidence of cancer in humans. Some data, however, suggest that such a relationship may exist(20,21), at least for certain classes of carcinogenic chemicals, although no acceptable method is currently available for quantifying the possible errors that may be involved in such an extrapolation procedure.

8. EXPLANATORY NOTES ON THE CONTENTS OF MONOGRAPHS ON CHEMICALS AND COMPLEX MIXTURES

These notes apply to the format of most monographs, except for those that address industries or life-style factors. Thus, sections 1 and 2, as described below, are applicable in monographs on chemicals or groups of chemicals; in other monographs, they may be replaced by sections on the history of an industry or habit, a description of a process and other relevant information.

(a) Chemical and Physical Data (Section 1)

The Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name (Ninth Collective Index)(22) and the IUPAC Systematic Name(23) are recorded in section 1. Other synonyms and trade names are given, but the list is not necessarily comprehensive. Some of the trade names may be those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular, data that might be relevant to identification, environmental fate and human exposure, and biological effects, including carcinogenicity.

A separate description of the composition of technical products includes available information on impurities and formulated products.

(b) Production, Use, Occurrence and Analysis (Section 2)

The purpose of section 2 is to provide indications of the extent of past and present human exposure to the chemical.

Monographs on occupational exposures to complex mixtures or exposures to complex mixtures resulting from human habits include sections on: historical perspectives; description of the industry or habit; manufacturing processes and use patterns; exposures in the workplace; chemistry of the complex mixture.

(i) *Synthesis*

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. This information allows a reasonable estimate to be made of the date before which no human exposure could have occurred. In addition, methods of synthesis used in past and present commercial production are described.

(ii) *Production*

Since Europe, Japan and the USA are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those regions. It should not, however, be inferred that those areas or nations are the sole or even necessarily the major sources or users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications. In some cases, separate production data on organic chemicals manufactured in the USA are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be inferred from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the annual sales value or production volume exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals and plastics; in fact, the minimal reportable level for annual sales value ranges from $1000-$50 000, and the minimal reportable level for annual production volume ranges from 450-22 700 kg for different classes of use. Data on production are also obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled by country, and the resulting estimates of production are included in the individual monographs.

(iii) *Use*

Information on uses is usually obtained from published sources but is often complemented by direct contact with manufacturers. Some uses identified may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.

Statements concerning regulations and standards (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries may not reflect the most recent situation, since such standards are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the chemical.

(iv) *Occurrence*

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupational environments, air, water, soil, foods and tissues of animals and humans. When no published data are available to the Working Group, unpublished reports,

deemed appropriate, may be considered. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

(v) *Analysis*

The purpose of the section on analysis is to give the reader an overview, rather than a complete list, of current methods cited in the literature. No critical evaluation or recommendation of any of the methods is meant or implied.

(c) Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)

In general, the data recorded in section 3 are summarized as given by the author; however, comments made by the Working Group on certain shortcomings of reporting, of statistical analysis or of experimental design are given in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

(i) *Carcinogenicity studies in animals*

The monographs are not intended to cover all reported studies. A few studies are purposely omitted because they are inadequate (e.g., too short a duration, too few animals, poor survival) or because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when they are the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the test material has been adequately tested and of all species in which relevant tests have been done(24). In most cases, animal strains are given. Quantitative data are given to indicate the order of magnitude of the effective carcinogenic doses. In general, the doses and schedules are indicated as they appear in the original report; sometimes units have been converted for easier comparison. Experiments in which the compound was administered in conjunction with known carcinogens and experiments on factors that modify the carcinogenic effect are also reported. Experiments on the carcinogenicity of known metabolites and derivatives are also included.

(ii) *Other relevant biological data*

LD_{50} data are given when available, and other data on toxicity are included when considered relevant.

Data on effects on reproduction, on teratogenicity and embryo- and fetotoxicity and on placental transfer, from studies in experimental animals and from observations in humans, are included when considered relevant.

Information is given on absorption, distribution and excretion. Data on metabolism are usually restricted to studies that show the metabolic fate of the chemical in experimental animals and humans, and comparisons of data from animals and humans are made when possible.

Data from short-term tests are also included. In addition to the tests for genetic activity and cell transformation described previously (see pages 20-21), data from studies of related effects, but for which the relevance to the carcinogenic process is less well established, may also be mentioned.

The criteria used for considering short-term tests and for evaluating their results have been described (see pages 21-23). In general, the authors' results are given as reported. An assessment of the data by the Working Group which differs from that of the authors, and comments concerning aspects of the study that might affect its interpretation are given in square brackets. Reports of studies in which few or no experimental details are given, or in which the data on which a reported positive or negative result is based are not available for examination, are cited, but are identified as 'abstract' or 'details not given' and are not considered in the summary tables or in making the overall assessment of genetic activity.

For several recent reviews on short-term tests, see IARC(24), Montesano *et al.*(25), de Serres and Ashby(26), Sugimura *et al.*(27), Bartsch *et al.*(28) and Hollstein *et al.*(29).

(iii) *Case reports and epidemiological studies of carcinogenicity to humans*

Observations in humans are summarized in this section. These include case reports, descriptive epidemiological studies (which correlate cancer incidence in space or time to an exposure) and analytical epidemiological studies of the case-control or cohort type. In principle, a comprehensive coverage is made of observations in humans; however, reports are excluded when judged to be clearly not pertinent. This applies in particular to case reports, in which either the clinico-pathological description of the tumours or the exposure history, or both, are poorly described; and to published routine statistics, for example, of cancer mortality by occupational category, when the categories are so broadly defined as to contribute virtually no specific information on the possible relation between cancer occurrence and a given exposure. Results of studies are assessed on the basis of the data and analyses that are presented in the published papers. Some additional analyses of the published data may be performed by the Working Group to gain better insight into the relation between cancer occurrence and the exposure under consideration. The Working Group may use these analyses in its assessment of the evidence or may actually include them in the text to summarize a study; in such cases, the results of the supplementary analyses are given in square brackets. Any comments by the Working Group are also reported in square brackets; however, these are kept to a minimum, being restricted to those instances in which it is felt that an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader.

(d) Summary of Data Reported and Evaluation (Section 4)

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

(i) *Exposures*

Human exposure to the chemical or complex mixture is summarized on the basis of data on production, use and occurrence.

(ii) *Experimental data*

Data relevant to the evaluation of the carcinogenicity of the test material in animals are summarized in this section. The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated. Dose-response data are given when available.

Significant findings on effects on reproduction and prenatal toxicity, and results from short-term tests for genetic activity and cell transformation assays are summarized, and the latter are presented in tables. An overall assessment is made of the degree of evidence for genetic activity in short-term tests.

(iii) *Human data*

Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Other biological data that are considered to be relevant are also mentioned.

(iv) *Evaluation*

This section comprises evaluations by the Working Group of the degrees of evidence for carcinogenicity of the exposure to experimental animals and to humans. An overall evaluation is then made of the carcinogenic risk of the chemical or complex mixture to humans. This section should be read in conjunction with pages 20 and 24 of this Preamble for definitions of degrees of evidence.

When no data are available from epidemiological studies but there is *sufficient evidence* that the exposure is carcinogenic to animals, a footnote is included, reading: 'In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity in animals as if they presented a carcinogenic risk to humans' (pp. 24-25).

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WORLDWIDE USE OF SMOKING TOBACCO

1. Production of and trade in tobacco

(a) Historical aspects

When Columbus landed in the New World on 11 October 1492, he was offered dried tobacco leaves at the House of the Arawaks. Although the Chinese claimed that they grew and used tobacco long before the discovery of America, no convincing documentation is available (Tso, 1986).

Various names were given to the tobacco plant, including 'Nicotiana', after Jean Nicot, French Ambassador at Lisbon. Nicot was one of the first people to grow tobacco in Portugal and was largely responsible for introducing the plant to the royal court in Paris; the Duc de Guise proposed using his name in 1585. However, the word 'tobacco' had become established in North America and survived all others for common usage. Early writers differ as to the origin of this name; it seems to have been used originally not for tobacco itself but for a type of tube used by natives for inhaling smoke from tobacco, or for a cylinder of tobacco leaf prepared for smoking (Encyclopaedia Britannica, Inc., 1966). 'Nicotiania' was retained as the generic name.

The tobacco plant thus belongs to the genus *Nicotiana*, which is a member of the family Solanaceae. The tobacco grown in France and Spain was *Nicotiana tabacum*, from seed originating in Brazil and Mexico. The species first grown in Portugal and England was *N. rustica*, the seed in Portugal coming from Florida and that used in England from Virginia (Tso, 1986).

There is no clear record of the history of tobacco cultivation in different areas of the world. Several reports, including that of Akehurst (1981), have presented partial information on the distribution of tobacco species in various locations. Table 3 gives a summarized chronicle of early tobacco cultivation and use and is based on those reports (Tso, 1986).

Originally, tobacco was smoked in pipes; gradually cigarettes and cigars became more popular. The primitive form of cigarettes was tobacco stuffed into a hollow reed or cane tube, or crushed tobacco leaves and shreds rolled in a corn husk or other vegetable wrapper. During the eighteenth century, the cigarette became more widely accepted; the first cigarette-machine factories were set up in Havana, Cuba, in 1853, in London in 1856 and in the American colonies in 1860 (Encyclopaedia Britannica, Inc., 1966).

Table 3. Chronicle of early tobacco cultivation and use[a]

Date	Event
1492 (11 Oct.)	Columbus sighted the home of the Arawaks and was offered 'dried' tobacco leaves.
1499	Amerigo Vespucci recorded the use of chewing tobacco on an island off Venezuela.
1545	Iroquois Indians near Montreal, Canada, were found to have smoking habits.
1556	Tobacco was first grown or became known in France.
1558	Tobacco was used in Brazil and Portugal.
1559	Tobacco was used in Spain.
1560	*Nicotiana rustica* was used in Central Africa.
1565	Tobacco was used in England.
1600	Tobacco was introduced to Italy, Germany, Norway, Sweden, Russia, Persia, India, Indochina, Japan, China, and the west coast of Africa.
1612	John Rolfe, at Jamestown, Virginia, was the first man known to grow tobacco commercially for export.
1631	Tobacco production extended to Maryland and then gradually to other areas.
1650s	Portuguese took tobacco to South Africa and other countries. Spaniards distributed tobacco to the Philippines, Guatemala and other Central and South American countries and to the West Indies. Tobacco cultivation was begun in Indonesia. Tobacco cultivation was extended in Europe.
1900s	Tobacco was produced in New Zealand. *Nicotiana tabacum* species were introduced to Australia (*N. suaveolens* had been grown prior to this period).

The term 'cigar' is derived from the Spanish word *cigarro*, which was probably an adaptation of *sik'ar*, the Mayan term for smoking. The primitive form of cigar was a long, thick bundle of twisted tobacco leaves wrapped in a dried palm or maize leaf; this was the form that Columbus observed being smoked by American Indians. Cigars were introduced to Spain in 1600 and to Connecticut in 1762. The first cigars were manufactured in Sweden in 1814 (Swedish Tobacco Co., 1982). The first cigar-making factory was established in New Jersey, USA, in 1919 (Encyclopaedia Britannica, Inc., 1966).

(b) Tobacco types

A special terminology has developed with regard to the cultivation and handling of tobacco, which may differ to some extent with locality. In general, either individual green leaves or the entire stalk is cut and hung up in a barn to 'cure'. A roughly regulated regime of ventilation, temperature and humidity slowly dries the leaves and favours those catabolic processes considered desirable (Tso, 1972).

The methods of harvesting and curing different types of tobacco differ radically. There are two distinct methods of harvesting tobacco — priming and stalk cutting. For flue-cured tobacco, individual leaves are cut, or 'primed', as they ripen, two or three leaves at a time, starting from the bottom of the plant. For air-cured tobacco, including cigar filler and binder, burley, Maryland, dark air- and fire-cured, sun-cured and Perique tobacco, the entire plant is harvested by cutting the stalk near ground level. Oriental (aromatic or Turkish) tobacco and shade-grown cigar wrapper tobacco are harvested by priming (Tso, 1972).

There are two major methods of curing tobacco. In flue-curing, tobacco is dried entirely by artificial heat and in such a way as to prevent smoke from coming into contact with the leaf. In air-curing, little or no artificial heat is applied. Several other minor methods are also used, including (1) fire-curing, in which tobacco is partially cured by heat from open fires made on the floor of the barn and smoke is allowed to come into contact with the leaf; (2) sun-curing, in which tobacco is placed on scaffolds in the sun; and (3) combined sun-curing and air-curing, as for oriental tobacco (Tso, 1972).

A general list of tobacco types is given in Table 4.

(c) Production and trade

Since its discovery, tobacco has played an important role in farm economics and international trade. In the early 1600s, when tobacco began to be cultivated commercially in Virginia, shipping of the tobacco leaf greatly helped the development of England's merchant navy and opened up a valuable export. The Anglo-American tobacco colonies continued to supply the fast-spreading tobacco market throughout the colonial period.

In the late 1920s and early 1930s, large amounts of dark fire-cured and dark air-cured tobaccos were consumed. Immediately before the Second World War, the demand for light flue-cured types increased radically with the new popularity of cigarettes. During recent years, there has been a worldwide trend to increase taxes on tobacco, resulting in higher prices and reductions in production and consumption (see p. 74).

Table 4. Tobacco types and method of curing[a]

Types of tobacco (common names)	Method of curing
Flue-cured, yellow, blond, bright, Virginia	Flue-curing
	Air-curing
Burley, Maryland	light air-curing
'One sucker', 'Green River', black (slightly fermented)	dark air-curing
Cigar binder, cigar filler, cigar wrapper	for cigars
Fire-cured, dark-fired, black fat	Fire-curing
Sun-cured	Sun-curing
Aromatic, oriental, Turkish	Combined sun-curing and air-curing
Perique, etc.	Miscellaneous

[a]Adapted from Tso (1972)

Total areas of tobacco cultivated, total yield and quantity of production in certain continents and countries in 1981 and 1982 are shown in Table 5. China, the USA, India and Brazil were the leading producers in both years.

Trends in tobacco production and trade have changed extensively over the years. No definite relationship exists between the amount of tobacco a country produces and the extent of its exports or imports: the USA, one of the largest producing countries, also exports and imports the most; China is the largest producer of tobacco in the world but exports little, due to the high domestic demand.

Countries that produce well-defined types of good quality leaf export a large part of the crop. Examples are the exports of flue-cured tobacco from the USA; high-grade cigar tobacco from Cuba; and fine oriental leaf from Greece, Bulgaria and Turkey. Countries that import large quantities of leaf tobacco due to insufficient supply to meet consumption requirements are the Federal Republic of Germany, France, Japan, the Netherlands and the UK.

Table 6 shows international trade in unmanufactured tobacco during 1980 and 1981 (US Department of Agriculture, 1983). Countries with the highest exports were: first, the USA; second, Brazil; third (1980)/fourth (1981), Zimbabwe; fourth (1980)/third (1981), Turkey; and fifth, India. Other countries, such as Greece, Italy, Bulgaria, Thailand and Malawi, also exported considerable amounts of tobacco during those years. Certain countries that exported unmanufactured tobacco also imported considerable amounts. In 1981, the USA was the leading tobacco importer, followed by the Federal Republic of Germany, the UK, the USSR, Japan and China.

Table 5. Areas, yields and quantities of tobacco produced in certain areas of the world, 1981-1982[a]

Continent or country	Area (hectares)		Yield (kg/hectare)[b]		Production (tonnes)	
	1981	1982	1981	1982	1981	1982
World total	4 075 138	4 276 392	1.46	1.56	5 947 631	6 660 964
North and Central America (total)	592 761	562 396	2.08	2.06	1 234 209	1 158 506
Canada	47 356	40 875	2.37	1.19	112 360	77 947
Cuba	60 000	60 000	0.83	0.75	50 000	45 000
USA	395 181	365 853	2.37	2.43	936 266	890 240
South America (total)	345 810	356 453	1.29	1.46	446 939	519 641
Brazil	239 000	246 000	1.31	1.51	314 000	372 000
Europe (total)	501 294	510 046	1.48	1.49	740 098	760 086
Bulgaria	113 080	114 881	1.24	1.36	140 500	156 000
France	16 996	14 970	2.52	2.72	42 774	40 770
Germany, Federal Republic of	3 161	3 056	2.48	2.41	7 839	3 350
Greece	91 152	93 320	1.40	1.39	127 401	130 017
Italy	60 688	60 600	2.16	2.20	130 971	133 500
Poland	48 590	48 200	1.97	1.70	95 523	82 000
Spain	21 522	22 764	2.02	1.94	43 534	44 125
USSR (Europe and Asia)	183 000	186 000	1.49	1.56	273 000	290 000
Africa (total)	242 968	254 856	0.96	1.08	234 228	274 624
Malawi	68 880	69 545	0.74	0.85	50 700	58 800
Zimbabwe	39 752	49 018	1.75	1.89	69 408	92 380
Middle East and Asia (total)	2 201 445	2 399 246	1.36	1.52	3 001 888	3 642 525
China	757 000	930 000	1.98	2.15	1 500 000	2 000 000
India	451 500	448 300	1.07	1.17	480 800	525 000
Philippines	94 655	104 485	0.86	0.87	81 366	90 878
Thailand	86 497	91 415	0.87	0.99	75 230	90 020

[a]From US Department of Agriculture (1983); data for 1982 have not been finalized

[b]Dried material

Table 6. International trade in unmanufactured tobacco, 1980-1981 (tonnes)[a]

Continent or country	1980		1981	
	Exports	Imports	Exports	Imports
World total	1 345 989	1 444 838	1 484 144	1 512 638
North and Central America (total)	352 953	208 548	380 480	242 890
Canada	19 491	7 565	33 041	2 754
Cuba	500	-	15 000	-
Mexico	27 000	-	18 000	-
USA	273 477	195 468	266 104	234 910
South America (total)	193 096	11 950	185 224	11 967
Brazil	143 396	-	148 000	-
Europe (total)	293 044	807 958	319 568	772 675
Bulgaria	60 000	3 500	60 000	3 500
France	4 017	71 037	2 558	64 546
Germany, Federal Republic of	30 698	189 285	29 442	182 366
Greece	70 673	2 772	86 430	3 665
Italy	46 450	29 759	75 810	23 228
Poland	8 894	23 099	4 700	25 544
Spain	7 487	77 088	2 788	71 082
UK	5 030	118 438	5 535	130 977
USSR (Europe and Asia)	2 356	83 394	2 200	86 000
Africa (total)	189 109	71 543	187 208	85 989
Malawi	63 772	-	48 000	-
Zimbabwe	98 977	40	116 552	240
Middle East and Asia (total)	314 898	246 131	410 018	298 626
China	10 000	50 000	10 000	80 000
India	73 193	100	104 862	100
Japan	6	71 418	-	84 301
Philippines	20 369	13 936	29 438	15 389
Thailand	39 057	10 618	41 000	12 000
Turkey	83 727	-	130 969	-
Oceania (total)	533	15 314	446	14 491

[a]From US Department of Agriculture (1983)

As an indication of the destinations of most exported tobacco, US tobacco exports are shown in Table 7 by country and type for 1981 and 1982 (US Department of Agriculture, 1983). Japan purchases the most US tobacco, followed by the Federal Republic of Germany, the UK, Switzerland, Spain, Italy, the Netherlands and Thailand.

Table 7. US exports of tobacco by country of destination and type, 1981-1982 (tonnes)[a]

Tobacco type	Country of destination	1981	1982
All types	Total	265 143	259 487
	Germany, Federal Republic of	37 719	30 913
	Italy	12 015	12 734
	Japan	53 063	50 041
	Netherlands	12 976	11 395
	Spain	15 145	14 437
	Switzerland	18 081	12 129
	Thailand	8 355	12 559
	UK	17 884	13 903
Flue-cured	Total	175 191	158 036
	Germany, Federal Republic of	23 213	16 591
	Japan	33 430	29 951
	Spain	12 740	12 320
	UK	13 742	10 311
Burley	Total	33 636	47 014
	Germany, Federal Republic of	7 985	9 000
	Italy	5 218	5 443
	Japan	6 166	7 860
	Switzerland	3 149	4 626
Dark-fired (Kentucky, Tennessee)	Total	7 385	8 517
Black fat	Total	1 149	1 000
Dark-fired (Virginia) and sun cured	Total	694	1 245
Maryland	Total	3 308	3 027
	Switzerland	1 836	2 238
Cigar wrapper, binder, filler	Total	1 440	622
Miscellaneous	Total	38 133	35 579

[a]From US Department of Agriculture (1983)

(*d*) *Modification of raw materials*

A reduction in the yields of toxic agents in smoke may be achieved both by manipulating the tobacco plant and leaf material and by physical and chemical methods during manufacturing processes (Tso, 1980). The latter are described under 'Product design and delivery', pp. 57-60.

The botanical, chemical and physical properties of leaf tobacco are affected by genetic make-up, environmental conditions, culture practices and post-harvest treatment. Variables such as differences in variety, field spacing, fertilization, number of leaves per plant, agricultural chemicals, degree of maturity at harvesting and curing all affect the composition of the final products (Tso, 1972).

The interrelationship between variables of leaf components, smoke constituents and biological activity have been studied in order to establish a theoretical model for modified tobacco. Vast genetic resources and a better understanding of the dynamic balance during plant growth and the metabolic changes that occur during senescence and curing can be used to produce plant materials that approach the theoretical model, by developing new varieties and new culturing and curing practices using selected botanical, chemical and physical markers. The homogenized-leaf-curing procedure to promote biochemical changes and remove undesirable products, when perfected and applied in the future for mass production, may have many advantages, including (1) removal of undesirable components that cannot be eliminated by genetic or cultural manipulation, (2) inhibition of the formation of undesirable smoke precursors and (3) control of physical characteristics through reconstitution (Tso, 1980).

The total nitrogen content of leaf tobacco is known to be associated with many potentially hazardous variables in cigarette smoke (Tso & Chaplin, 1977), and there is a correlation between nitrogen content and the content of dry total particulate matter, benzo[*a*]pyrene, benz[*a*]anthracene, hydrogen cyanide, phenols, carbon monoxide and carbon dioxide. Although some of these smoke constituents do not contain nitrogen, the total amount of nitrogen in plants strongly affects the formation of other organic components and thus the properties of tobacco. Furthermore, since the pyrolysis products of soluble proteins include hydrogen cyanide, nitrogen oxides, quinolines and, possibly, nitrosamines, removal or reduction of soluble protein and other nitrogen fractions by the homogenized-leaf-curing process might be expected to result in a less toxic tobacco (Tso, 1980).

2. Manufacture and usage

(*a*) *Forms utilized*

Most of the wide variety of smoking products manufactured throughout the world contain varieties of *N. tabacum*, although, in some areas, certain varieties of *N. rustica* are used as cigarette and pipe tobaccos (Garner, 1951; Wynder & Hoffmann, 1967; Tso, 1972; Akehurst, 1981).

(i) *Cigarettes*

Cigarettes are made from fine-cut tobaccos and are wrapped in paper or a maize leaf. Those manufactured in the Federal Republic of Germany, Italy, Japan, Sweden, Switzerland, the USA and many other countries are blended with varying proportions of different grades of flue-cured (also called 'Virginia'), burley, Maryland and oriental tobaccos. In Canada, Finland and the UK, cigarettes made entirely of flue-cured tobaccos are preferred, whereas in France and in some North African and some South American countries, cigarettes filled with dark air-cured tobaccos are more popular. Cigarettes measure between 60 and 120 mm in length and between 20 and 30 mm in circumference, and range in weight from 500 to 1200 mg. Before cutting, cigarette tobacco is usually sprayed with 'casing', a 'sauce' composed primarily of sugars, humectants and/or aromatic substances.

A type of cigarette popular in the USSR is the *papirossi* (Cooper, 1982), which is often characterized by a long, hollow mouthpiece that can be twisted before smoking. Such cigarettes are filled either with pure oriental tobacco or a mixture of tobaccos; they are also hand-rolled from granulated tobacco leaves and from midribs of *N. rustica*.

(ii) *Cigars*

Cigars consist of filler, binder and wrapper, all of which are made of air-cured (see Table 4) and fermented tobaccos (Cornell *et al.*, 1979). Since about the mid 1950s, the binder or wrapper, or both, of many brands of cigars consists of reconstituted cigar tobaccos. The aroma and flavour of cigars are in large measure the result of precisely controlled treatment during fermentation, which is a process that promotes hydrolysis and oxidative deamination under conditions of elevated temperature and humidity (Tso, 1972). Although they are usually hand-made, machines for manufacturing cigars have been available since 1919.

Cigars vary greatly in form, length and diameter; they can weigh more than 10 g. They include a large variety of products, which have as a common property that they are wrapped either in tobacco leaf, reconstituted tobacco or paper that has been treated with tobacco extract. Consumption of cigars has decreased drastically over the last 15 years. Since about 1970, manufacturers in many countries have marketed 'little cigars', which are made primarily of cigar tobaccos rolled in cigarette paper that has been saturated with tobacco sauce. These products weigh less than 1.5 g. Cigars weighing between 1.5 and 3.0 g are often called 'small cigars' or, in Europe, 'cigarillos'. They are characterized by being open ended and often have tapered mouthpieces.

Cheroots are a type of small cigar made of heavy-bodied tobaccos, and are found all over the world. In southern Germany and Switzerland, where they are called *Stumpen* (Schüler *et al.*, 1980), they are usually square. In parts of Asia, especially in India, cheroots are called *chuttas*. They are hand-made, have no wrapper and a single binder; they consist of cured tobacco folded into a dried tobacco leaf (Sanghvi *et al.*, 1980). The *chutta* is frequently associated with the remarkable habit of 'reverse' smoking, during which the burning end is held inside the mouth; often, a wet cloth is wrapped around the smoking end to act as a filter and to reduce heat (Pindborg *et al.*, 1971).

(iii) *Pipes*

Probably the earliest fashion for tobacco use, pipe smoking had great ceremonial importance in the cultures where it originated. Pipes more than 1000 years old have been found in the Mississippi Valley, USA, and are represented in stone carvings of the Mayas. They were integral to the religious ceremonies of ancient Mexican priests. As a symbol of peace and tranquillity and as a means of delivering a desired dose of nicotine, opium or marijuana, pipe smoking was spread by sailors from the Americas to Europe and thence to the rest of the world (Encyclopaedia Britannica, Inc., 1966). The carved slate peace pipe of the American Indians differed little in principle from the clay pipe of the Elizabethans or the elegant briar of the English gentleman. In parts of India and Nepal, *chillum* (Voges, 1984) and *sulpa* (Anon., 1983a) clay pipes are used. Pipe smoking has been on the decline since the beginning of the twentieth century.

Many pipe tobaccos are blends of 20-25 different leaf tobaccos; however, some of the most popular ones, especially in the USA, may be made of burley varieties only. Some pipe tobaccos contain midrib tissues. Frequently, 'casings' or 'sauces' are added to pipe tobaccos, which contain liquorice, sweetening agents, sugars and/or flavouring agents. Some pipe tobaccos may contain as much as 30% of additives (Hoffmann *et al.*, 1963). Pipe smoke is slightly cooler than cigarette smoke and slightly alkaline.

A large variety of water pipes (known as hookahs, *gozas*, hubble-bubbles, narghiles and *sheeshas*) is used in the Middle East, in Asia, including China, and in some areas of Africa. In the Middle East, the narghile is popular (Voges, 1984). Cut or shredded tobacco is burned in the head, *boori*, the smoke is drawn through a long tube inside the water pipe (*kootbi*), filtered through water in a container called a *shishi*, and reaches the smoker's mouth *via* a long flexible tube, the *kaseba* (Hoffmann *et al.*, 1963). An even greater variety of tobaccos, or mixtures of tobaccos with other plant products, is used in such pipes. For example, in Saudi Arabia, *jurak*, a mixture of tobacco, banana pulp and molasses, is smoked in *sheeshas* (Sardar, 1982). In Afghanistan and Pakistan, primarily *N. rustica* is smoked in such pipes (Ahmad, 1983). In China, *N. rustica* is used, commonly in combination with linseed oil and rapeseed oil (Houqing, 1984).

The smoking of water pipes is one of the more ancient forms of tobacco use and is widely practised as a form of social communication among groups, usually of men, who sit around a communal pipe. A relatively deep inspiratory effort is required to overcome the resistance of the long narrow airway. Ibrahim (1982) suggests that the water is a relatively effective filter, which may reduce the tar content of the smoke; interestingly, he also indicates that this form of smoking is an efficient way of spreading tuberculosis.

(iv) *Bidis*

The *bidi* (*biri*) is representative of a number of eastern smoking products. It contains a relatively small amount of locally grown tobacco (0.2 - 0.3 g), usually sun-dried and -cured, which is flaked and hand-rolled in a rectangular piece of dried *temburni* leaf (*Diospyros melanoxylon*). They are sometimes rolled in other leaves, and the size varies considerably. They may produce a smaller volume of smoke than cigarettes (Sanghvi *et al.*, 1980; Jussawalla, 1982); but the longer variants may allow two or three times as many puffs as an

ordinary cigarette and deliver up to 40 or 50 mg of tar (Hoffmann *et al.*, 1974). Since *bidis* lack added burning agents, they must be puffed continuously to be kept alight and therefore probably deliver a relatively high dose of tar to the smoker.

(v) *Kreteks*

Kreteks are cigarettes that are widely manufactured in Indonesia, both by small industries and in factories. They may be similar in size to western cigarettes, but they include a substantial addition of cloves, which gives both the *kretek* and the smoke a characteristic aroma. Other flavourings may be added (Voges, 1984).

(vi) *Sticks*

Brus is the tobacco grown in Papua New Guinea and cured in the sun. It is usually shredded and rolled in paper to produce a long, large cigarette, generally known as a *stick*. Endemic paper shortages in the villages of Papua New Guinea decades ago led to efficient recycling of newspaper as a wrapping for *brus*. Now that cigarette paper is available, this population still prefers to buy a form that is printed with out-of-date news. *Sticks* are now manufactured from commercial tobacco and have been shown to produce 14-25 mg of tar, 1-2 mg of nicotine and 7-8 mg of carbon monoxide. Hand-made *sticks* containing *brus* deliver 18-80 mg of tar, 2-8 mg of nicotine and a volume of carbon monoxide that was too large to be measured in the test system described (Brott, 1981).

(vii) *Others*

A wide variety of home-made smoking materials is prepared from home-grown tobaccos in many traditional societies, e.g., in China, Zambia, Pakistan and Thailand, each with its own characteristics and name. No attempt has been made to itemize all of these here.

(*b*) *Product design and delivery*

Significant changes have been made in the design of cigarettes over the past few decades. Some of these developments occurred as a result of an increased demand for cigarettes with lower yields of certain smoke components, especially of total particulate matter and nicotine. The major changes in cigarette design include: more specific blend selection, variations in length and circumference, addition of filters, the use of reconstituted tobacco sheet, expanded tobacco, and the development of ventilation techniques (Norman, 1982; Baker, 1984; Grise, 1984; Kassman, 1984). A manufacturer may alter several of these parameters to achieve the desired final product in terms of delivery. The exact specifications, especially blend selection, are of a proprietary nature; however, some general statements can be made with regard to the effect of different parameters of cigarette design on the yield of smoke components.

(i) *Blend*

Tobaccos of different genetic origins and differently cured vary in leaf chemistry. For example, US air-cured burley tobacco, US flue-cured tobacco and oriental types result in smoke which differs in flavour and aroma. A low-tar, research cigarette produced at the

University of Kentucky (1R4F) was designed to represent a typical blend (Davis, D.L. *et al.*, 1984). It consists of approximately 33% flue-cured, 20% burley, 11% oriental and 1% Maryland tobacco, and 27% reconstituted sheet (described below), the remainder being additives (reducing sugars and glycerine). When smoked under standard laboratory conditions, this cigarette has a yield of 9.2 mg tar, 0.80 mg nicotine, 11.6 mg carbon monoxide and 0.34 mg nitrogen oxides. The 'puff count', or the number of puffs required to machine-smoke the cigarette, is lower than that of a high-yield Kentucky reference cigarette.

(ii) *Reconstituted sheet*:

The idea of making reconstituted tobacco resulted from a desire to use all of the tobacco purchased from a grower. It is produced by a paper-making process using either small sections of leaf otherwise lost during threshing or leaf stems. The resulting product generally contains more cellulose, fibre, lignin and ash and fewer alkaloids, nitrogenous compounds and reducing sugars (Norman, 1982). The process was first developed and commercialized in the early 1950s for the manufacture of cigars and, subsequently, cigarettes. Reconstituted tobacco now makes up a significant fraction of US cigarette blends and is also widely used in other countries. By using the reconstitution processes, both physical and chemical characteristics that affect not only combustion but also the levels of the constituents of smoke can be changed, e.g., less particulate, condensate, nicotine and isoprene (Selke, 1980). Reconstitution, like the homogenized-leaf-curing procedure for harvested, mature tobacco may remove specific constituents from cured leaf material.

(iii) *Expanded tobacco*

To obtain cigarettes with lower tar and nicotine yields, less tobacco may be used per cigarette; in order to maintain the volume, a procedure for expanding tobacco was developed, in which the tobacco leaf is expanded or 'puffed' to produce a less dense tobacco with more filling capacity. Cigarettes with a high content of expanded tobacco burn more rapidly than other cigarettes (Grise, 1984) and have lower puff counts. This practice was introduced into American blends in the late 1960s and continues to be an important characteristic of many of the 'very-low-tar' brands.

(iv) *Filters*

The major reduction of 'tar' levels in cigarette smoke has been achieved by the design of filter tips (Browne *et al.*, 1984). The popularity of filter cigarettes increased markedly from the early 1950s after the publication of papers demonstrating a causal relationship between smoking and lung cancer. In many countries, filter cigarettes dominate the market. In 1982, they accounted for 90% or more of the cigarette market in a number of countries (Anon., 1983b). A comparison with the percentages in 1973 is shown in Table 8.

Cellulose acetate filters are the most widely used; however, charcoal filters continue to be placed on some brands. In comparison with non-filter cigarettes, filtered types have significantly less dry particulate matter and nicotine, although carbon monoxide delivery may be higher (Wald *et al.*, 1976). The phenol content has been greatly reduced by the use of plasticized, cellulose acetate filters.

The filter tips of these cigarettes vary in length between 12 and 30 mm and consist of cellulose acetate or cellulose 'tow' or crepe paper. Most filter material contains a small percentage of plasticizers, such as triethylene glycerol diacetate. Filters may be made either

Table 8. Percentage of the total production of cigarettes represented by filter cigarettes in various countries[a]

Country or territory	1973	1982[b]
Algeria	85	90
Argentina	90	100
Australia	93	95
Austria	85	97
Barbados	87	90
Belgium and Luxembourg	68	84
Brazil	74	93
Bulgaria	70	70
Canada	90	95
Chile	84	85
China (Shanghai)[c]		
Colombia	14	61
Costa-Rica	82	90
Czechoslovakia	48	90
Denmark	50	60
Dominican Republic	75	88
Ecuador	10	84
Egypt	92	100
El Salvador	98	99
Finland	90	98
France	47	47
Germany, Federal Republic of	85	89
Greece	79	92
Guatemala	94	99
Guyana	96	99
Honduras	93	90
Hong Kong	80	89
Hungary	50	80
India	15	29
Indonesia	31	35
Iran	37	45
Ireland	78	88
Israel	97	99
Italy	74	83
Japan	96	98
Kenya	79	80
Lebanon	33	83
Malaysia	82	90
Mexico	61	83
Morocco	39	45
Netherlands	50	67
New Zealand	91	100
Nicaragua	80	100
Nigeria	75	93
Norway	62	91
Panama	100	100
Philippines	55	93
Poland	23	45
Portugal	76	84
Republic of Korea	61	98
Sierra Leone	47	38
Singapore	69	95
South Africa	90	90
Spain	51	90
Spain (Canary Islands)	60	90
Sweden	79	92
Switzerland	96	97
Syrian Arab Republic	73	99
Taiwan	94	99
Thailand	19	73
Tunisia	59	84
Turkey	18	76
UK	83	94
USA	85	93
USSR[d]	20	30
Venezuela	99	99
Yugoslavia	88	97
Zaire	20	35

[a]From US Department of Agriculture (1983)

[b]Estimates are included in the absence of reasonable data.

[c]26% in 1984 (Gao, 1986)

[d]Without *papirossi*

of a single, basic filter material or are composite filters, which combine cellulose acetate, processed cellulose paper, activated carbon, other absorbents and/or solid plastic devices (Reynolds, 1978).

Cigarettes with charcoal filters are especially popular in Japan (62% of all cigarettes sold in 1981; Shien, 1982). They are usually made of two segments — one of tow, the other of charcoal — or of three segments, with charcoal granules sandwiched between tow. Sometimes the entire length of the tow in a filter tip is dusted with charcoal particles (Reynolds, 1978). [It is not known what contribution charcoal filters have made to changing the tar content of cigarettes in Japan.]

Another type of filter tip is the ventilated filter, which dilutes the smoke by allowing air to enter through perforations in the tip and *via* longitudinal air channels at the periphery of the filter, which also reduce the carbon monoxide concentration in smoke (Hoffmann *et al.*, 1983a; Baker, 1984).

(v) *Ventilation*:

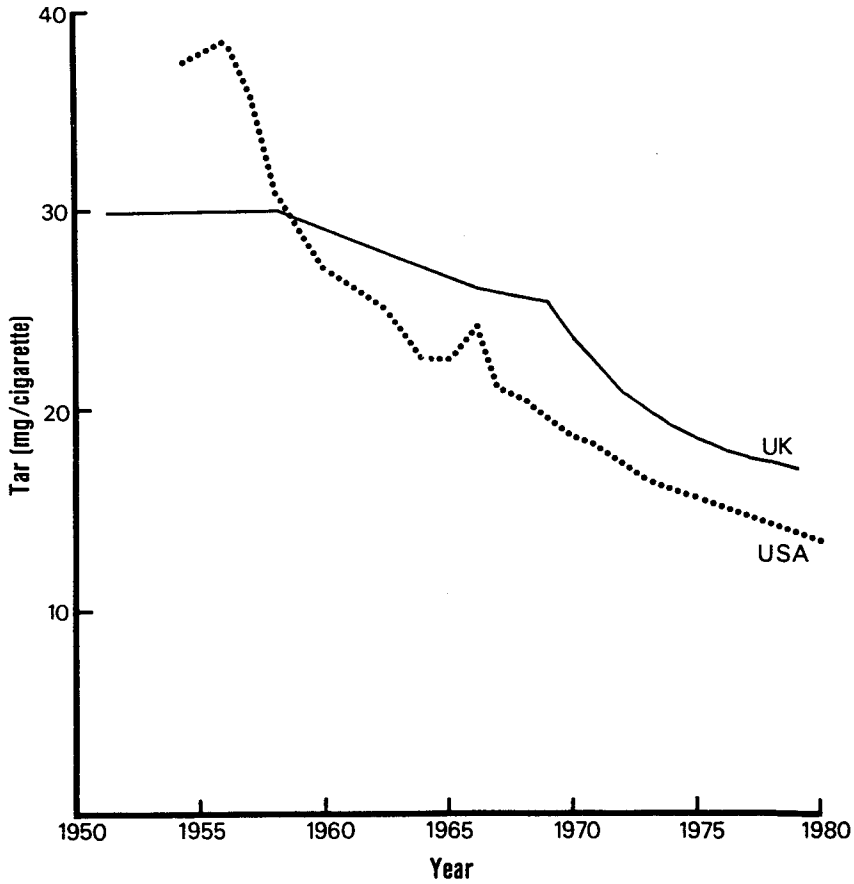
Ventilation may be achieved either by increasing the permeability of the cigarette paper or by providing ventilation holes at the filter. With greater ventilation, a smaller proportion of the puff volume is drawn through the pyrolysis zone; less tobacco is burned, and the level of most mainstream smoke components is thus decreased. (For definitions of mainstream and sidestream smoke, see p. 83) All mainstream smoke products are also diluted by the incoming air. The outward diffusion of light gases, such as carbon monoxide, is increased, thereby increasing their levels in sidestream smoke. As ventilation is increased, a larger proportion of tobacco is consumed between the puffs (smoulder period), and the sidestream:mainstream smoke ratio increases (Baker, 1984). The total ventilation of a ventilated cigarette changes as the cigarette is consumed, affecting the delivery of smoke components per puff of cigarette. The percentage of air dilution in the low-yield Kentucky research cigarette (1R4F) is about 28% (Davis, D.L. *et al.*, 1984).

(*c*) *Tar and nicotine yields*

The effect of these changes in cigarette design is reflected in a trend of declining sales-weighted average tar and nicotine levels in the smoke of cigarettes in many countries since 1955. In 1978-1979, scientists in the UK collected cigarettes from 1934 to 1979 that were still available in adequate numbers (Wald *et al.*, 1981a). These old cigarettes were rehumidified and smoked under standard laboratory conditions in the UK Laboratory of the Government Chemist. In cigarettes of early years (1934-1940), the tar values were about 33 mg, carbon monoxide 19 mg and nicotine 2.0 mg per cigarette. By 1979, these smoke yields had decreased, reaching sales-weighted average values of 17 mg tar, 17 mg carbon monoxide and 1.4 mg nicotine. Thus, since 1934, nicotine yields have decreased to a lesser extent than those of tar, and carbon monoxide yields have changed even less.

In the USA in 1956, sales-weighted average tar and nicotine values were about 38 mg and 2.7 mg, respectively. By 1982, these levels had been reduced to about 13 mg tar and 1.0 mg nicotine (Tobacco Institute, 1984). Figures 1 and 2 graphically document the decline in tar and nicotine levels, denoting the technical modifications that have been introduced.

Fig. 1. Sales-weighted average tar yields of UK and US cigarettes by year of manufacture[a]



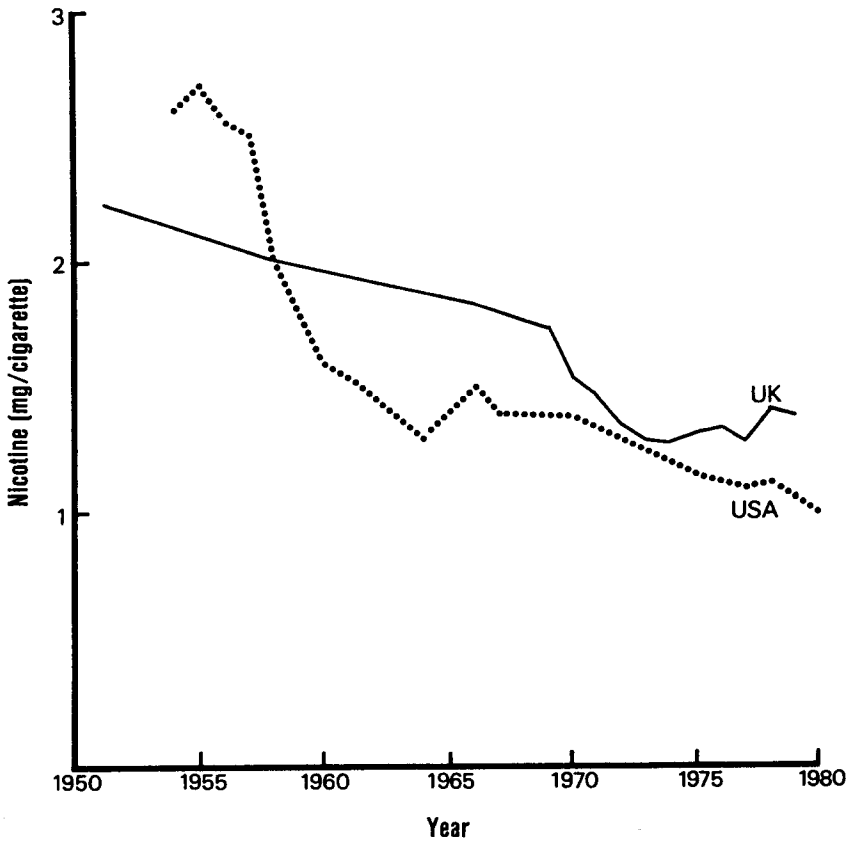
[a]From Wald *et al.* (1981a) and Norman (1982)

The following system of classifying cigarettes on the basis of tar yields, as determined under the most widely used laboratory conditions, was adopted by the Working Group:

Description of yield	*Tar yield (mg/cigarette)*
Very low	≤4.9
Low	5-9.9
Moderate	10-14.9
High	15-19.9
Very high	20 and over

The laboratory conditions comprise a 35-ml puff volume, a 2-sec puff duration, 1 puff per 60 sec and smoking to a 23-mm butt length for nonfilter cigarettes and to 3 mm in front of the

Fig. 2. Sales-weighted average nicotine yields of UK and US cigarettes by year of manufacture[a]



[a]From Wald *et al.* (1981a) and Norman (1982)

filter overwrap for filter cigarettes. The cigarettes are conditioned in an environmental chamber maintained at 60% relative humidity at 24°C (Jenkins, R.A. *et al.*, 1983). It was recognized, however, that the tar delivery of a cigarette is altered if it is smoked under different conditions, and this must be taken into account when describing human smoking experience. (See also section 3, pp. 163-194 of the chapter on 'Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans.') In addition, although machine-smoking parameters can differ substantially from the puff drawing of smokers, especially in the case of cigarettes that deliver low yields of nicotine, publication of tar level measurements was considered to be useful for public health purposes, since it may, over the years, encourage a general lowering of the particulate matter delivered by cigarettes.

A series of research cigarettes has been developed, which is referred to in other sections of this monograph; the tar, nicotine and carbon monoxide levels in these cigarettes are presented in Table 9.

Table 9. Smoke component levels of US research cigarettes as measured under standard laboratory conditions

Designation	Tar (mg/cig)		Nicotine (mg/cig)		Carbon monoxide (mg/cig)	
	23 mm	30 mm	23 mm	30 mm	23 mm	30 mm
Kentucky series[a]						
1R1	34.3	30.1	2.16	1.98	20.8	18.1
2R1	36.8	32.9	2.45	2.19	25.1	22.2
2R1F	-	23.4	-	1.74	-	22.0
2A1[b]	36.4	31.8	0.48	0.42	25.2	22.8
1A2	34.0	29.5	2.08	1.75	21.4	17.1
1A3	29.0	25.8	1.28	1.14	21.9	18.2
1A4	35.5	29.8	2.61	2.20	19.6	17.4
1R4F[c]	-	9.2	-	0.80	-	11.6
NCI series[d]						
SEB-1	18.5	-	1.83	-	16.1	-
SEB-16	12.7	-	0.99	-	14.8	-
SEB-20	22.3	-	1.64	-	22.1	-
1R1	30.0	-	2.80	-	17.6	-

[a]From Davis, D.L. *et al.* (1984)

[b]Equivalent to original 1A1

[c]35-mm butt length

[d]From Gori (1976a); carbon monoxide levels given in ml/cigarette

Governmental agencies in several countries issue periodic reports on the tar, nicotine and carbon monoxide values for commercial cigarettes. In the USA, the US Federal Trade Commission (1985) reports twice yearly the levels of tar (<0.5-28 mg), nicotine (<0.05-2.1 mg) and carbon monoxide (<0.5-23 mg) for more than 200 marketed brands. Similar reports are released twice annually by the Health Departments of the United Kingdom (1984) (tar, <4-25 mg; nicotine, <0.3-2.5 mg; carbon monoxide, <3-19 mg). Reports on the tar and nicotine yields of commercial cigarettes are also published on an irregular basis in Australia, Austria, Canada, the Federal Republic of Germany, Japan, Switzerland and elsewhere.

Tar and nicotine yields of commercial cigarettes vary widely around the world (Table 10). Cigarettes delivering more than 35 mg of tar existed in 1983 in Austria, France, India,

Table 10. Ranges of tar and nicotine yields of commercial cigarettes from selected locations[a]

Location (year cigarettes bought)	Tar		Nicotine		No.of samples
	mg/cig.	median	mg/cig.	median	
Austria (not given)	6-36	19	0.2-2.7	0.9	27
China (1981)	21-33	26	0.7-1.2	0.9	10
France (1978)	15-44	23	0.6-2.2	1.3	10
Germany, Federal Republic of (1979)	2-25	14	0.2-1.5	0.8	18
Hong Kong (1975, 1976, 1981)	1-32	19	0.1-2.6	1.2	47
India (1980)	21-38	27	1.1-2.0	1.5	16
Indonesia (1980)	18-55	36	0.8-2.8	1.7	20
Israel (1979)	9-26	21	0.6-1.3	0.9	10
Italy (1977, 1979)	14-36	23	0.4-2.2	1.1	23
Japan[b] (1980)		15.9		1.05	
(1981)		15.6		1.02	
Kenya (1978)	16-32	23	1.0-3.4	1.7	15
Philippines (1975, 1977)	22-44	32	0.8-2.3	1.4	64
Scotland (1979)	9-33	18	0.7-2.4	1.4	11
Singapore (1981)	13-24	20	0.8-1.6	1.3	14
South Africa (1978)	12-39	28	0.5-2.4	1.7	68
UK (1978)	17-28	21	0.9-1.8	1.1	6
USA (1981)[c]	1-27	14	0.1-1.8	1.1	32
USSR (1983)[d]	21-31	25	1.3-1.9	1.6	17

[a]From Jenkins, R.A. *et al.* (1986), unless otherwise specified

[b]From Shien (1982), mean values

[c]From Jenkins, R.A. *et al.* (1983)

[d]From Laboratory of the Government Chemist (1984)

Italy, Indonesia, the Philippines and South Africa. One brand in Indonesia delivered 55 mg of tar (Jenkins, R.A. *et al.*, 1986). The tar content of cigarettes in developing countries is thus frequently very high, as is that of products such as *bidis* and *chuttas*.

By contrast, sales-weighted tar and nicotine yields have fallen in many countries, as shown in Figures 1 and 2 for the UK and the USA. For example, in Egypt, Finland, Saudi Arabia, Oman and Australia, brands delivering more than 20 mg of tar do not exist (as a result of legislation or voluntary agreement). The decline in sales-weighted tar yields is also quite widespread in some developing countries (Lee, P.N., 1984) (Table 11).

During 1979-1980 in Finland, the sales-weighted average tar yield decreased progressively from 21 to 16 mg/cigarette. According to analyses made in 1978, the *papirossi* cigarettes (with a hollow mouthpiece) commonly used in the 1950s delivered 26-27 mg of tar and 1.5-1.7 mg of nicotine (Central Statistical Office of Finland, 1980, 1984). During 1950-1970, filter cigarettes displaced the *papirossi* cigarettes; the latter were used by one-half of Finnish smokers in 1960 and by less than 10% in 1970 (Lee, P.N., 1975; Rimpelä, 1978).

The wide range of cigarettes available also results in varying yields of other smoke components. Jenkins, R.A. *et al.* (1983) report that, under laboratory conditions, carbon monoxide yields of US cigarettes ranged from 1-19 mg/cigarette, oxides of nitrogen from 28-543 μg/cigarette, hydrogen cyanide from 7-362 μg/cigarette and acrolein from 3-141 μg/cigarette. Most of the individual constituents were proportional to the tar deliveries within a factor of two. (This measurement did not apply to volatile nitrosamines.)

3. Smoking and public health considerations

The number of tobacco-associated cancers that occurs throughout the world is related to the long-term dose of carcinogens in tobacco. The target organ that is affected depends largely on the way in which tobacco is used; the forms of its use are as diverse as the cultures and countries in which it is used and the people who use it. It is therefore difficult to compare different populations, as habits vary greatly and may be mixed. Although individual differences within countries abound, however, there is some basic uniformity within national habits, e.g., almost all Japanese smokers use cigarettes.

With regard to dose, using cigarettes as an example, the indices bearing on it are: numbers of cigarettes smoked, amount of carcinogen delivered per cigarette (much of this being included in the tar component), duration of the habit and inhalation practice. The components of dose are different and less measurable for such practices as chewing (IARC, 1985a).

In developed countries now, exposure to tobacco components is almost entirely through smoke. The products used are mainly cigarettes, although pipes and cigars provided more of the exposure earlier in the lives of the population at risk today. Three measures bear on the ways in which some populations are exposed to tobacco smoke: estimates of national tobacco consumption, regularly published sales estimates and surveys of smoking habits (which are rarely available in developing countries).

Table 11. Sales-weighted average tar deliveries in various countries, 1982[a]

Tar yield (mg/cigarette)	Developed countries	Developing countries or territories
0-10	None	None
11-16	Australia Belgium Canada Finland Germany, Federal Republic of Netherlands New Zealand Sweden Switzerland UK USA	Chile El Salvador Fiji Guatemala Kenya Mauritius Nicaragua Panama Papua New Guinea Trinidad and Tobago Venezuela
17-22	France Italy	Argentina Bangladesh Barbados Brazil Costa Rica Cyprus Hong Kong India Malawi Malaysia Malta Mexico Nigeria Sierra Leone Singapore South Africa Sri Lanka Suriname Zimbabwe
23-28	Denmark	Indonesia Pakistan Zaire
29+	None	None

[a]As supplied by the tobacco industry; from Lee, P.N. (1984)

These measures, discussed below, may provide useful trend lines, with certain limitations. Firstly, it is a common finding that surveys fail to account for total consumption, partly due to restriction of the age groups covered and partly to a tendency to underestimate amounts smoked in personal histories (Todd, 1978). Secondly, changes in cigarette design and composition [e.g., many cigarettes contain less tobacco and deliver smaller quantities of both tar and nicotine (see above)] have come about due to economic and technical factors affecting production as well as to public health pressures. These variations are of such magnitude that numbers of cigarettes alone may no longer constitute a satisfactory measure of exposure for the purpose of international comparisons although such estimates retain some value in individual countries, particularly where tar contents are known and published.

Measurements of reductions in tar and nicotine yields by analytical techniques involving standardized machine smoking of cigarettes do not accurately reflect the variations in yields experienced by smokers of low-yield products. This applies especially to cigarettes with low nicotine yields, true levels of exposure to which are governed by frequency of puff-drawing, size of puff volume, depth of inhalation of the smoke, and, possibly, lip pressure (see section 3, pp. 163-194, of the chapter on 'Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans'). While it has been observed that smokers compensate for low-nicotine delivery by altering their smoking patterns (Russell, 1980; Kozlowski *et al.*, 1980; Herning *et al.*, 1981; Hoffmann *et al.*, 1983a), there appears to be a limit for such compensation when the nicotine yield is $\leqslant$ 0.5 mg/cigarette (Hill, P. & Marquardt, 1980). Table 12 summarizes the methodological approaches towards reducing both total smoke yields and the amounts of individual or grouped smoke constituents.

Reduction of an individual compound or of a group of smoke constituents is considered to be selective when it exceeds the reduction of tar to a significant extent. Various methods for selective reduction of toxic and/or carcinogenic smoke constituents have been devised and tested in order to lower the tumorigenic potential of tobacco smoke to mouse skin and/or to hamsters by inhalation (Wynder & Hoffmann, 1967; Dontenwill, 1974; Weber, K.H., 1976; Wynder & Hoffmann, 1979, 1982; Browne *et al.*, 1984).

(a) Estimates of tobacco consumption in different countries

Such trends generally reveal rising consumption in most countries from the 1920s to the 1960s, interrupted in certain cases by major events, such as war, financial depression and reports by health bodies such as the US Surgeon General and the Royal College of Physicians of London. Table 13 gives the consumption of cigarettes per adult in selected countries during the period 1923-1983. This table does not reflect the reduced tobacco consumption in some countries as a consequence of the Second World War, and it conceals some quite substantial differences in smoking practice among a group of relatively developed countries. In Finland, the UK and the USA, the per-caput consumption increased steadily from 1920 to the 1960s and has been declining in recent years (Fig. 3).

The per-caput consumption of manufactured cigarettes in 110 countries in 1982 is shown in Table 14, and ranges from 17 to over 3700 manufactured cigarettes/year. Table 15 gives the proportions of tobacco used for different forms of tobacco consumption in some countries in 1923, 1953 and 1973 (Lee, P.N., 1975).

Table 12. Reductions in smoke constituents of experimental cigarettes[a]

Method[b]	Smoke constituent		
	Tar	Nicotine	Benzo[*a*]pyrene
Agricultural methods			
Tobacco type (flue-cured burley)[c]	*	*	*
Cultivars	*	*	*
Fertilizing (nitrate)	*	*	*
Tobacco processing			
Cut	0	0	0
Use of stems	*	*	*
Reconstituted tobacco sheets[d]	*	*	*
Reconstituted tobacco sheet-paper process	**	*	*
Expanded tobacco	*	**	*
Expanded stems	*	**	*
Cigarette production			
Paper porosity	*	*	*
Cellulose acetate filters	*	*	*
Charcoal filters[e]	*	*	*
Perforated filters	**	**	**

[a]From Wynder and Hoffmann (1982)

[b]Methods known to be applied to commercial US cigarettes. Reductions: **, > 50%; *, 'significant'; 0, 'insignificant'

[c]Replacing flue-cured with burley tobaccos

[d]Data relate to those not made by the paper process

[e]Reductions of tar, nicotine, benzo[*a*]pyrene (and other nonvolatiles) and volatile *N*-nitrosamines are, in general, greater with cellulose acetate filters than with charcoal filters.

Machine-made cigarettes dominate the modern market, particularly in Japan. Hand-rolling persists in Norway and to a lesser extent in Australia, Belgium, Denmark, the Netherlands, Sweden, the UK, the USA and other countries. Smokeless tobacco retains a significant market, for example, in Scandinavia and the USA (see IARC, 1985a). Cigars are still smoked in Belgium, Denmark and the USA, but their consumption is negligible in Japan, Australia and Norway. Long-term consumption

Table 13. Annual consumption of cigarettes per adult in selected countries in the period 1923-1983[a]

Country	Year						
	1923	1933	1943	1953	1963	1973	1983
Australia	540	430	660	1420	2550	3080	
Austria	600	1000	1540	1320	1840	2550	
Belgium	650	880	290	1190	1760	2730	
Denmark	460	420	360	1230	1580	1850	
Finland	1290	1170	1340	1780	2190	2040	1829[b]
% papirossi			(70%)	(45%)	(19%)	(3%)	
France	-	570	330	1120	1420	1920	
Japan	750	790	1140	1570	2170	3240	
Mexico	900	1150	1460	1530	1530	1360	
Netherlands	410	670	-	1370	1900	2370	
Norway	-	280	230	520	520	640	
South Africa	370	410	1070	1220	1000	1380	
Sweden	250	390	440	950	1310	1580	
UK	1030	1470	2330	2370	2790	3230	
males 15+ years	1980	2820	3930	3690	3820	3980	
males 16-19 years[c]	1150	1650	2350	1850	2950	3450	
USA	840	1230	2510	3380	3910	3850	3494[d]

[a]From Lee, P.N. (1975), unless otherwise specified

[b]From Central Statistical Office of Finland (1984)

[c]The first UK age-specific survey data are from 1980

[d]From US Department of Agriculture (1984)

figures are available for only a few developing countries. In 1973, tobacco consumption in India was as follows — cigarettes, 30%; cigars/cheroots, 5%; *bidis*, 34%; hookah, 9%; chewing tobacco, 19%; and snuff, 2%. In Indonesia, cigarettes claimed 28% and *kreteks* 72% of the measured market (Lee, P.N., 1975).

Table 14. Manufactured cigarette consumption in 110 countries or territories in 1982[a]

Rank	Country or territory	Per-caput consumption
1	Cyprus	3 117
2	Greece	2 927
3	Cuba	2 857
4	Canada	2 797
5	USA	2 678 (3 746)[b]
6	Spain	2 658
7	Japan	2 636
8	Hungary	2 570
9	Poland	2 517
10	Bulgaria	2 472
11	Australia	2 340
12	Yugoslavia	2 323
13	New Zealand	2 305
14	Switzerland	2 171
15	Austria	2 111
16	Belgium and Luxembourg	2 055
17	Singapore	1 961
18	Hong Kong	1 957
19	Lebanon	1 926
20	Germany, Federal Republic of	1 867
21	Italy	1 854
22	UK	1 818
23	Czechoslovakia	1 812
24	German Democratic Republic	1 796
25	Ireland	1 778
26	Republic of Korea	1 747
27	USSR	1 715
28	Libyan Arab Jamahiriya	1 688
29	Israel	1 656
30	Netherlands	1 652
31	Denmark	1 636
32	France	1 608
33	Romania	1 593
34	Sweden	1 543
35	Taiwan	1 531
36	Portugal	1 428
37	Philippines	1 371
38	Trinidad and Tobago	1 318
39	Turkey	1 305
40	Uruguay	1 241
41	Malaysia	1 222
42	Mauritius	1 215
43	Finland	1 148
44	Argentina	1 136
45	Venezuela	1 089
46	Brazil	1 051
47	Syrian Arab Republic	1 049
48	Democratic Yemen	1 038
49	South Africa	1 002
50	Fiji	986
51	Suriname	975
52	China	900
53	Colombia	873
54	Egypt	872
55	Costa Rica	868
56	Jordan	867
57	Algeria	861

Table 14 (cont)

Rank	Country or territory	Per-caput consumption	Rank	Country or territory	Per-caput consumption
58	Belize	850	85	Iran	364
59	Chile	847	86	Sri Lanka	341
60	Nicaragua	846	87	Guatemala	325
61	Albania	786	88	Zimbabwe	319
62	Barbados	785	89	Haiti	316
63	Tunisia	768	90	Kenya	283
64	Democratic People's Republic of Korea	713	91	Zambia	223
			92	Mozambique	221
65	Guyana	656	93	Ghana	218
66	Jamaica	650	94	Peru	216
67	Dominican Republic	614	95	Lao People's Democratic Republic	209
68	Thailand	606			
69	Panama	595	96	Bolivia	206
70	Indonesia	577	97	Malawi	197
71	Iraq	574	98	Tanzania	181
72	Honduras	563	99	Cameroon	175
73	Norway	556	100	Bangladesh	170
74	Morocco	537	101	Uganda	146
75	Congo	531	102	India	141
76	Paraguay	521	103	Zaire	129
77	El Salvador	508	104	Cape Verde	117
78	Ecuador	508	105	Nigeria	98
79	Senegal	448	106	Nepal	93
80	Viet Nam	424	107	Burma	71
81	Ivory Coast	422	108	Ethiopia	48
82	Sierra Leone	419	109	Sudan	37
83	Pakistan	396	110	Guinea	17
84	Angola	375			

[a]From Collishaw (1984)

[b]From US Department of Agriculture (1984)

Table 15. Proportions of tobacco used for various forms of tobacco consumption in selected countries in 1923, 1953 and 1973 (millions of kg)[a]

Country	Year	Cigarettes		Cigars		Snuff		Handrolled/pipe/chewing		Total
Australia	1923	2.1	(26%)	0.3	(3%)		-	5.7	(70%)	8.1
	1953	9.1	(47%)	0.1	(0.5%)		-	10.3	(53%)	19.4
	1973	27.6	(86%)	0.3	(0.8%)		-	4.1	(13%)	32.0
Austria	1923	3.2	(32%)	0.7	(7%)	0.1	(1.4%)	5.9	(59%)	9.9
	1953	7.1	(80%)	0.3	(4%)		-	1.4	(16%)	8.9
	1973	14.5	(95%)	0.4	(2.4%)		-	0.4	(3%)	15.3
Belgium	1923	3.8	(20%)	2.1	(11%)		-	13.0	(69%)	18.9
	1953	8.2	(41%)	1.8	(9%)		-	10.0	(50%)	20.0
	1973	20.2	(71%)	3.6	(13%)		-	4.7	(16%)	28.5
Denmark	1923	1.4	(20%)	1.8	(25%)	0.3	(4%)	3.5	(50%)	6.9
	1953	4.9	(45%)	2.5	(23%)	0.5	(5%)	3.0	(27%)	10.9
	1973	9.2	(65%)	2.7	(19%)	0.2	(2%)	2.0	(14%)	14.1
Japan	1923	27.2	(52%)	0.1	(0.1%)		-	24.7	(47%)	51.9
	1953	89.6	(92%)		-		-	7.4	(8%)	97.0
	1973	267.0	(99%)		-		-	0.5	(0.2%)	267.5

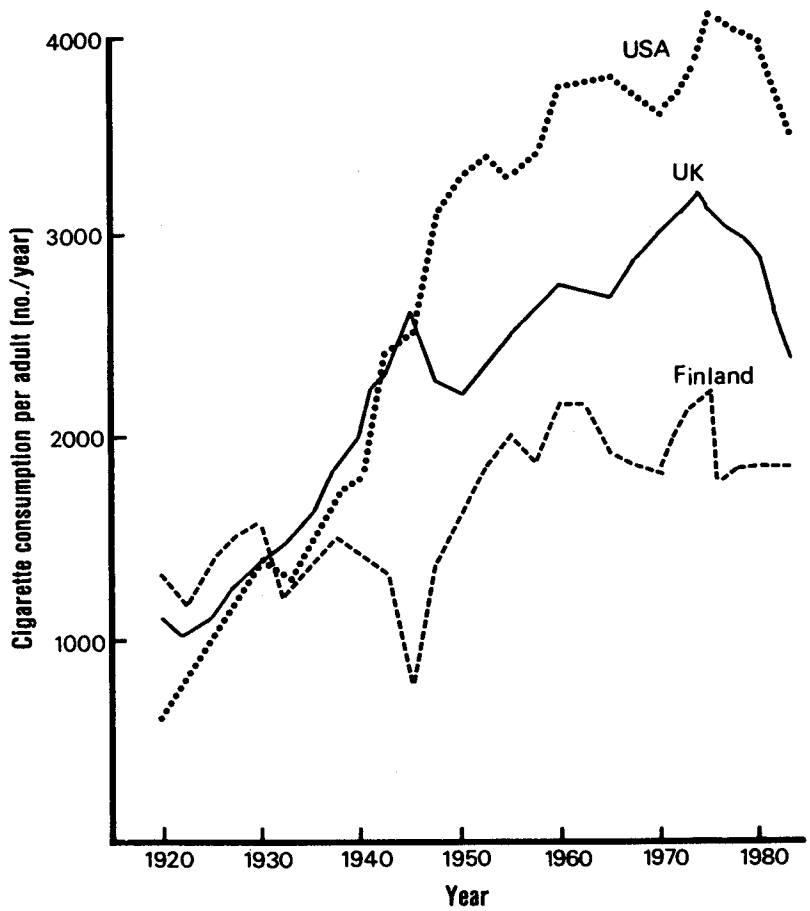
Table 15 (contd)

Country	Year	Cigarettes		Cigars		Snuff		Handrolled/pipe/chewing		Total
Norway	1923	-		-		-		-		-
	1953	1.5	(31%)	0.05	(1%)	0.5	(11%)	2.9	(58%)	5.0
	1973	2.0	(29%)	0.1	(1%)	0.3	(4%)	4.4	(65%)	6.8
Sweden	1923	0.6	(7%)	0.6	(7%)	5.5	(70%)	1.2	(16%)	7.9
	1953	5.6	(53%)	0.4	(4%)	2.9	(28%)	1.5	(15%)	10.4
	1973	7.1	(60%)	0.5	(4%)	2.7	(23%)	1.5	(12%)	11.8
UK	1923	34.1	(53%)	1.2[b]	(2%)	-	-	28.6	(45%)	63.9
	1953	90.2	(84%)	0.4	(0.3%)	0.4	(0.3%)	16.3	(15%)	107.3
	1973	103.9	(87%)	3.3	(3%))	0.2	(0.2%)	11.7	(10%)	119.1
USA	1923	64.6	(20%)	63.4	(20%)	17.9	(6%)	169.2	(54%)	315.1
	1953	409.9	(74%)	51.6	(9%)	17.7	(3%)	75.5	(14%)	554.7
	1973	508.5	(79%)	59.7	(9%)	11.6	(2%)	60.8	(10%)	640.6

[a]Adapted from Lee, P.N. (1975), by converting from pounds to kg

[b]Including snuff

Fig. 3. Annual per-caput consumption of cigarettes in Finland[a], the UK[b] and the USA[c], 1920-1983



[a]From Central Statistical Office of Finland (1980, 1984)

[b]From Lee, P.N. (1975)

[c]From US Department of Agriculture (1984)

(b) Sales trends

Sales are published as millions of 'pieces', i.e., items of manufactured product. Table 16 shows some selected sales figures from developed and developing countries (see also Appendix 1). While short-term trends may be variable, some long-term trends are apparent. Sales increases are not confined to developing countries. Sales figures are influenced by a number of factors, particularly taxation, socioeconomic circumstances, advertising pressure and the presence or absence of anti-smoking programmes. Regular increases in taxation generally produce quite significant falls in sales (Ontario Council of Health, 1982).

(c) Surveys of smoking behaviour

Only from surveys can it be ascertained who is smoking, what is smoked, how much, for how long and (sometimes) in what way. Regular surveys provide useful public health

information, as they may identify populations at risk and some of the reasons they are at risk. Reliable random-sample surveys are carried out routinely in most developed countries and, if similar definitions are used, allow useful international comparisons. Table 17 shows a selective sample of smoking rates collected from the literature, from governmental and national cancer societies and from the World Health Organization. It provides an overview of habits in adults around the world, even though the classification of 'smokers', 'nonsmokers' and 'ex-smokers' varies somewhat and is generally based on self reporting.

Given the variable quality of the available data, some striking trends stand out. Women in Hunan, Shanghai, Japan, Hong Kong, Singapore, Moscow, Romania, Egypt, Kuwait, Tunisia and urban Nepal smoke little, if at all; whereas about a third smoke almost everywhere else, except Maoris in New Zealand and women in some other areas in the developing world where rates have not been measured. Male smokers generally represent between one-third and one-half of the population; Japan is one of the few higher exceptions in the developed world.

Adolescent smoking rates, although of considerable public health importance as an indication of future trends, are extremely difficult to measure accurately and, consequently, to compare. It is usual for smoking habits to become established during adolescence, and smoking rates of young people in their late teens may approximate those of adults.

The detailed anatomy of national smoking habits can be discerned only by regular measures of smoking rates, although, because of problems of underreporting, it is often advisable to use questionnaire responses merely to distribute total sales among various categories (e.g., of age, sex). The results of a nationwide survey in Australia of the proportions of cigarette smokers by year, sex and education are shown in Table 18.

(d) Indices of dose in developing countries

Although the relationship between tobacco smoke and lung cancer in developed countries may be the most researched subject in medical history, there remains a paucity of precise information concerning daily dosage of tobacco in developing countries. That the daily dose may be high is attested to by the exposure levels measured in case-control studies in Bombay (Notani & Sanghvi, 1974).

There is no way of estimating precisely lifetime exposure to smoking products such as *bidi*, *chutta*, *brus*, *sticks* and hookah or the formidable *khi yo* cigars of Thailand. As shown in Table 17, between 30 and 90% of men in Asia smoke compared with less than one-third of women, who, in some parts of the developing world, smoke hardly at all.

It is already clear that there exists a worldwide trend towards the sale of machine-made cigarettes. On the one hand, manufacture of *bidis*, chews and the various other home-grown, home-made products cannot be quantified readily because it is based on village cultivation or, at best, small industry. These products are generally cheap, vary widely from district to district, and may or may not be subject to taxation. On the other hand, cigarettes are mass produced centrally, or imported, easy to count and almost invariably taxed before sale. For this reason, increases in sales can be measured, and taxation figures can be used to monitor sales trends. What cannot be seen is the effect of the market expansion of manufactured cigarettes on the use of other tobacco products. It is not clear how far the

Table 16. Tobacco sales in millions of 'pieces'[a]

Country	1968[b]	1976	1983[b]	Peak number	Peak year
Argentina	26 188	37 000	35 000	38 300	1980
Australia	23 600	30 900	33 400	34 400	1983
Austria	11 936	14 400	15 500 (1982)	15 700	1979, 1981
Belgium	16 100	20 200	19 800 (1981)	25 700	1974
Brazil	68 125[c]	115 000	129 200	142 700	1980
Canada	47 113	60 700	62 800	66 500	1981
Denmark	5 799	7 500	7 300	7 800	1982
Egypt	11 141	22 300	35 000 (1982)	35 000	1982
Finland	6 300	6 400	6 900 (1982)	8 100	1975
France	67 200 (1970)	81 200	86 400 (1982)	87 900	1979
Germany, Federal Republic of	104 600	128 000	113 700	129 800	1981
Greece	15 862	20 000	23 500 (1981)	23 500	1981
Guatemala	2 206	2 600	2 200 (1982)	2 700	1977, 1980
Hungary	21 520	24 600	26 500	26 500	1983
India	60 137	66 000	87 700 (1981)	87 700	1981
Israel	3 340	5 500	6 200 (1982)	6 200	1982
Italy	66 600	89 700	102 000	102 000	1983
Japan	196 000	291 772	311 900	313 800	1979, 1982
Mexico	37 707	45 000	49 100	53 300	1980
Netherlands	18 497	22 500	22 000	26 900	1977
Norway	1 800	1 720	1 800	2 200	1980
Philippines	38 224	49 600	60 100	60 200	1982
Poland	63 300	88 052	83 741	94 245	1980
Portugal	9 277	11 834	13 700	13 700	1983
Singapore	2 560 (1969)	3 200	4 200	4 200	1983
Spain	44 797	63 100	75 400	75 400	1983
Sweden	9 700	12 000	12 100 (1982)	12 100	1982
Turkey	35 650	-	78 000 (1982)	78 000	1982
UK	121 800[c]	130 600	101 600	137 400	1973
USA	528 700	603 530	596 190	627 150	1981
Venezuela	10 368	18 500	20 800	21 600	1978

[a]From Maxwell (1976-1984)

[b]Unless otherwise specified

[c]Consumption

Table 17. Percentage of adult[a] male and female smokers in various countries

Country or territory	Comment	Year of survey	Products used[b]	% of total who smoke		Source
				Male	Female	
Australia[c]	national	1983	ct	37	30	Hill, D. & Gray (1984)
Bangladesh[d]	market-place	1979	ct, B, P	71	20	Anon. (1983a); WHO (1983)
	Dhaka urban	1984	ct, B	70	20	Masironi & Rothwell (1985)
Brazil[c]	São Paolo	1972	ct	54	20	Joly, D.J. (1975)
	workers	1983	ct	52	37	Masironi & Rothwell (1985)
Brunei	Tutong urban	1979	ct	20	7	Masironi & Rothwell (1985)
Canada	national	1983	ct, C, P	41	32	Josse (1985)
China[c]	Hunan	1981	ct	56	1	WHO (1983)
	Shanghai county	1981	ct	44	3	Parker, R.L. *et al.* (1982)
	Ghanzhou urban	1984	ct	95	-	Masironi & Rothwell (1985)
Egypt[c]	national	1982	ct, P	40	1	Omar *et al.* (1982)
France	national	1978	ct	47[e]	20	Ledez (1978)
Germany, Federal Republic of[c]	national	1980	ct, C, P	40	29	Anon. (1980)
Guatemala[c]	urban	1972	ct	36	10	Joly, D.J. (1975)
Hawaii	state-wide	1979	ct			Masironi & Rothwell (1985)
	Caucasians			61	50	
	Hawaiians			57	47	
	Chinese			37	18	
	Filipinos			48	28	
	Japanese			53	26	
Hong Kong[c]	national	1982	ct	37	5	Government Information Services (1982)
	national	1984	ct	33	4	Masironi & Rothwell (1985)

Table 17 (contd)

Country or territory	Comment	Year of survey	Products used[b]	% of total who smoke		Source
				Male	Female	
India[d]	Goa	1976	B, P, C	66	26	WHO (1983)
	Goa urban	1984	ct, B, P	29	3	Masironi & Rothwell (1985)
	Goa rural	1984	ct, B, P	61	7	Masironi & Rothwell (1985)
Indonesia	various sites	1984	ct[f]	61-75	5-10	Masironi & Rothwell (1985)
Ireland[c]	national	1980	ct, C, P	49	36	Health Education Bureau (1980)
Israel[c]	national	1983	ct	44	30	Ben-Sira (1983)
	20-21-yr olds	1984	ct	50	-	Masironi & Rothwell (1985)
	21-yr olds	1984	ct	37	-	Masironi & Rothwell (1985)
Italy[c]	national	1981	ct	54	32	Tamburini *et al.* (1981)
Ivory Coast	Abidjan	1981	ct	24	0.8	Masironi & Rothwell (1985)
Japan[c]	national	1980	ct	70	14	Tominaga (1982)
Kuwait[c]	national	1980	ct	52	12	WHO (1983)
Malaysia		1983	ct	18	2	Masironi & Rothwell (1985)
Nepal[c]	rural plains	1984	ct, B, P	66 (30-39 yr)	68 (50-59 yr)	Masironi & Rothwell (1985)
	urban	1980	ct, B, P	85	14	WHO (1983)
	hills	1984	ct, B, P	95 (40+ yr)	72 (40+ yr)	Masironi & Rothwell (1985)
	Kathmandu valley	1981	ct, B, P	79	58	Masironi & Rothwell (1985)
New Zealand[c]	national	1981	ct	35	29	Hay (1984)
Norway[c]	national	1982	ct	40	34	Löchsen *et al.* (1982)
Pakistan[d]	Karachi	1972	ct, B, P, C	49	4	WHO (1983)
	Karachi	1982	ct, B, P, C	44[g]	6[g]	Masironi & Rothwell (1985)
Papua New Guinea	highlands	1981	ct + *brus*	77	80	Masironi & Rothwell (1985)
	southcoast	1981	ct + *brus*	85	76	Masironi & Rothwell (1985)

Table 17 (contd)

Country or territory	Comment	Year of survey	Products used[b]	% of total who smoke		Source
				Male	Female	
Poland[c]	national	1980	ct, C, P	63	29	Oles (1983)
Romania[c]	urban, rural	1970	ct	52	9	Racoveanu *et al.* (1975)
Singapore[c]	national	1975	ct, C, P	51	8.3	Lee, H.P. (1980)
Sri Lanka	Kandy urban	1968	ct, B	48	2	Masironi & Rothwell (1985)
Sweden[c]	national	1982	ct	30	30	Anon. (1983b)
Switzerland[c]	Zurich county	1980	ct, C, P	50	26	Schüler *et al.* (1980)
Thailand	urban, nationwide	1976-81	ct	51	4	Masironi & Rothwell (1985)
	rural	1981	ct + local types	70	40	Masironi & Rothwell (1985)
Tunisia	Tunis urban	1984	ct, P	58	6	Masironi & Rothwell (1985)
UK[c]	national	1982	ct	38	33	Office of Population Censuses and Surveys (1983a)
USA[c]	national	1980	ct	38	30	US Department of Health and Human Services (1983)
USSR[c]	Moscow	1981	ct	44	10	Cooper (1982)
Zambia	Lusaka urban	1984	ct	63	56	Masironi & Rothwell (1985)

[a]In most studies, 15 years and older

[b]ct, cigarettes; C, cigars, cheroots; P, pipe, hookah; B, *bidi*

[c]Sample probably representative

[d]Sample not representative

[e]Per inhabitant, not per adult

[f]May also include *kreteks*

[g]Including chewers

Table 18. Australian smoking rates 1980 and 1983 — % of men and women smokers by level of occupation and education[a]

	Men		Women	
	1980	1983	1980	1983
Occupational level[b]				
Upper white collar	30	32	31	25
Lower white collar	36	32	29	28
Upper blue collar	45	40	32	30
Lower blue collar	47	43	30	36
Educational level				
9 years school	44	41	31	31
10-11 years school	44	41	32	32
12 years school[c]	31	28	27	27

[a]From Hill, D. and Gray (1984)

[b]Upper white collar, professional, managerial, farmer; lower white collar, clerical, sales; upper blue collar, skilled manual worker; lower blue collar, semi-skilled, unskilled or farm worker, unemployed, pensioner, housewife not stating a previous occupation

[c]Includes tertiary edcuated

habit of cigarette smoking is becoming a substitute for *bidi* smoking or for chewing, or whether cigarette smoking is becoming an additional habit. Mixed tobacco habits are common. Jussawalla and Deshpande (1971) recorded in a case-control study of 2005 patients with head-and-neck cancers that there were 1205 smokers, including 979 *bidi* smokers, 129 cigarette smokers, 54 *bidi* and cigarette smokers, and 1152 chewers, and that these groups included 595 patients with both chewing and smoking habits.

Use of tobacco is indeed worldwide. Although Sikhs, Seventh Day Adventists, Mormons, large populations of women, and the majority of people in developed countries do not use it, there is no country where tobacco is not available for smoking or chewing. After three decades of battle by public health interests in the developing world, the rate of expansion of the tobacco market has been slowed, and in many places sales and consumption have been decreased.

4. Summary

Tobacco was brought from America to the Old World by Columbus in 1492, and its use spread to many countries during the sixteenth century. Tobacco is now produced and consumed in almost every part of the globe; total world production in 1982 reached 6.7 million tonnes. Many types of tobacco are available, which differ in plant variety and in cultivation and curing methods; each type is generally used for one specific product. Recent trends indicate changes in production and utilization, particularly in consumption in developed countries. Modification of raw products and manufacturing techniques to reduce the yields of toxic agents in smoke is being studied widely and, in some cases, used widely,

Many different smoking products are used by hundreds of millions of persons throughout the world. The majority of these products are cigarettes, cigars and pipe tobaccos. During the present century, there has been a significant increase in the consumption of machine-made cigarettes in many countries.

The yields of mainstream smoke components are greatly affected by cigarette design, including ventilation (filter-tip dilution and paper porosity), tobacco composition (blended, reconstituted-sheet and expanded tobacco) and filtration. The yields of sidestream smoke components can be affected by tobacco composition and, to a lesser extent, by ventilation. The standard laboratory methods of determining particulate yields (tar and nicotine) have limited relation to specific human dosage. Individual smoking patterns are important.

Since 1950, there has been a substantial decline in the sales-weighted tar delivery of cigarettes sold in the UK, the USA and some other countries, although it is unlikely that smokers have reduced their tar intake to a similar extent. However, cigarettes with very high tar yields (35-55 mg) remain on the market in many parts of the world, and consumption and sales are increasing worldwide.

During the twentieth century, both the number of smokers and the number of cigarettes sold increased until the 1960s. By the early 1980s, some countries had recorded falls in total consumption, total sales and smoking rates.

3. Chemical composition

Inside a burning tobacco product, a large variety of chemical and physical processes occur in an oxygen-deficient, hydrogen-rich environment with a steep temperature gradient. The existence of these specific conditions greatly determines the formation of the vast majority of smoke components (Baker, 1980). In this overview, emphasis is placed on those smoke components that are biologically active and have been studied in the laboratory for toxicity and/or carcinogenicity. The concentrations of some of these agents in nonfilter cigarette MS are shown in Table 19.

The structures of some of the chemical constituents of tobacco smoke are given in Figure 5.

Table 19. Concentrations of biologically active agents in nonfilter cigarette mainstream smoke

Smoke constituent	Concentration/cigarette
Total particulate matter	15-40 mg
Carbon monoxide	10-23 mg
Nicotine	1.0-2.3 mg
Acetaldehyde	0.5-1.2 mg
Acetic acid	0.1-1.0 mg
Acetone	100-250 μg
Methanol	90-180 μg
Nitrogen oxides	100-600 μg
Formic acid	80-600 μg
Hydrogen cyanide	400-500 μg
Hydroquinone	110-300 μg
Catechol	100-360 μg
Ammonia	50-130 μg
Benzene	20-50 μg
Acrolein	60-100 μg
Phenol	60-140 μg
Croton aldehyde	10-20 μg
Formaldehyde	70-100 μg
Pyridine	16-40 μg
3-Methylpyridine	20-36 μg
2-Cresol	14-30 μg
3- and 4-Cresol	40-80 μg
3- and 4-Methylcatechol	31-45 μg
Carbazole	1 μg
2-Nitropropane	0.2-2.2 μg

Table 19 (contd)

Smoke constituent	Concentration/cigarette
N'-Nitrosonornicotine	200-3000 ng
4-(Methylnitrosamino)-1-)3-pyridyl)-1-butanone	80-770 ng
N'-Nitrosoanabasine	0-150 ng
N-Nitrosodiethanolamine	0-36 ng
N-Nitrosopyrrolidine	0-110 ng
N-Nitrosodimethylamine	2-20 ng
N-Nitrosomethylethylamine	0-2.7 ng
N-Nitrosodiethylamine	0-2.8 ng
N-Nitrosodi-*n*-propylamine	0-1 ng
N-Nitrosodi-*n*-butylamine	0-3 ng
N-Nitrosopiperidine	0-9 ng
Hydrazine	32-43 ng
Urethane	20-38 ng
Vinyl chloride	1.3-16 ng
Benz[*a*]anthracene	20-70 ng
Benzo[*b*]fluoranthene	4-22 ng
Benzo[*j*]fluoranthene	6-21 ng
Benzo[*k*]fluoranthene	6-12 ng
Benzo[*a*]pyrene	20-40 ng
Dibenz[*a,h*]anthracene	4 ng
Dibenzo[*a,i*]pyrene	1.7-3.2 ng
Indeno[1,2,3-*cd*]pyrene	4-20 ng
5-Methylchrysene	0.6 ng
Dibenz[*a,j*]acridine	2.7 ng
Dibenz[*a,h*]acridine	0.1 ng
7*H*-Dibenzo[*c,g*]carbazole	0.7 ng
2-Naphthylamine	1.7-22 ng
4-Aminobiphenyl	2.4-4.6 ng
ortho-Toluidine	32-160 ng
Maleic anhydride	Present
2,3-Dimethylmaleic anhydride	Present
Succinic anhydride	Present
Coumarin	Present

BIOLOGICAL DATA RELEVANT TO THE EVALUATION OF CARCINOGENIC RISK TO HUMANS

1. Carcinogenicity studies in animals

(a) Inhalation of tobacco smoke

Although the evidence for carcinogenicity of tobacco smoke emerged first in humans, there was need for an inhalation model in experimental animals in which the carcinogenicity of different types of tobacco and tobacco products could be studied. The availability of animal models also permits the comparison of different products and the investigation of various modifying factors in the development of respiratory cancer.

Early inhalation studies in rodents were reviewed by Wynder and Hoffmann (1967). From about 1960, the animal species selected most often for model studies was the Syrian golden hamster, which has a low background incidence rate of spontaneous pulmonary tumours and few interfering respiratory infections. The discovery that inhalation of tobacco smoke caused carcinomas in the larynx of hamsters established a model system in which the carcinogenicity of tobacco smoke for hamsters has been confirmed repeatedly (*vide infra*). Few bioassays have been conducted, however, in longer-lived mice, rats and dogs, because of low priority and high cost; therefore, the spectrum of possible tumour responses in animals to inhalation of tobacco smoke is little known.

In order to study the response of animals to smoke inhalation, it was necessary to develop methods and equipment to deliver smoke in a standardized, effective way. A number of exposure devices have been employed, some involving whole-body exposure and some 'nose-only' exposure. Usually, in order to simulate human smoking patterns, a 2-second puff from a burning cigarette is diluted with air and forced into a chamber for a short period, followed by an air purge. However, animals, which are being forced involuntarily to inhale the smoke, undergo avoidance reactions and change their breathing patterns to shallow, hesitant inspirations with reduced minute volumes. This affects the doses delivered to the different parts of the respiratory system. Because rodents are obligatory nose-breathers and because rodents and dogs have more convoluted and intricate nasal turbinate patterns than humans, the dynamics of particle deposition in the upper respiratory tract might be expected to be different (see Wynder & Hoffmann, 1967; Nagano *et al.*, 1982; Proctor & Chang, 1983; Reznik, 1983).

Under experimental conditions, the smoke in the chamber can be assayed for total particulate and carbon monoxide, and animals can be examined at intervals to determine the levels of carboxyhaemoglobin, nicotine or cotinine in blood, and for particulate deposition and retention in tissues, which give some indication of the doses administered. In typical experiments, rodents were exposed to the smoke of seven to ten cigarettes per day on five to seven days per week (Dalbey *et al.*, 1980; Wehner, A.P. *et al.*, 1981) and developed carboxyhaemoglobin levels of 20-40% (Bernfeld *et al.*, 1974).

Inhalation of tobacco smoke is irritating and toxic to animals (see pp. 140-149). They can adapt to many short exposures over a period of time, but require varying periods of recovery between exposures, depending somewhat on the species. Both smoke-exposed and sham-exposed animals have reduced body weights, and may live longer (see also pp. 140-149).

Mouse: Groups of 100 male and 100 female young adult C57Bl mice were exposed (nose only) for 12 min/day to a mixture of fresh cigarette smoke/air (1/39, v/v) every other day for life. [The cigarettes were made from a composite blend of flue-cured tobaccos typical of the major nonfilter cigarette brands smoked in the UK (Harris, R.J.C. *et al.*, 1974).] The concentration of nicotine in the mixture was about 0.1 mg/ml and that of carbon monoxide, 0.064 vol %. The nicotine content in the lungs of mice that died during exposure amounted to 14-17 μg. Groups of 100 males and 100 females were used as controls. No lung tumour, either adenoma or carcinoma, was found in control mice. Lung tumours (alveologenic adenocarcinomas) were found in 4/100 male and in 4/100 female exposed mice [$p = 0.06$]. Some of the adenocarcinomas were transplantable. Mice exposed to smoke often showed emphysema and marked peribronchial and perivascular infiltration with lymphocytes, independent of the presence of tumours (Harris, R.J.C. & Negroni, 1967).

A total of 126 C57Bl and 126 BLH mice [sex and initial group sizes unspecified] were exposed to the gas phase of 12 cigarettes [unspecified] puffed for 2 sec/min. The gas phase was generated by passing the smoke through a Cambridge filter which retained the particulate matter. The mice were exposed in a 200-l chamber for 90 min daily (approximately the maximal tolerated dose) until spontaneous death (for approximately 27 months). Survival rates for more than 12 months of treatment were not affected by treatment in either strain of mice [numbers not provided]. The percentages of mice with lung adenomas were 5.5 and 32% in exposed C57Bl and BLH mice and 3.4 and 22% in 90 C57Bl and 60 BLH controls, respectively. The percentages of BLH mice with lung adenomas that survived at least 10 months were 37% of the treated group and 31% of the controls. The difference in adenoma incidence between control and treated groups was stated to be not statistically significant (Otto & Elmenhorst, 1967). [The Working Group noted the incomplete reporting of the experiment.]

A group of 50 male C57Bl6/Mil mice, six weeks of age, were exposed to cigarette smoke from 85-mm nonfilter cigarettes [unspecified] in a vacuum chamber for 15 min, five times per week for 63 weeks. The nicotine content in the lungs of mice that were killed ranged from 14-27 μg. When the nasal cavity and respiratory tree were examined microscopically, the incidences of hyperplasia and metaplasia were increased in exposed mice. These conditions were considered to be secondary to inflammation. No tumour was found (Wynder *et al.*, 1968). [The Working Group noted the relatively short duration of the study.]

Groups of 100 male and 100 female C57Bl mice, aged 14-18 weeks, were exposed (nose only) to a mixture of fresh cigarette smoke/air (1/39, v/v) for a 12-min period, generally on alternate days, for life. Groups were exposed to the whole smoke of two different types of cigarette: one made from flue-cured and the other from air-cured tobacco. The latter more closely resembled flue-cured cigarettes than typical air-cured cigarettes which contain, for example, burley tobacco. A further group was exposed to the gas phase only of smoke from the flue-cured cigarette, which was generated by passing the whole smoke through a Cambridge filter to remove the particulate matter. A group of 200 males and 200 females served as controls. The experiments with whole smoke were performed again under similar conditions with another group of 100 males and 100 females. Mean survival time in eight of ten groups of mice exposed to whole smoke was 4-14 weeks longer than that in controls (see also p. 140). The incidences of lung tumours in controls were 3/160 in males and 1/159 in females; those in mice exposed to whole smoke of cigarettes made from flue-cured tobacco were 9/162 in males and 7/164 in females [$p = 0.07$ and 0.04, respectively]; incidences in mice exposed to the gas phase of cigarettes made from flue-cured tobacco were 3/81 in males [$p > 0.05$] and 2/88 in females [$p > 0.05$]; and those in mice exposed to the whole smoke of cigarettes made from air-cured tobacco were 7/189 in males [$p > 0.05$] and 0/173 in females. The majority of the lung tumours were adenomas (Harris, R.J.C. *et al.*, 1974).

Groups of Snell's mice, three to four months of age at the start of treatment, were exposed to two puffs (15-ml puff volume, 2-sec duration, 58-sec interval between puffs) of either whole fresh cigarette smoke [unspecified] (160 males and 118 females) or to the gas phase (100 males and 89 females); 117 males and 83 females served as controls. Animals were exposed in individual containers once a day (except for holidays and weekends) for life. When body weight loss was 4 g or more, animals were withdrawn from exposure for periods varying from two days to two months. Two popular brands of nonfilter cigarettes were used; each cigarette was smoked to a butt length of 23 mm. The gas phase was produced by passing the smoke through a Cambridge filter. Effectiveness of exposure was assessed by determining the carbon monoxide level in blood and the nicotine content of the lungs (about 5 μg). Survival after 12 months of age was distinctly affected by treatment, being about 92% (184/200), 60% (172/278) and 40% (88/189) in the control, whole-smoke and gas-phase groups, respectively. After 12 months of age, there was an earlier occurrence of pulmonary tumours in exposed mice than in controls. At the end of the experimental period (26 months), the proportions of mice surviving 12 months or more that had pulmonary adenomas were 8/106 and 1/78 in male and female controls, 7/107 and 2/65 ($p = 0.475$) in male and female whole-smoke-exposed animals and 1/44 and 3/44 ($p = 0.15$) in male and female gas-phase-exposed animals, respectively. The proportions of mice with pulmonary adenocarcinomas were 5/106 and 3/78 in male and female controls, 11/107 ($p = 0.15$) and 5/65 ($p = 0.35$)in whole-smoke-exposed animals and 10/44 ($p = 0.005$) and 5/44 ($p = 0.15$) in male and female gas-phase-exposed animals (Leuchtenberger & Leuchtenberger, 1970).

A group of 117 female BALB/c mice, nine weeks old, were exposed to smoke from 'high-tar' (16 mg tar, 1.1 mg nicotine) cigarettes diluted with air (7:1, air:smoke) for 7-8 min per day on five days per week for 95 weeks; exposure was interrupted for three weeks between the 48th and 49th week of treatment. An untreated group of 130 females served as

controls. Approximately 16 control and 16 exposed mice were killed after 56, 64, 72 and 80 weeks of treatment. Twenty control and ten exposed mice survived until termination of the experiment after 95 weeks. The 'relative incidence' of neoplasms, reported as bronchial adenomas, was calculated by the authors to be higher in the exposed groups of mice than in the control groups after 83 weeks, but similar in the two groups after 95 weeks of exposure. The authors also reported an increase in the 'relative incidence' of lymphomas after both 83 and 95 weeks of exposure (Keast *et al.*, 1981). [The Working Group noted that insufficient numerical data were provided in relation to the number of animals at risk.]

Rat: A group of 408 female Wistar rats, 10 weeks of age, were exposed (nose only) to a 1:5 smoke:air mixture generated from T29 cigarettes (specially manufactured from a composite blend of flue-cured tobaccos, representing the major nonfilter cigarette brands smoked in the UK during 1967-1968), for 15 sec/min during 11 min, twice a day on five days per week for life. After one year, the rats received 5% carbon dioxide in air instead of air for 5 min before the start of each smoke exposure session and for the 45-sec/min interval during which smoke was not generated. Measurement of an arsenious sulphate tracer showed that 8.5 and 17.5% of the delivered tar was recovered in the lungs of rats with the air and with the air/carbon dioxide regimes, respectively. Two control groups of 104 animals were available, one sham-exposed and one untreated. The smoke-exposed and sham-exposed animals had lower body weights than untreated controls. About 25% of the treated rats were still alive at 100 weeks compared with 73% of 102 untreated controls and 66% of 102 sham-exposed controls. All treated animals had died by 140 weeks compared with 160 weeks in controls. Three smoke-exposed rats had pulmonary squamous neoplasms of uncertain malignancy, and one had an invasive squamous-cell carcinoma of the lung. No lung tumour was observed in the sham-treated or untreated controls. The incidence of benign mammary tumours was lower in smoke-exposed rats than in sham-exposed or untreated controls (Davis, B.R. *et al.*, 1975a).

A group of 18 female Wistar rats, 13-14 weeks of age, were exposed (nose only) to the gas phase of smoke (produced by passing the smoke through a Cambridge filter) from a standard British reference cigarette diluted 1:5 with air. Exposure was for 15 sec followed by air for 45 sec during 11 min, twice daily on five days per week for life. A control group of 16 animals was available. Average length of survival was 100 weeks for treated animals and 114 weeks for controls. No lung tumour was reported in exposed or control rats (Davis, B.R. *et al.*, 1975b). [The Working Group noted the small number of animals used.]

A group of 80 female Fischer 344 rats, 12-14 weeks of age, were exposed (nose only) to a 1:10 smoke:air mixture for 28-30 sec/min followed by air for 30 sec during standard smoking of a US reference nonfilter cigarette (average, 8.4 exposures/cigarette). Mean smoke particulate and nicotine levels observed during chamber monitoring were 18.4 mg and 0.89 mg per cigarette, respectively. The animals were exposed to 1 cigarette/h, 7 cigarettes/day, on five days per week for 128 weeks, followed by observation for a further six months. The mean pulmonary particulate deposition during exposure was 0.25 mg/cigarette (total, 1.75 mg/rat per day). A group of 63 rats served as untreated controls, and 30 rats were sham-exposed. The length of survival of smoke-treated, sham-treated and untreated controls was not significantly different, but smoke- and sham-treated animals had

lower mean body weights. Since the tumour incidences in untreated and sham-treated controls were similar, the two groups were combined (93 animals). One alveologenic carcinoma and two pulmonary adenomatoid lesions were observed in three control rats. Ten respiratory tumours were observed in seven smoke-exposed rats: one nasal adenocarcinoma, one nasal squamous-cell carcinoma, five pulmonary adenomas, two alveologenic carcinomas and one squamous-cell carcinoma ($p < 0.05$). Of the smoke-exposed animals, 21 developed subcutaneous sarcomas at sites of ulcerations on the forelimbs ($p < 0.05$); four rats developed benign tumours of the oral tissues ($p < 0.1$); and four developed one adenoma and three carcinomas of the adrenal gland ($p < 0.1$). No such tumour occurred in controls. The incidences of tumours of the hypophysis, uterus and ovary, haematolymphatic system and mammary gland were lower in smoke-exposed rats than in controls (Dalbey *et al.*, 1980).

Three groups of 80 female Fischer 344 rats were exposed to a 1:10 smoke:air mixture generated from three US research cigarettes (25.4 mg tar, 0.16 mg nicotine; 13.3 mg tar, 1.06 mg nicotine; or 25.7 mg tar, 1.91 mg nicotine; see also Griest *et al.*, 1980). Each rat was exposed for 28 sec/min followed by air for 30 sec during standard smoking of the cigarettes, to provide 10-11 exposures/cigarette. The animals were exposed to 8 cigarettes/day during a 16-h period, on seven days per week for 96 weeks, at which time all survivors (50-70% of animals) were killed. Groups of 80 animals served as untreated and sham-treated controls. The occurrence of squamous metaplasia of the laryngeal and tracheal epithelium was significantly increased in smoke-exposed rats. One squamous-cell carcinoma of the lung was observed in a rat exposed to low-tar-medium-nicotine smoke; the incidences of other tumours were similar in treated and control animals (Wehner, A.P. *et al.*, 1981). [The Working Group noted that, in contrast to the study described previously, all surviving animals were killed at 104 weeks and that the method for sampling for histopathology was not fully reported.]

Hamster: In a study involving 4440 animals, including 600 controls, groups of 80 male and 80 female Syrian golden hamsters, eight weeks old, were exposed to a 1:15 smoke:air mixture generated during a 7-10-min period from 30 German reference cigarettes, or a modification thereof, once, twice or three times a day on five days per week for lifespan or up to 52 weeks (830 animals). One group of 80 males and 80 females was exposed to the smoke of black (dark air-cured)-tobacco cigarettes twice a day. One group of animals received the vapour phase of the reference cigarette, generated from 30 cigarettes during a 10-min period three times a day. The average length of survival was 52-65 weeks for treated males and 41-49 weeks for treated females; a shorter survival time and loss of body weight were noted in animals exposed to smoke as compared with untreated controls (see also pp. 140-141). In all treated groups, 'the most remarkable and severe alterations' were observed in the larynx, and their severity depended on duration of treatment and dosage. The incidence of laryngeal leukoplakias ranged from an average of 11.3% in animals exposed for 10 min to 30.6% in those exposed for 30 min to the reference cigarette; the incidence in animals exposed to smoke from black-tobacco cigarettes was 10%; and in controls slight leukoplakia was observed in 1-5% of animals. The incidences of laryngeal carcinomas were 0.62-10.6% in

animals exposed to smoke from the reference cigarette and 1.25% in animals exposed to smoke from black-tobacco cigarettes. No such tumour was observed in controls nor in animals exposed to the vapour phase (Dontenwill *et al.*, 1973).

Similar results were obtained in a study involving 2160 hamsters exposed to the smoke from German reference cigarettes or a modification thereof (Dontenwill *et al.*, 1977a).

In a study in which a modification of the method of Dontenwill (above) was used on inbred hamsters, groups of 102 male BIO® 87.20 and BIO® 15.16 hamsters (13 weeks of age) were exposed to smoke (1:5 in air) from Ky 1R1 (US) reference cigarettes twice a day on five days per week for up to 100 weeks. Groups of 60 animals served as sham-exposed or cage-held controls for each strain. Smoke exposure for up to 100 weeks had no effect on length of survival; however, a reduction in body weight was noted. Over 90% of the smoke-exposed animals of both strains showed hyperplastic or neoplastic changes in the larynx; and benign squamous-cell papillomas of the larynx were observed in both strains. Laryngeal cancer was nearly five times more frequent in strain BIO® 15.16, however, and two animals of this strain developed nasopharyngeal tumours. The incidences of tumours at locations other than the respiratory tract were similar in the two strains (Bernfeld *et al.*, 1974).

Groups of 35-64 male BIO® 15.16 inbred Syrian golden hamsters, 60-70 days old, were exposed to concentrations of 11 or 22% smoke from commercial UK filter cigarettes or filter cigarettes composed of tobacco and Cytrel®, or cigarettes made of 100% Cytrel® twice a day (12-min sessions of 27 smoke exposures/min) on seven days per week for up to 74-80 weeks. Groups of 40 sham-exposed animals and 51 untreated animals served as controls. Survival rates were reduced markedly in all groups after 59 weeks of age; a reduction in body weight was noted in treated animals as compared with controls. Laryngeal carcinomas occurred in 47.4% of the animals exposed to smoke from the UK filter cigarettes, the first tumours occurring after 59 weeks in hamsters treated with the highest dose of smoke. The incidence of this type of tumour was dose-related and decreased as the proportion of Cytrel® in the blends increased. No such tumour was observed in controls. Laryngeal papillomas, laryngeal epithelial hyperplasia and a few tracheal papillomas were also observed in treated animals. Histopathological findings at other sites did not appear to be related to smoke inhalation (Bernfeld *et al.*, 1979).

A group of 51 male Syrian golden hamsters, two months of age, were exposed three times a day for 10 min to smoke from Ky 1R1 (US) reference cigarettes on five days per week for life. Another group of 51 male hamsters served as sham-exposed controls. The smoke-exposed animals survived longer (mean, 19.6 months) than the sham-exposed animals (mean, 15.3 months) (see also p. 140). The smoke-exposed animals had significantly higher incidences of epithelial lesions of the larynx than sham-exposed controls (22% *versus* 0%, $p < 0.01$) and a significantly higher total number of tumours than sham-exposed controls (28% *versus* 6%; $p < 0.05$). The laryngeal changes in the smoke-exposed group ranged from inflammatory conditions, with growth abnormalities of the epithelium, to squamous-cell papilloma formation (Wehner, A.P. *et al.*, 1974, 1975a,b, 1976). [The Working Group noted the inadequate reporting of the histopathological results.]

Rabbit: Thirty rabbits were exposed daily in individual compartments to the smoke from 20 cigarettes (2 puffs/min, 2 cigarettes at each treatment period) for up to 66 months. No tumour that could be related to the exposure was observed in 30 exposed rabbits or in 31 controls that survived for 24 months or more (Holland *et al.*, 1958, 1963). [Details of the types of cigarettes, method of smoke generation and doses delivered are not provided.]

Dog: Groups of male beagle dogs, 1.7-3.3 years old, trained to inhale cigarette smoke through tracheostomata, were exposed to (1) smoke from seven nonfilter cigarettes containing 34.8 mg tar and 1.85 mg nicotine per day (62 dogs); (2) smoke from cigarettes containing the same tobacco but with filters, containing 17.8 mg tar and 1.17 mg nicotine (12 dogs); or (3) smoke from 3.5 nonfilter cigarettes/day (12 dogs). Eight non-exposed tracheotomized dogs served as controls. The body weights of dogs in the various groups did not differ significantly. Between day 57, when the training period ended, and day 876, when killing of the surviving dogs began, 28 dogs died: 24 in the first group, 2 in the second, 2 in the third and no control. Examination of the lungs and bronchial tree at autopsy and microscopically was extensive. Tumours of the lung, described as 'bronchioloalveolar, invasive and noninvasive', were found in 23/62 in group 1; two of the tumour-bearing dogs in this group also had small bronchial carcinomas. Noninvasive bronchioloalveolar tumours were also found in 4/12 dogs in group 2, 7/12 dogs in group 3 and 2/8 control dogs. The bronchioloalveolar tumours tended to be multiple, with as many as 20/lung lobe, and were found in 41 of the 203 lung lobes from the 29 dogs with such tumours. No distant metastasis was found (Auerbach *et al.*, 1970; Hammond *et al.*, 1970). [The Working Group noted that no data were given on specific smoking parameters or measures of exposure. They also noted the small number of control dogs used and the unusually high incidence of lung tumours in these animals, since these are tumours that rarely occur spontaneously in dogs. The focal inflammatory lesions usually found in the lungs of animals exposed to smoke were not mentioned in the report. Examination of the upper respiratory tract and other organ systems is not reported. The authors' interpretation of the photomicrographs as representing neoplasia was considered to be not entirely convincing.]

As part of a study on the combined effects of radon daughters or uranium ore dust and cigarette smoke on the induction of respiratory tumours (see below), 19 beagle dogs of both sexes, 24-30 months of age, were exposed to cigarette smoke only. The dogs were exposed to the smoke of 10 Ky 1R1 (US) cigarettes/day (three in the morning, four at midday and three in the afternoon) on seven days per week for 48-60 months; individual masks permitted smoke to be inhaled at every tenth breath. Eight further dogs served as sham-exposed controls. Carboxyhaemoglobin levels in smoke-exposed dogs increased with the duration of the experiment, from 2% at 19 months to 4.7% after 50 months; the corresponding mean values for sham-exposed dogs were 1.4% and 1.8%. Smoke-exposed animals killed after 49 (6 dogs), 60 (6 dogs), 64 (6 dogs) and 65 (3 dogs) months were available for analysis. No significant respiratory lesion and no lung tumour was found in either group (Cross *et al.*, 1982). [The Working Group noted the small sizes of the groups and the limited evidence of smoke delivery.]

(*b*) *Inhalation of cigarette smoke in conjunction with administration of known carcinogens and other agents*

Benzo[a]pyrene: A group of 84 Wistar *rats* received a single intratracheal instillation of 2 mg benzo[*a*]pyrene (with infusine and carbon black) followed by exposure to cigarette smoke (T29, UK reference, diluted 1:5 with air) twice daily, five times per week for life. Three developed squamous-cell carcinomas of the lung. One squamous-cell carcinoma of the lung was observed in 84 rats treated with the benzo[*a*]pyrene mixture alone, and four squamous-cell neoplasms (of which only one was clearly malignant) occurred among 408 rats exposed to cigarette smoke only. The mean survival times were 65 weeks for animals exposed to smoke plus benzo[*a*]pyrene mixture, 63 weeks for animals exposed to smoke alone and 108 weeks for rats treated with the benzo[*a*]pyrene mixture alone. No lung tumour was observed in untreated or sham-exposed controls (Davis, B.R. *et al.*, 1975a).

A group of 40 *hamsters* received a single intratracheal administration of 5 mg benzo[*a*]pyrene mixed with ferric oxide, followed by exposure to cigarette smoke twice for 10 min daily, five times per week for 48 weeks. Two papillomas of the larynx and three pseudoepitheliomatous hyperplasias of the larynx were observed. No such lesion was observed in control groups of 20 hamsters that received benzo[*a*]pyrene plus ferric oxide or smoke alone, and no lung tumour was observed (Hoffmann *et al.*, 1979).

Dimethylbenz[a]anthracene (DMBA): Groups of 80 male and 80 female Syrian golden *hamsters* received 500 μg DMBA intratracheally, followed by a 10-min exposure to cigarette smoke twice daily, five times per week for life. A total of 32 squamous-cell carcinomas of the larynx were observed, in comparison with 17 in hamsters exposed to cigarette smoke only and none in controls treated with DMBA alone. A significant increase in the incidence of laryngeal leukoplakia was also observed. No increase was found in the incidences of tumours at other sites as compared with animals treated with DMBA alone. Mean survival rates were comparable in all groups (Dontenwill *et al.*, 1973). Similar results were observed in other experiments in which Syrian golden hamsters were exposed to DMBA and cigarette smoke (Kobayashi, N. *et al.*, 1974; Hoffmann *et al.*, 1979).

Blue Cape asbestos: Groups of 80 male and 80 female Syrian golden *hamsters* were exposed to a single intratracheal instillation of asbestos, followed by exposure to cigarette smoke twice daily, five times per week for life. No significant difference in the occurrence of laryngeal lesions or tumours was observed when compared to another group exposed to cigarette smoke alone. No laryngeal tumour occurred in a control group exposed to a single dose of asbestos alone (Dontenwill *et al.*, 1973).

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (*NNK*): Groups of 10 male and 9-10 female Syrian golden *hamsters* received a single subcutaneous injection of NNK at doses ranging from 1-10 mg, followed by exposure to cigarette smoke twice daily for 69 weeks. Tumours of the respiratory tract were observed in NNK-treated hamsters; their incidence was not affected by exposure to cigarette smoke (Hecht *et al.*, 1983).

Radon daughters: Groups of 28-50 Sprague-Dawley *rats* were exposed to radon daughters at cumulative doses of 4000, 500 or 100 work-level-months (WLM)[1], with or without concurrent exposure to cigarette smoke, by inhalation on four days per week for one year. Of the 47 rats exposed to 4000 WLM radon daughters without smoke, 17 developed carcinomas of the lung, compared to 34 carcinomas in 48 rats also exposed to cigarette smoke. In the groups of rats exposed to 500 WLM radon daughters, 8 carcinomas of the lung were seen among the 30 rats also exposed to cigarette smoke, as compared to 2/25 rats exposed to radon daughters alone. No lung tumour was observed in rats exposed to 100 WLM radon daughters with or without exposure to cigarette smoke; one carcinoma occurred among 27 rats exposed to cigarette smoke alone (Chameaud *et al.*, 1982).

Nineteen beagle *dogs* of both sexes, 24-30 months old, were exposed by inhalation to a combination of radon (105 nCi/l [3900 Bq/l]), radon daughters (605 WL) and uranium-ore dust (12.9 mg/m^3) daily, on five days per week, for 54 months. A second group of 19 beagle dogs was exposed to the smoke from 10 cigarettes/day on seven days per week at intervals between similar exposures to radon dust. Lifespan was shortened in both groups in comparison to controls. Eight dogs exposed to radon dust alone had nine respiratory tumours (two nasal carcinomas, six pulmonary carcinomas, one pulmonary fibrosarcoma); and 2/19 dogs in the group that received radon dust plus cigarette smoke had respiratory tumours (one nasal carcinoma, one pulmonary carcinoma) (Cross *et al.*, 1982). [The Working Group noted the small sizes of the groups and the incomplete reporting.]

Influenza virus: The possible interaction between various types of influenza viruses and inhalation of cigarette smoke in the induction of lung tumours in *mice* has been examined in a series of studies (Harris, R.J.C. & Negroni, 1967; Harris, R.J.C. *et al.*, 1974; Wynder *et al.*, 1968). No additive or synergistic effect was observed.

(c) *Administration of tobacco-smoke condensates*[2]

Attempts to induce tumours with tobacco products were reported as early as 1911 (for a summary of early studies, see Wynder & Hoffmann, 1967). Wynder *et al.* (1953) painted CAF_1 mice with cigarette-smoke condensate (CSC) suspended in acetone; after 24 months, 48/81 mice developed papillomas and 36/81 developed carcinomas at the sites of application.

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[1]WL is defined as any combination of the short-lived radon daughters in 1 litre of air that will result in an ultimate emission of 1.3 x 10^5 MeV of potential alpha energy in their decay through RaC^1 (^{214}Po). WLM is equivalent to 170 h of exposure to 1 WL.

[2]The terms 'smoke condensate' and 'tar' are often used interchangeably. Cigarette-smoke condensates (CSC) are produced by passing smoke through cold traps and recovering the material retained within them. This material is often washed from the traps with a volatile solvent, which is later removed, and unknown amounts of the volatile and semivolatile constituents are lost. Total particulate matter (TPM) is that material which is retained in a high-efficiency particulate filter. If this material is washed from the filter and concentrated as above, semivolatiles are lost. In the USA, the term 'tar' as used in official reports of tar yield is equivalent to TPM less nicotine and water.

During the next decade, methods to generate CSC and to treat animals were refined and standardized within and among laboratories. At the present time, cigarettes are machine smoked, generally using a 35-ml puff drawn for 2 sec each minute. The condensate is collected in glass vessels at low temperatures and removed using a volatile solvent, such as acetone, under reduced pressure. Animals have also been treated with a diluted suspension of CSC in a suitable solvent. Some of the variables that have not been standardized among different laboratories include choice of animal (or strain), dose and frequency of treatment, choice of solvent, conditions of storage of CSC, the puff profile of the smoking machine, and the number of cigarettes that are puffed simultaneously.

Nevertheless, when mouse skin has been used as the test tissue in experiments carried out over the last 20 years, the results from various laboratories are similar with respect to the overall degree of carcinogenic activity of CSC and to the major differences in activity among CSC from cigarettes of different design (Wynder *et al.*, 1957a; Davies, R.F. & Day, 1969; Dontenwill *et al.* 1972; Bernfeld & Homburger, 1976; Dontenwill *et al.*, 1977a; Lee, P.N. *et al.*, 1977; Gori 1976a,b, 1977, 1980). Subtle differences in smoking technique, CSC storage and animal exposure procedures do not appear to affect the results critically.

Animal studies conducted prior to 1964 provided an important measure of support for the epidemiological demonstration that cigarette smoke is an important human carcinogen. Since that time, the mouse-skin studies have served primarily to determine whether differences in cigarette design affect the carcinogenic effects of CSC and whether these effects can be correlated with the chemical composition of the condensates. In addition, mouse-skin studies may help to elucidate the mechanisms through which CSC induce tumours in animal tissues. For example, it has been shown that CSC contains tumour initiators (Hoffmann & Wynder, 1971) and that CSC and some of its fractions and components can exhibit tumour-promoting activity (see, for example: Wynder & Hoffmann, 1961b; Bock *et al.*, 1969; Hoffmann & Wynder, 1971; Lazar *et al.*, 1974; Van Duuren & Goldschmidt, 1976). The relative activities of different CSCs in short-term promoting assays based either on the disappearance of the sebaceous glands or on thickening of the cutaneous epithelium may be similar to their relative activities in long-term assays for promotion on mouse skin, based on the appearance of skin tumours (Lazar *et al.*, 1974), although the data available are insufficient to establish this point clearly.

(i) *Skin application*

Mouse: CSC produces both benign and malignant tumours on mouse skin. The carcinogenic potency of the CSC is a function of tobacco variety, use of replacement materials (sheet or semi-synthetics) and presence of additives (see, for example, Wynder *et al.*, 1957a; Davies, R.F. & Day, 1969; Dontenwill *et al.*, 1972; Gori, 1976a,b; Dontenwill *et al.*, 1977b; Gori, 1977, 1980). The tumours induced are usually of epidermal origin. Ohmori *et al.* (1981) reported a low, but significant incidence of mastocytomas in a series of mouse-skin experiments with CSC.

An example of mouse skin studies is given in a series of four publications (Gori, 1976a,b, 1977, 1980) that report the results of skin-painting experiments in which more than 100 CSC were tested in female ICR Swiss mice. These data permit an evaluation of the overall carcinogenicity of CSC and of intralaboratory variation in bioassay results over time, since,

in these studies, Ky 1R1 and SEB cigarettes stored at -20°C were tested in four series of studies begun in 1970, 1972, 1974 and 1975 (Table 34), and the results are representative of the tumour response found in such studies. The purpose of the studies was to investigate possible relationships between biological activity and cigarette design as well as chemical characteristics of cigarette smoke. CSC derived from reference cigarettes and specially modified cigarettes was applied generally at two dose levels, usually 25 mg and 50 mg, per 0.1-ml application in six weekly applications for 78 weeks. Acetone was used as the solvent. In some instances, 3, 6 and 12.5 mg were also given, and, for a single type of CSC, doses of 10 mg and 20 mg were given twice daily or five times a week for 78 weeks. Concurrent solvent-treated and untreated controls were available. Test groups size usually comprised 100 animals, but up to 800 controls were used; 6400-9200 mice were used for each of the four sets of experiments. A skin tumour was observed in 3/800 acetone-treated controls; otherwise, no tumour and no carcinoma was found in control animals. Skin tumours, frequently malignant, were found in every CSC-treated group.

Table 34. Percentages of animals with skin tumours[a] after treatment with smoke condensates from reference cigarettes[b]

Series	Date of start of study	Reference cigarette				
		1R1	SEBI	SEBII	SEBIII	SEBIV
I	1970	41	44	-	-	
II	1972	49	58	48	-	
III	1974	49	51	-	46	
IV	1975	48	-	-	44	41

[a]Not corrected for interim deaths; tumours classified as 'papillomas' and 'carcinomas' in series I and II, as 'papillomas' and 'other malignancies' in III, and as 'tumours' in IV.

[b]From Gori (1976a,b, 1977, 1980)

[c]Age of animals at start: 'approximately' six weeks in series I and II; 'at least' six weeks in III and IV.

[These extensive studies reported differences in the activity of CSCs from cigarettes of different design. The Working Group noted that, although the trends of the differences were often consistent, different statistical procedures were used to analyse the data, and insufficient data are provided to permit a uniform analysis for quantitative comparison of these data.]

Cigar and pipe smoke condensates have also been tested on mouse skin. In one such study, a 1:1 (w/v) acetone solution of nicotine-free cigar or pipe tar was painted three times a week on the skin of female Swiss mice. A 1:1 acetone solution of whole CSC was also employed. At the end of 19 months, skin papillomas were produced in 65% and carcinomas in 41% of 46 mice treated with the nicotine-free cigar tar, in 69% and 33% of 45 mice treated with the nicotine-free pipe tar and in 47% and 33% of 86 mice treated

with CSC. No tumour was produced in 23 acetone-treated controls. At nine months, when the first tumours appeared, 78% of the controls and 70-91% of the tar-treated animals were still alive (Croninger *et al.*, 1958). [The Working Group recognized that the nicotine-free cigar and pipe tars were prepared in a manner that would cause unknown changes in composition.]

Rat: McGregor (1976) and McGregor and Myers (1982) reported that CSC appeared to act as a cocarcinogen with β-irradiation on rat skin. CSC alone was reported to induce one benign tumour in 72 normal rats and six benign skin tumours in 78 rats in which the skin keratin layer had been removed prior to skin painting. [The Working Group noted that the data, as presented, are not adequate to permit evaluation of these reports.]

Hamster: Bernfeld and Homberger (1983) reported that hamster skin is not responsive to CSC applied alone. [The Working Group noted that only 16 of the 50 animals treated with CSC alone were observed for up to 46-47 weeks.]

Rabbit: CSC was applied to the inner surface of the ears of 38 rabbits five times a week as a 50% w/v suspension in acetone using a brush. On alternate weeks, the accumulated surface tar was removed using an acetone-soaked cotton ball or forceps. After four to six years of treatment, all of the rabbits had developed large papillomas, and four had skin cancer. Of seven control animals treated with acetone, none developed cancer, but five had small papillomas on the ears (Graham, E.A. *et al.*, 1957).

(ii) *'Initiation-promotion' studies*

Mouse: A number of investigators have found that CSC and its fractions can act as cocarcinogens when applied with other agents. In one assay for tumour-initiating activity, 50 μl of an acetone solution containing 2.5 mg of a CSC fraction (0.6% of the whole tar) was applied to the dorsal skin of mice during the second telogen phase of hair growth. This procedure was repeated on alternate days for a total of ten doses. Ten days after the last initiating dose, the mice were painted three times a week with 2.5% croton oil in acetone. After 12 months, 67% of 30 mice had developed papillomas and 13% had carcinomas; after 15 months, 73% had papillomas and 13% carcinomas. Sixty-five mice treated with croton oil only developed no tumour, either malignant or benign. The first tumour appeared within four months (Hoffmann & Wynder, 1971).

Groups of 30 female Swiss mice were painted twice weekly with a 50% acetone solution of CSC for 12 months. Of animals treated first with 75 μg DMBA, 13/30 developed papillomas and 8 had carcinomas in 15 months; without DMBA treatment, only 4/40 had papillomas and 1 a carcinoma. Of 50 mice painted three times weekly with a 50% acetone solution of CSC, 22 (44%) developed skin papillomas and 11 had carcinomas. Of 30 animals treated first with a single dose of DMBA, 19 (63%) developed skin papillomas and 11 had carcinomas. Of mice treated with DMBA alone, 3/30 had skin papillomas and 2 had carcinomas. When a 10% solution of the phenolic fraction in acetone was applied three times weekly, 30% of the animals developed papillomas, but no carcinomas, when DMBA was applied first; no tumour was seen in mice without DMBA initiation (Wynder & Hoffmann, 1961b). [The Working Group noted that the data do not establish that this effect was due to promotion or whether it represented an additive effect of two weak tumorigenic stimuli.]

(iii) *Topical application to oral mucosa*

Mouse: The lips and oral areas of groups of 100 ICR/Ha Swiss mice were painted five times a week for 15 months with approximately 26 mg CSC in an acetone suspension. Control groups of 100 mice were either untreated or treated with acetone alone. The study was terminated after 18-19 months, at which time 81-90% of the animals were still alive. Of the surviving mice in the experimental group, 64% developed lung tumours, in contrast to 22% in the control groups. In addition, 21% of the experimental animals developed tumours of other organs, primarily lymphomas, in contrast to 3-8% in the two control groups (DiPaolo & Levin, 1965).

(iv) *Intrapulmonary administration*

Rat: Stanton *et al.* (1972), following up earlier studies of Blacklock (1961), injected 0.05 ml of 1:1 beeswax:tricaprylin containing 24 mg CSC into the lungs of female Osborne-Mendel pathogen-free rats after thoracotomy. The pellets thus formed were large enough to entrap bronchioles. Residues of the pellets could be recognized for more than two years after treatment. Fourteen of 40 rats that died between 43 and 120 weeks developed epidermoid carcinomas. The nonpolar constituents of CSC appeared to be an important but not the sole contributor to this activity. Thus, when the beeswax contained 12 mg of the heptane-soluble fraction of CSC, epidermoid carcinomas developed in 5/18 rats. No tumour was seen in 76 rats injected with beeswax:tricaprylin alone.

These observations were confirmed by Dagle *et al.* (1978) using CSC from two different types of cigarettes. They observed a dose-dependent incidence of lung carcinomas when either condensate was injected in beeswax:tricaprylin. No carcinoma was induced by beeswax:tricaprylin alone. With the highest dose of CSC (67 mg), carcinoma prevalence reached 42% in 120 weeks. No difference was observed in tumour response to the two CSCs.

CSC without vehicle was injected every two weeks into rat lungs by intratracheal instillation. There was a dose-dependent increase in the mean grade of squamous lesions in the groups treated with CSC and with several fractions of CSC. With CSC and most fractions, tumours were not observed, but with the fraction containing most of the polynuclear aromatic hydrocarbons, 5/54 rats developed neoplastic lung lesions (Davis, B.R. *et al.*, 1975c). The Working Group noted that the relatively infrequent dosage employed by Davis *et al.* may have been less adequate as a stimulus than prolonged release of the material from a lipid vehicle that persists at the injection site. There may also have been injury from injection of material into the lung, from the heat of the melted wax or from chemical constituents in the wax.]

Hamster: CSC and the 'nitromethane-soluble' fraction of CSC were found to be weak carcinogens when injected in beeswax directly into hamster lung (Ketkar *et al.*, 1979). The method used was similar to that of Stanton *et al.* (1972) in rats; 0.03 ml of a 1:1 beeswax:tricaprylin mixture was used as the solvent. A group of 31 hamsters injected with 50 mg CSC developed one bronchogenic adenoma; two animals exhibited metaplasia. When 25 mg of the nitromethane fraction of CSC were given to another group of 31 animals, three had bronchogenic adenomas and nine had metaplasia.

2. Other relevant biological data from experimental studies

(a) Toxicity of tobacco smoke in animals

Tobacco smoke contains hundreds of chemicals that are potentially toxic to animals (see the section 'Chemistry and Analysis of Tobacco Smoke', pp. 83-126). Only the toxicity of whole tobacco smoke is discussed below; studies on the carcinogenicity of tobacco smoke and tobacco smoke condensate are discussed in the previous section (pp. 127-139), and mutagenicity and short-term tests are discussed on pp. 153-163.

(i) *Survival*

Measurement of the toxicity of tobacco smoke by the length of survival of exposed animals is complicated by differences in such factors as the use of naive *versus* preadapted animals, continuous *versus* intermittent exposure, concentration of smoke, duration of exposure, type of cigarette, and species and strain of animals. Some of these factors are discussed on pp. 127-128 above.

The mean survival times of mice exposed to smoke from 11 different cigarettes (using an intermittent regimen) ranged from 10 min (i.e., ~ 3 cigarettes) to >175 min (i.e., 54-66 cigarettes). There was a weak correlation between tar and/or nicotine content and length of survival, but the difference in toxicity of certain cigarette types was greater than would be expected from differences in their tar or nicotine content. The nature of the material that caused this differential toxicity is not known but presumably occurred in the particulate phase, since Cambridge-filtered smoke (i.e., gas phase) was approximately 10-20 times less toxic than whole smoke (Bernfeld, 1975). Using an intermittent exposure regimen, Schell and Griffith (1972) showed that survival is (1) closely associated with the nicotine content of cigarettes and (2) dependent on the strain of mice employed: a more than three-fold variation in sensitivity was observed among strains. The occurrence of lung haemorrhage in hamsters parallelled the nicotine but not the carbon monoxide content of the experimental cigarettes to which they were exposed intermittently (Reznik-Schuller, 1980); however, with a continuous exposure regimen, the toxicity of cigarette smoke to mice was correlated with both nicotine and carbon monoxide levels (Reckzeh *et al.*, 1969).

Studies of survival with longer periods of daily exposure (i.e., 14-90 days) are usually not informative, because, if animals survive an acute exposure regimen, they usually survive such subchronic exposures. For these studies, other measures of toxicity must be used to determine the effects of tobacco. It is of interest to note, however, that smoke-exposed and sham-exposed animals can outlive unexposed animals (Wehner, A.P. *et al.*, 1976).

(ii) *Rate of weight gain* (see also section 1, pp. 129-133)

The rate of weight gain of hamsters (Wehner, A.P. *et al.*, 1976) and rats (Kendrick *et al.*, 1976; Smith *et al.*, 1978) exposed daily to tobacco smoke is generally slower than that of sham-exposed controls; and sham-exposed controls usually have a slower rate of weight gain than untreated controls (Kendrick *et al.*, 1976; Smith *et al.*, 1978). Both food consumption and rate of weight gain are increased when daily exposure to smoke is stopped (Smith *et al.*, 1978).

(iii) *Cellular and chemical responses*

Carboxyhaemaglobin (COHb) levels of 17 and 29% were observed in rats exposed to the smoke of one and five-to-ten cigarettes, respectively (Kendrick *et al.* 1976). The effects in rats and mice of a six-week exposure to smoke are described in preliminary reports by Henry *et al.* (1984) and Curren *et al.* (1984). The results can be summarized as follows: (1) the numbers of serum neutrophils and segmental alveolar macrophages in the lung were increased; (2) the mitotic index of the pulmonary epithelium was not altered; and (3) pulmonary lavage fluids from exposed rats, as compared to sham-exposed animals, showed an increased level of γ-glutamyl transpeptidase, but not of alkaline phosphatase or total protein. Serum oxalacetic transaminase and serum lactate dehydrogenase activities were unchanged as a result of chronic exposure.

A major clinical change that has been associated with exposure to smoke is alteration in pulmonary function. Daily exposure to cigarette smoke has resulted in: (1) increases in lung compliance in rats (Coggins, 1980) and decreases in lung compliance and increased pulmonary resistance in mice (Aviado & Watanabe, 1974); (2) alterations in tidal volume and in respiratory rates in mice and in minute volume in mice, rats and hamsters (Aviado & Watanabe, 1974; Kendrick *et al.*, 1976; Klimisch & Dontenwill, 1977; Coggins *et al.*, 1982); (3) impairment of tracheal mucociliary transport in dogs (Park, S.S. *et al.*, 1977); and (4) increased permeability of airways in guinea-pigs (Boucher *et al.*, 1980; Hulbert *et al.*, 1981).

(iv) *Histopathological manifestations following subchronic exposure to tobacco smoke*

Histopathological and related changes in respiratory tissue of model animal systems following subchronic exposure to cigarette smoke are summarized in Table 35. The studies involved daily exposure of rats, mice, hamsters and dogs to cigarette smoke for six- to ten-week periods. In general, hamsters and rats were more responsive to the effects of smoke and showed high incidences of epithelial hyperplasia of the larynx, trachea, bronchioli and alveoli (Kendrick *et al.*, 1976; Smith *et al.*, 1978; Walker *et al.*, 1978a,b; Coggins *et al.*, 1980). The pulmonary tissue of dogs showed evidence of fibrosis and emphysema (Frasca *et al.*, 1983). All animals showed increased accumulation of pulmonary alveolar macrophages. Most of these effects were attributed to constituents in the particulate phase of smoke (Coggins *et al.*, 1980) and were correlated in a dose-related fashion to the total particulate matter of the cigarette smoke (Walker *et al.*, 1978a); some of the effects were reversible when the animals were no longer exposed to smoke (Smith *et al.*, 1978).

Table 35. Histopathological manifestations in model animal systems during subchronic exposure to cigarette smoke

Study reference	Experimental conditions[a]	Histopathology[b]
Smith *et al.* (1978)	Rats; reference filter cigarettes (19.6 mg TPM/cigarette); 8% smoke; 10-min exposure twice/day on week-days and once per day on weekends for 42 or 84 days; groups of animals removed after 42 days to evaluate reversion	Goblet-cell hyperplasia of tracheal and bronchial epithelia Increased PAM and alveolar metaplasia Increased squamous metaplasia and hyperplasia of larynx Larynx, trachea and bronchus all reverted to normal Alveolar metaplasia not reverted
Kendrick *et al.* (1976)	Rats; NCI references nonfilter cigarettes (codes 9 and 16); 10% smoke from 7 or 10 cigarettes/day for 12-18 months	Chronic alveolitis Increased PAM, mast cells and PMN Increased bronchial and alveolar hyperplasia Bronchiolitis of terminal bronchioles
Walker *et al.* (1978a,b)	Rats; 4 types of reference cigarette; 8%, 12.5% and 20% smoke twice/day, 7 days/week, for 47 days	Increased PAM correlated with TPM content of cigarettes Increased incidence of alveolar metaplasia in rats exposed to high levels of TPM Increased squamous metaplasia and keratinizing hyperplasia in the larynx, and goblet-cell hyperplasia in the nasal cavity, trachea and bronchus, all in parellel with TPM content of cigarettes, except for hyperplasia in trachea
Jones, R. *et al.* (1973, 1978)	Rats; reference cigarette (13.7 mg TPM and 2.0 mg nicotine); 1% smoke for 6 or 4 min for 4 h/day for 1 day and up to 6 weeks (25 cigarettes/day, 4-6 days/week for up to 6 weeks)	Apparent number of goblet cells in extrapulmonary airways decreased after 1 day; but increased in extra- and intrapulmonary regions by 3 days and up to 6 weeks of smoke exposure Increased incidence of goblet cells containing acid glycoprotein Addition of anti-inflammatory agent, phenylmethyloxadiazole, protects against increased number of goblet cells
Frasca *et al.* (1983)	Dogs; NCI reference cigarette (code 26); undiluted smoke from 2-7 cigarettes/day *via* tracheostomy for 2-4 months	Increases in PAM Increases in pulmonary fibrosis and emphysema No bronchitis or bronchiolitis

Table 35 (contd)

Study reference	Experimental conditions[a]	Histopathology[b]
Bernfeld *et al.* (1983)	Hamsters; reference filter cigarette plus cigarettes containing cellulose-derived tobacco supplement; 22% smoke from 1 cigarette, twice/day, 7 days/week for up to 20 weeks	Increased incidence of laryngeal hyperplasia and papillomas Increase in PAM Increased hyperplasia of terminal bronchiolar epithelium Effects most severe in animals exposed to all-tobacco cigarettes.
Coggins *et al.* (1980)	Rats; commercial filter cigarettes; 3.5% smoke, 20 min smoke/day, twice/day, 5 days/week for 12 weeks	Epithelial hyperplasia, squamous metaplasia and epithelial thickening in nasal passages and larynx Tracheal changes similar, but more diffuse than in larynx Bronchial thickening from hypertrophy of ciliated cells and squamous metaplasia; bronchiolar hypertrophy and alveolar metaplasia; increased numbers of goblet cells Electron microscopy showed loss of cilia and extensive squamous-cell production Gas phase of smoke failed to induce these changes
Lam, R. (1980)	Rats; 4 types of commercial filter cigarettes; 1-8% smoke from 6 cigarettes over 1-h period	Partial or complete loss of epithelium on ventral wall of larynx Regeneration and hyperplasia Regenerative phase delayed with higher concentrations of smoke Gas phase failed to induce effects
Lewis, D.J. (1981)	Rats and hamsters; commercial cigarette (12 mg tar); 6% smoke for 4 x 10 min/day on 7 days/week or 2 x 10 min/day for rats and 7% smoke at 2 x 30 min/day, 7 days/week for hamsters. Rats exposed for 6 or 12 weeks and hamsters for 10 weeks	Laryngeal hyperplasia at specific locations Hyperplasia and metaplasia of squamous epithelium of larynx Keratinization of squamous epithelium Effects smoke-dose-related Distribution of lesions influenced by anatomy, histology, airflow and smoke characteristics
Henry *et al.* (1984)	Mice and rats; commercial cigarette; 10% smoke (5 mg total particulate matter/litre) from 9 cigarettes/day, 5 days/week for 6 weeks	Increase in PAM in mice In rats, increase in PAM, increase in squamous metaplasia of nasal passages and hypertrophy of larynx, trachea and bronchial epithelium Increase in squamous metaplasia and hyperplasia of trachea and larynx in rats

[a]TPM, total particulate matter

[b]PAM, pulmonary alveolar macropages; PMN, polymorphonuclear neutrophils

(v) *Reproductive toxicity following exposure to smoke*

The effect of tobacco smoke exposure on the reproductive system of model animal systems and of humans has been reviewed (Mattison, 1982) and is not discussed in detail here. In summary, cigarette smoke may play a role in: (1) decreasing sperm number and increasing the frequency of sperm-shape abnormalities; (2) altering hypothalamic-pituitary relationships resulting in changes in levels of hormones associated with reproduction; (3) altering the motility of the female reproductive tract; (4) impairing implantation of embryos; and (5) reducing the number of primary ovocytes.

Two recent studies came to slightly different conclusions regarding the effects of exposure to smoke on fetal growth. Bertolini *et al.* (1982) reported that exposure of pregnant rats to smoke during gestation resulted in slower maternal weight gain, but that there were no effects on delivery rate, litter size, weight of offspring, percent weight of brain, number of dead fetuses, offspring mortality during lactation, or sex ratio of offspring. Bassi *et al.* (1984) observed, however, that when pregnant rats were exposed to smoke during gestation fetal weight was significantly reduced in comparison to pair-fed controls. No effect was observed on fetal brain weight or nucleic acid content, but fetal lung and liver weights (and nucleic acid content) were decreased by exposure to smoke. No effect on placental growth was observed. [The Working Group concluded that maternal exposure to smoke is capable of altering fetal growth, but the magnitude of the response and the subsequent effects on normal tissue function remain to be determined.]

(vi) *Immunotoxicity*

Exposure to cigarette smoke causes both short- and long-term effects on the immune system of animals. The effects may be either localized to pulmonary tissues or may be systemic.

The cellular components of the pulmonary defense system consist of several cell types that are present on and in the airway epithelium. Cells on the surface are studied by means of bronchial lavage and comprise pulmonary alveolar macrophages, lymphocytes and various polymorphonuclear cells. These cells play a vital role in the defence of the lung against inhaled particles by taking up particulates, functioning in the development of an immune response, and secreting tissue-destroying enzymes. The latter function is discussed in more detail below (see pp. 149-152). Exposure to cigarette smoke causes a prompt decrease in the numbers of pulmonary alveolar macrophages and polymorphonuclear neutrophils (Rylander, 1973), but it is transient, and usually an increase is seen in the numbers of these cell types following more than two to three weeks of daily exposure to smoke (see Tables 35 and 36). The new alveolar macrophages usually have an increased capacity for phagocytosis (Fogelmark *et al.*, 1980), a decreased capacity for phagolysosome fusion (Harris, J.O. & Gonzalez-Rothi, 1984) and quite different morphometry (Lewis, D.J. *et al.*, 1979) compared to cells from control animals. In-vitro exposure of alveolar and peritoneal macrophages to tobacco smoke also resulted in impaired phagocytic function, metabolism and viability (Green, G.M. & Carolin, 1967; Holt *et al.*, 1978).

Table 36. Metabolic responses of rodent pulmonary tissue following exposure to cigarette smoke

Metabolic response	Experimental conditions[a]	Result	Reference
Protein synthesis	Rats; 1R1 or 1A1 cigarettes, 1 or 3 cigarettes twice daily for 30 days	Decreased by 30% by exposure to 1R1; slightly decreased by exposure to 1A1	Hamosh *et al.* (1979)
Glyprotein synthesis	Rats; 1R1 or 1A1 cigarettes, 1 or 3 cigarettes twice daily for 30 days	Increased 2 fold by exposure to both 1R1 and 1A1	Hamosh *et al.* (1979)
Lipid metabolism	Rats; 1R1 or 1A1 cigarettes, 1 or 3 cigarettes twice daily for 30 days	Palmitic acid uptake and esterification unchanged	Hamosh *et al.* (1979)
DNA synthesis	Hamsters; 4 commercial cigarettes every 6 h for 48 h	Percent cells in S-phase increased in bronchi, bronchioles and alveoli within 72 h after exposure	Boren (1970)
	Mice; 2A1 cigarettes, 10% smoke, 50 min/day for up to 17 weeks	Replication DNA synthesis increased by more than 2 fold	Rasmussen *et al.* (1981)
	Mice; 3A1 or 2R1 cigarettes, 10% smoke for 126 min (15 sec of smoke, followed by 45 sec of air per min), 5 days/week for 3-13 weeks	Percent cells in S-phase increased by 3 to 10 fold	Henry *et al.* (1983)
Cyclic nucleotide activity	Rats; minced tissues exposed to gas phase of commercial cigarettes *in vitro*	Guanylate cyclase activity increased by 2 to 36 fold in various tissues	Arnold *et al.* (1977)
Glucose metabolism	Rats; 1R1 or 1A1 cigarettes, 1 or 3 cigarettes twice daily for 30 days	CO_2 production increased by 20-25% by exposure to 1A1; lactate production unchanged; glucose incorporation into lipid increased by 30% by 1A1; greater response to 1A1 than to 1R1	Hamosh *et al.* (1979)
In alveolar macrophages	Rats; 2R1 cigarettes, 10% smoke from 10 cigarettes, 3 times per day for 30 days	CO_2 production from glucose carbon-6 slightly increased; CO_2 production from glucose carbon-1 slightly decreased; lactate production increased by 65%	Drath *et al.* (1978)

Table 36 (contd)

Metabolic response	Experimental conditions[a]	Result	Reference
In alveolar macrophages	Hamsters; 2R1 cigarettes, 4 exposures of 15 min to cigarette smoke/day, 5 days/ week for 2 or 6 weeks	CO_2 production increased by 4-5 fold; O_2 consumption increased by 1.5 fold	Hoidal & Niewoehner (1982)
Arachidonic acid (AA) metabolism	Perfused rat and hamster lung; ventilated with six commercial cigarettes	Decreased AA incorporation in lung phospholipid only with high-tar non-filter cigarettes; decreased prostaglandin E_2 formation and metabolism; high-tar cigarette more active	Matintalo & Uotila (1983); Matintalo *et al.* (1983)
	Rats; 2R1 cigarette; 10-min exposure/day for 4-8 weeks	Increased 12-lipooxygenase activity but no effect on cyclooxygenase levels in platelets; suggested increases in 12-(S)-hydroxy-5,8,10,14- eicosatetraenoic acid	Chang *et al.* (1983)
	Rats exposed to whole smoke from 2R1 cigarettes 10 min/day, 5 times/week for 10 weeks	Metabolism of AA to prostaglandin I_2 by pulmonary microsomes decreased by 50-70%; metabolism of AA to thromboxane by pulmonary microsomes increased by 150-200%	Lubawy *et al.* (1983)
α-1-Antiprotease (α_1-PI) levels	Aqueous smoke solution from 2 commercial cigarettes	Human α_1-PI inactivated by cigarette smoke *in vitro*	Carp & Janoff (1978)
	Rats; 2A1 cigarettes; 10% smoke; single exposure	α_1-PI inactivated in lungs	Janoff *et al.* (1979)
	Aqueous solution of cigarette smoke or dimethylsulphoxide extract of CSC	α_1-PI not inactivated by smoke *in vitro*; slowly inactivated by CSC extract	Wyss *et al.* (1984)
	Fluid from broncho-alveolar lavage from smokers	No decrease in α_1-PI activity	Stone *et al.* (1983)

Table 36 (contd)

Response	Experimental conditions[a]	Result	Reference
Oxidant/antioxidant levels	Rats; commercial cigarettes; 3 cigarettes/day for 35 days	Glucose-6-phosphate dehydrogenase level increased by 27%	Peirce *et al.* (1976)
In lungs	Rats; 1R1 cigarettes; 13 cigarettes/day for 21 days	Glutathione peroxidase level increased by 34%; glutathione reductase level increased by 24%; glucose-6-phosphate dehydrogenase level increased by 38%	York *et al.* (1976)
In lungs	Rats; 1A1 cigarettes, 50 puffs (10% smoke)/day for 7 days	Glutathione, glutathione peroxidase and glucose-6-phosphate dehydrogenase levels increased	Chow *et al.* (1984)
In alveolar macrophages	Hamsters; 2R1 cigarettes, 4 exposures of 15 min to cigarette smoke/day, 5 days/week for 2 or 6 weeks	Superoxide anion levels increases by 1.5-3 fold	Hoidal & Niewoehner (1982)
In alveolar macrophages	Rats; 2R1 cigarettes, 10% smoke, 3 times/day for 30 days	Superoxide anion levels unaffected; hydrogen peroxide levels increased by 2 fold	Drath *et al.* (1978)
Pulmonary alveolar macrophage (PAM) activity			
Number of PAM	Mice; 2A1 cigarettes, 10% smoke, 8 cigarettes/day for 4 weeks	Increased by 2 fold	White *et al.* (1979)
	Hamsters; 2R1 cigarettes, 4 exposures of 15 min to cigarette smoke/day, 5 days/week for 2 or 6 weeks	Increased by 2 fold	Hoidal & Niewoehner (1982)
	Mice; 2A1 cigarettes, 20% smoke, 3 cigarettes twice daily, 5 days/week for up to 24 weeks	Increased by 8 fold	Matulionis & Traurig (1977)
	Rats; 2R1 cigarettes, 10% smoke, 10 cigarettes 3 times/day for 30 days	Not affected	Drath *et al.* (1978)

Table 36 (contd)

Response	Experimental conditions[a]	Result	Reference
Function of PAM	Mice; 2A1 cigarettes, 10% smoke, 8 cigarettes/day for 4 weeks	Elastase secretion increased by 2 fold	White *et al.* (1979)
	Mice; 2A1 cigarettes, 20% smoke, 3 cigarettes twice daily, 5 days/week for up to 36 weeks	Lysosomal enzymes (e.g., β-glucuronidase and glucosaminidase) increased by more than 3 fold	Matulionis & Traurig (1977)
	Rats and hamsters; 2R1 cigarettes, 0.4% smoke, 7 hr/day for 45 days	Rate of phagocytosis increased	Fogelmark *et al.* (1980)
	Rats; commercial cigarettes (20.6 mg tar, 1.42 mg nicotine); 10% smoke; 3 cigarettes/day for 8 weeks	Decreased phagolysosome fusion; no effect on phagocytosis	Harris, J.O. & Gonzales-Rothi (1984)
DNA repair	Mice; 2A1 cigarettes, 10% smoke, 50 min/day for up to 17 weeks	4-Nitroquinoline-1-oxide and methylmethane-sulphonate-induced unscheduled DNA synthesis depressed by 40-50% by 11 weeks of daily exposure	Rasmussen *et al.* (1981)
Microsomal mono-oxygenases		Variety of cytochrome P-450-dependent enzymes increased (see Table 37 for details)	

[a]Characteristics of the reference cigarettes tested, including 'tar' levels, are given in the section on 'Worldwide Use of Smoking Tobacco', p. 63.

Exposure to smoke can also alter the systemic immune response of test animals. Studies involving chronic exposure of mice to cigarette smoke have shown that: (1) T-cell function is inhibited progressively with time both in terms of humoral and cell-mediated responses (Thomas, W.R. *et al.*, 1974, 1975; Holt *et al.*, 1976; Holt & Keast, 1977; Keast & Ayre, 1980); (2) B-cell function is less affected (Thomas, W.R. *et al.*, 1975); (3) the effects on B and T cells are mediated by both smoke particulates and gaseous (i.e., nitrogen oxide) compounds (Esber *et al.*, 1973; Holt *et al.*, 1979); and (4) the phagocytic and killing capacity of peritoneal polymorphonuclear neutrophils is inhibited (Keast & Taylor, 1983). Exposure of lymphocytes *in vitro* to tobacco smoke and to nicotine decreases lymphocyte responsiveness to mitogen stimulation (Roszman *et al.*, 1975; Jacob *et al.*, 1980).

Smoke contains chemicals that inhibit blood coagulation; one prolongs the clotting time of plasma by delaying fibrin aggregation, and another inactivates factor XIIIa (Galanakis *et al.*, 1982).

Exposure to tobacco smoke causes similar changes in humans; these are discussed in section 3, p. 163.

(*b*) *Metabolic effects of tobacco smoke*

Exposure of animals to whole smoke from cigarettes or to the gas-phase constituents results in the alteration of a number of enzyme systems in pulmonary and other tissues. A summary of these metabolic responses is given in Table 36.

Levels of protein, glycoprotein and DNA synthesis are usually modified in pulmonary tissue following exposure to cigarette smoke: total protein synthesis may be decreased by 30%, while glycoprotein synthesis may be increased two fold. The latter change presumably reflects increases in mucus production (Hamosh *et al.*, 1979). DNA synthesis rates may be increased up to 10 fold following exposure to smoke (Boren, 1970; Rasmussen *et al.*, 1981; Henry *et al.*, 1983). This observation probably reflects in-situ stimulation of cells at all levels of the lung, i.e., bronchi, bronchioles and alveoli (Boren, 1970). Such general stimulation is also usually associated with increases in mitotic activity, as shown by the DNA labelling index (Henry *et al.*, 1983).

Some of the earliest effects of tobacco smoke are changes in levels of cyclic nucleotides. Pulmonary tissues contain high levels of cyclic guanosine monophosphate (cGMP), and levels of both cGMP and the enzyme that forms this intermediate, guanylate cyclase, are increased by gas-phase constituents of smoke (Maron *et al.*, 1984; Arnold *et al.*, 1977). cGMP levels can be increased up to seven fold within 2 sec of exposure to a single bolus of smoke; the levels return to control values within 2 min, and the process can be repeated (Maron *et al.*, 1984).

Lung tissues usually show higher rates of glucose metabolism following exposure to smoke. The level of carbon dioxide production is increased by ~ 25% in lung tissues of rats (Hamosh *et al.*, 1979) and by four to five fold in alveolar macrophages of hamsters (Hoidal & Niewoehner, 1982).

The lung plays two major roles in the metabolism of prostaglandins, and exposure to cigarette smoke can alter both functions. (1) Lung tissue has a high capacity for inactivating circulating prostaglandins, since it is particularly rich in two enzymes, 15-hydroxyprostaglandin dehydrogenase and 13,14-reductase, which degrade prostaglandins. (2) Lung tissue has a high capacity for converting arachidonic acid into a variety of prostaglandins and related substances (see Eling & Ally, 1984). Exposure to cigarette smoke results in a decreased rate of prostaglandin E_2 metabolism, which seems to be related to the 'tar' content of the cigarette, in that cigarettes with a very high 'tar' content cause greater inhibition (Matintalo & Uotila, 1983; Matintalo *et al.*, 1983). Chronic exposure to cigarette smoke also adversely alters arachidonic acid metabolism. Lung tissues from rats exposed to cigarette smoke once a day for 10 weeks synthesized more thromboxane and less prostaglandin GI_2 (i.e., prostacyclin) than sham-exposed animals (Lubawy *et al.*, 1983). Exposure to smoke

also results in higher activity of lipooxygenase in platelets but has a limited effect on cyclooxygenase activity (Chang *et al.*, 1983).

Smoke can be a major indirect or direct source of chemical oxidants and free radicals, and also causes a rapid influx of pulmonary alveolar macrophages and polymorphonuclear neutrophils into the lung. These actively phagocytic cells release a variety of oxidative intermediates when exposed to particulates such as those in cigarette smoke. The intermediates found in cigarette smoke and/or released by activated macrophages include superoxide anion, hydrogen peroxide and hydroxyl radical (Drath *et al.*, 1978; Baehner *et al.*, 1982; Hoidal & Niewoehner, 1982). As a result of their presence, a variety of cell components and extracellular materials undergo oxidative reactions. Pulmonary tissues respond to this insult by altering levels of glutathione, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase (Peirce *et al.*, 1976; York *et al.*, 1976; Chow *et al.*, 1984). One extracellular product that may be inactivated by these oxidative intermediates is the α_1-antiprotease inhibitor. This intercellular protein is the major antiprotease in the lungs and forms a covalent one-to-one complex with, and inactivates, a number of serine proteases, including elastase from polymorphonuclear neutrophils and pulmonary alveolar macrophages. Oxidation of α_1-antiprotease destroys its inhibitor function, and higher levels of elastase are observed. The higher level of elastase found in alveolar macrophages from lungs of smoke-exposed animals may cause enzymatic destruction of elastic fibres in the walls of the air spaces in the lungs (White *et al.*, 1979). Although certain laboratories have reported that smoke is capable of inactivating α_1-antiprotease inhibitor (Carp & Janoff, 1978; Janoff *et al.*, 1979), another laboratory has failed to observe a decrease in α_1-antiprotease in fluid obtained by broncholavage from smokers (Stone *et al.*, 1983).

The increased numbers and activity of pulmonary alveolar macrophages and polymorphonuclear neutrophils also cause an increase in lysosomal enzyme activity (Matulionis & Traurig, 1977). The increased levels of lysosomal acid hydrolases and decreased mucociliary mechanisms that occur after exposure to smoke render lung tissue that has been exposed to cigarette smoke at greater risk of tissue injury (Park, S.S. *et al.*, 1977).

One of the best studied metabolic alterations caused by exposure to tobacco smoke is the induction of the cytochrome P-450-dependent microsomal monooxygenases (MMO). These multicomponent enzymes metabolize a highly diverse group of lipid-soluble chemicals to more water-soluble forms (see Nebert *et al.*, 1978; Kouri *et al.*, 1980; Boobis & Davies, 1984). Studies in model animal systems have shown that MMO levels can be induced by a variety of chemicals, environmental pollutants and other foreign chemicals, that this induction is under genetic control, and that the genetic regulation can influence susceptibility to chemically-induced cancers (see review by Pelkonen & Nebert, 1982). MMO responses to smoke in six species of rodents are summarized in Table 37. The two most responsive organs are the lung and kidney, but induction of MMO by smoke has also been observed in small intestine (Uotila & Marniemi, 1976; Cohen, G.M. *et al.*, 1977; Uotila, 1977) and trachea (Simberg & Uotila, 1978). Lung tissue is also capable of metabolizing steroid hormones, e.g., testosterone: exposure to smoke inhibits rather than induces testosterone metabolism in lung tissue (Hartiala *et al.*, 1978).

Table 37. Effects of exposure to cigarette smoke on microsomal monooxygenase (MMO) activity in tissues of various rodent species

Species	Levels of MMO in tissues[a]	
	Lung	Kidney
Rat	Increased (Welch *et al.*, 1971; Van Cantfort & Gielen, 1975; Akin & Benner, 1976; Uotila & Marniemi, 1976; Van Cantfort & Gielen, 1977; Uotila, 1977; Bilimoria & Ecobichon, 1980)	Increased (Van Cantfort & Gielen, 1975; Uotila & Marniemi, 1976; Uotila, 1977; Van Cantfort & Gielen, 1977; Bilimoria & Ecobichon, 1980)
Mouse	Increased (Abramson & Hutton, 1975; Van Cantfort & Gielen, 1975; Akin & Benner, 1976; Kouri *et al.* (1979a)	No significant increase (Abramson & Hutton, 1975)
Hamster	Increased (Akin & Benner, 1976; Bilimoria & Ecobichon, 1980)	Increased (females only) (Bilimoria & Ecobichon, 1980)
Guinea-pig	Decreased (Bilimoria *et al.*, 1977); no effect (Bilimoria & Ecobichon, 1980)	Increased (Bilimoria & Ecobichon, 1980)
Gerbil	Increased (Bilimoria & Ecobichon, 1980)	No effect (Bilimoria & Ecobichon, 1980)
Rabbit	Decreased within 20 min (Lubawy & Isaac, 1980)	Not done

[a]Considered to be increased if more than two-fold increase observed within 24 h after exposure to smoke

Smoke-induced MMO have characteristics that distinguish them from those induced by 3-methylcholanthrene (MC) (Table 38). Smoke-induced levels increase more rapidly, are lower and have a longer half-life than MC-induced enzyme levels (Van Cantfort & Gielen, 1975, 1977; Kouri *et al.*, 1979a, 1980). Both enzyme systems require RNA and protein synthesis for induction (Van Cantfort & Gielen, 1977; Kouri *et al.*, 1979a). The inducing components occur in the particulate phase of smoke, since Cambridge-filtered (i.e., gas phase) smoke failed to induce pulmonary MMO (Akin & Benner, 1976). Certain strains of mice are more responsive to smoke (as they are to MC), but no clear-cut genetic regulation has been observed for smoke-induced MMO (Abramson & Hutton, 1975) as has been for MC-induced MMO (Nebert *et al.*, 1978; Kouri *et al.*, 1979a).

Exposure to cigarette smoke may also alter the levels of other enzymes, e.g., epoxide hydrolases and UDP-glucuronosyltransferase, which are associated with MMO. Pulmonary epoxide hydrolase levels have been shown to be decreased after exposure to smoke (Uotila & Marniemi, 1976; Uotila, 1977; Uotila *et al.*, 1977a), whereas levels in the small

Table 38. Comparison of characteristics of microsomal monooxygenase (MMO) induction in lung of rodents after exposure to smoke and to 3-methylcholanthrene (MC)[a]

Characteristic	Treatment	
	Smoke	MC
Time to peak response	4-6 h	24-48 h
Level of responsiveness	2 to 5 fold	10 fold
Half-life of induced enzymes	24 h	4-5 h
Dependent on RNA and protein synthesis	yes	yes
Dose-related responsiveness	inadequate data	yes
Genetic regulation	inadequate data	yes
Induced MMO metabolizes new substrates at higher rates	yes	yes
Induced MMO metabolizes chemicals to forms that bind to DNA	yes	yes

[a]From Abramson & Hutton (1975), Van Cantfort & Gielen (1975), Akin & Benner (1976), Van Cantfort & Gielen (1977), Cohen, G.M. *et al.* (1977) and Kouri *et al.* (1979b, 1980)

intestine are increased and those in kidney unchanged (Uotila & Marniemi, 1976; Uotila, 1977). The activity of UDP-glucuronosyltransferase in lung tissue (Uotila, 1977; Uotila & Marniemi, 1976) and in isolated perfused lungs (Uotila *et al.*, 1977b) has been shown to be practically unaffected by smoke levels, but levels in small intestine (Uotila, 1977) and trachea (Simberg & Uotila, 1978) are increased by exposure to smoke. In isolated rat lung, however, glucuronide conjugation is significantly increased by smoke (Uotila *et al.*, 1977b).

As a result of such altered levels of MMO and its associated enzymes, metabolism of chemicals such as benzo[*a*]pyrene by pulmonary tissues from smoke-exposed animals is altered (Cohen, G.M. *et al.*, 1977; Uotila *et al.*, 1977a; Lubawy & Isaac 1980). These benzo[*a*]pyrene intermediates are shown to bind covalently to cellular macromolecules, especially DNA, at much higher levels (Cohen, G.M. *et al.*, 1977). The higher MMO levels in lungs and/or other tissues of smoke-exposed rats also seem to account for the more rapid clearance times of drugs, such as phenacetin (Kuntzman *et al.*, 1977) and antipyrine (Nakagawa *et al.*, 1983).

Many of the alterations in metabolism caused by tobacco smoke described above have also been observed in humans exposed to tobacco smoke. (See section 3 of this chapter, pp. 186-189).

(*c*) *Mutagenicity and other short-term tests*

The results obtained from a variety of short-term tests on tobacco smoke and tobacco smoke condensate have been reviewed by DeMarini (1983) and by Obe (1984). Only a few of the studies deal with tobacco smoke; most are concerned with cigarette smoke condensate. The studies reviewed here are summarized briefly in Tables 39 and 40.

(i) *Tobacco smoke*

Tests with Salmonella typhimurium (Table 39)

Basrur *et al.* (1978) demonstrated that the smoke from four types of tobacco were mutagenic to *S. typhimurium* TA1538; the number of revertants per cigarette was at least two-fold greater with the smoke than with cigarette smoke condensate (CSC). Ong *et al.* (1984) showed that sidestream smoke (SS) was also mutagenic in a system in which bacterial plates were exposed directly.

Extracts of SS collected on filters were shown to account for most of the mutagenicity of the indoor air of an office building; the basic fraction of the air extract contained most of the mutagenic activity (Löfroth *et al.*, 1983). The air in which 157 cigarettes had been smoked within 6 h in a 110-m^3 room with poor ventilation was ten times more mutagenic than air from a control room (Bos *et al.*, 1983). [The Working Group noted that this study was designed so that cigarette smoke would have accounted for most of the mutagenic activity in the air; however, this does not imply that cigarette smoke would account for most of the mutagenicity of other indoor air samples.]

Extracts of particles collected in a room where moderate smoking occurred were more mutagenic than particles collected in a room with an open fireplace or than samples of urban air (Alfheim & Ramdahl, 1984).

Concentrated urine from 17 cigarette-smoking baboons had higher average mutagenic activity in *S. typhimurium* than that from 12 nonsmoking baboons. When the urine concentrates were further fractionated, some fractions were more active in strain TA100 and others more active in strain TA1538 (Marshall, M.V. *et al.*, 1983).

Exposure of rats to either SS or mainstream smoke (MS) of two to four filter cigarettes (13 mg tar; 0.9 mg nicotine per cigarette) smoked by an automatic smoking machine resulted in the excretion of frameshift mutagens in the urine, as detected by *S. typhimurium* TA1538 (Mohtashamipur *et al.*, 1984).

Tests in eukaryotic systems (Table 40)

A solution of the gas phase of cigarette smoke dissolved in phosphate buffer induced reciprocal mitotic recombination in *Saccharomyces cerevisiae* D3 and petite mutants in an

Table 39. Summary of studies on the mutagenicity of tobacco smoke and tobacco smoke condensates (CSC) in *Salmonella typhimurium*[a]

Tobacco	Metabolic system	Strain	Comments	Reference
Smoke and CSC from University of Kentucky K1R1-40 cigarette; standard experimental blend, no filter SEB 11-42; freeze-dried standard experimental blend FD-50; and straight burley, low-nicotine BLN-52	Rat liver (not stated if induced)	TA1538	Cigarette smoke more mutagenic than CSC	Basrur *et al.* (1978)
SS from 4 US brands	Aroclor-induced rat liver	TA98	After 4 h, increase in mutation frequency >10-fold average control value	Ong *et al.* (1984)
Extracts of particulate matter from SS of common US brands	Aroclor-induced rat liver	TA98	Most mutagenic activity found in basic fraction	Löfroth *et al.* (1983)
Smoke from cigarettes (brand not stated); extracts of particulates collected by filtration	Aroclor-induced rat liver	TA1538	Air in which 157 cigarettes were smoked in 6 h in a 110-m^3 room with poor ventilation 10 times more mutagenic than control air	Bos *et al.* (1983)
SS from cigarettes (brand not stated); extracts of particulates collected by filtration	Aroclor-induced rat liver	TA98	Cigarette smoke produced more mutagens in air than wood-burning in an open fireplace.	Alfheim & Ramdahl (1984)
Tobacco smoke[b]		TA1538 TA100	Urine of smoking baboons mutagenic	Marshall, M.V. *et al.* (1983)
MS and SS from cigarettes[c]		TA1538	Urine of exposed rats mutagenic	Mohtashamipur *et al.* (1984)
CSC from control and high-charcoal filter commercial cigarettes	Aroclor-induced rat liver and lung	TA1538	High-charcoal filters still allow mutagens to pass into smoke. Aroclor-induced rat liver and lung effective	Kier *et al.* (1974)
CSC from commercial and nitrate-treated, unfiltered cigarettes	Aroclor-induced rat liver and lung	TA1538 TA1535	CSC from nitrate-treated cigarettes contains directly acting mutagens detected in TA1535 and TA1538; all other CSCs required S9. Aroclor-induced rat liver and lung effective.	Kier *et al.* (1974)

Table 39 (contd)

Tobacco	Metabolic system	Strain	Comments	Reference
CSC, 12 Swain fractions and all fractions recombined from University of Kentucky 1A1 low-nicotine cigarettes	Aroclor-induced rat liver and lung	TA1538	Basic and some acidic fractions most mutagenic; neutral weakly mutagenic	Kier *et al.* (1974)
CSC and 19 fractions from University of Kentucky 1R1 cigarettes	Uninduced, PB- or MC-induced rat liver and lung; human liver	TA1538	MC a better inducer than PB for rat liver S9; uninduced, PB- or MC-induced rat lung and human liver not effective. Whole CSC and the water-insoluble fraction of CSC were mutagenic with uninduced rat liver S9	Hutton & Hackney (1975)
Whole CSC and 12 Swain fractions from University of Kentucky 1R1 cigarettes	MC-induced rat liver	TA1538	Basic and acidic fractions more mutagenic than neutral fractions	Hutton & Hackney (1975)
CSC from 8 American, 5 European and 5 Japanese cigarettes; 5 brands of cigars; and 3 pipe tobaccos	PCB-induced rat liver	TA98 TA100	TA98 more sensitive than TA100. Mutagenicity per mg of CSC nearly the same for low-tar and high-tar cigarettes and for CSC collected from either the first, middle or last third of cigarettes. Most filters reduced the amount of CSC by about 12%; however, the specific mutagenic activity of CSCs is similar for CSCs from filter and nonfilter cigarettes. Specific mutagenic activity of the smoke condensates was: cigar>cigarettes>pipe.	Sato *et al.* (1977)
CSC from 12 flue-cured tobaccos, 2 burley tobaccos, 6 Japanese domestic tobaccos, and 3 varieties of Japanese domestic tobaccos	PCB-induced rat liver	TA98	Total nitrogen, protein nitrogen, and soluble nitrogen positively related to increases in mutagenicity, but nicotine and nitrate were not. CSC from old leaves (low on the stalk) less mutagenic than CSC from young leaves (high on the stalk). CSC from tobacco with high sugar content less mutagenic than CSC from tobacco with low sugar content	Mizusaki *et al.* (1977a)
CSC from burley tobacco with 4 amounts of nitrogen fertilizer; flue-cured tobacco; 7 American, 4 Japanese, 3 UK and 1 German brand of cigarettes	MC-induced rat liver	TA1538	CSC from burley tobacco more mutagenic than CSC from flue-cured tobacco. CSCs from high-nitrate-containing cigarettes more mutagenic than CSCs from low-nitrate cigarettes. CSC prepared from cigarettes with high draw resistance more mutagenic than CSC from cigarettes with low draw resistance	Mizusaki *et al.* (1977b)

Table 39 (contd)

Tobacco	Metabolic system	Strain	Comments	Reference
Swain fraction 5 of CSC	Aroclor-, PB- or MC-induced, or uninduced maternal or fetal rat liver	TA98 TA100	Swain 5 (basic) fraction mutagenic in TA98 with PB-, MC- or Aroclor-induced S9. Fetal liver ineffective	Sehgal & Hutton (1977a,b)
CSC from burley and flue-cured tobacco	PCB-induced rat liver	TA98 TA100	Nitrite-treated CSC less mutagenic than untreated CSC in TA98, but nitrite treatment increased mutagenic potency of CSC in TA100	Yoshida & Matsumoto (1978)
CSC from 3 commercial brands of Japanese cigarettes	PCB-induced rat liver	TA98 TA100	Addition of sugar to tobacco reduced mutagenicity of resulting CSC, fructose and sorbitol being most effective	Sato *et al.* (1979)
CSC and 12 Swain fractions of 1A1 cigarettes	Aroclor-induced rat liver and lung	TA1538	Basic fractions most mutagenic	Kouri *et al.* (1979a)
CSC and 12 Swain fractions of 1A1 and 2A1 cigarettes	Aroclor-induced rat liver and TCDD-induced mouse liver and lung	TA98	TCDD-induced lung S9 from mice not effective; basic fraction most mutagenic	Kouri *et al.* (1979a)
CSC from 3 European brands	Aroclor-, PCB- and MC-induced or uninduced rat liver	TA98 TA100	Uninduced liver ineffective; TA98 more sensitive than TA100	De Raat (1979)
CSC from 2 types of flue-cured, burley, Japanese domestic and blended cigarette tobaccos	PCB-induced rat liver	TA98	CSCs from burley tobaccos more mutagenic than CSCs from flue-cured or blended tobaccos. CSCs from Japanese domestic tobaccos most mutagenic	Yoshida & Matsumoto (1980)
CSC and 10 fractions from University of Kentucky 1R1 cigarettes	Aroclor-induced rat liver	TA1538	Rankings of mutagenic potencies based on plate-incorporation vs. preincubation; protocols not significantly different: basic > acidic and neutrals	DeMarini (1981a)

Table 39 (contd)

Tobacco	Metabolic system	Strain	Comments	Reference
CSC from commercial defiltered low-tar cigarettes	Aroclor-induced rat liver S9 and S12 from human lung (parenchyma or bronchi)	TA98	Mutagenic with rat S9; borderline mutagenicity with human lung parenchyma S12	De Flora *et al.* (1984)
Smoke condensates from Transkei tobacco, pipe tobacco and commercial cigarette tobacco	Aroclor-induced rat liver	TA98 TA100 TA1538 TA1537	Mutagenic activities were: Transkei> pipe>cigarette. Potencies associated positively with nitrogen content of tobaccos	Wehner, F.C., *et al.* (1980)
Transkei pipe tobacco residues	Rat liver induced by combined treatment with PB and MC	TA98 TA100	Pipe tobacco residues mutagenic in TA98 and TA100	Hewer *et al.* (1978)

[a]Abbreviations. PB, phenobarbital; MC, 3-methylcholanthrene; PCB, polychlorinated biphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin

[b]Urine from tobacco smoke-exposed baboons

[c]Urine from rats exposed to mainstream and sidestream smoke

isolate of strain D3 (Izard *et al.*, 1976, 1980). Fresh cigarette smoke induced mitotic gene conversion, reverse mutation and reciprocal mitotic recombination in strain D7 of *S. cerevisiae*; the nicotine content of the cigarette did not affect the activity of the smoke (Gairola, 1982). In the root-tip cells of garlic the gas phase of cigarette smoke induced chromosomal aberrations (Pandey *et al.*, 1978).

Induction of sex-linked recessive lethal mutations was observed in *Drosophila melanogaster* larvae exposed to two to three puffs of cigarette smoke per day for seven days. However, treatment of adult males with cigarette smoke resulted in no significant increase in the number of sex-linked recessive lethal mutations over that in controls (Pescitelli, 1979). Kale and Baum (1982) confirmed these results and demonstrated that sex-linked recessive lethal mutations occur at a specific stage of germ cells, i.e., in spermatocytes.

A solution of the gas phase of cigarette smoke was shown to induce dose-dependent increases in the incidence of sister chromatid exchanges (SCEs) in cultured human lymphocytes obtained from smoking and nonsmoking subjects. The increases in SCE frequency were dose-dependent (Valadaud-Barrieu & Izard, 1979; Izard *et al.*, 1980).

Table 40. Summary of studies on the mutagenicity and other related effects of tobacco smoke condensate (CSC) and tobacco smoke in eukaryotes[a]

Endpoint	Type of condensate or smoke	Test organism	Result	Reference
FUNGI				
Reciprocal mitotic recombination	Gas phase	*Saccharomyces cerevisiae* D3	+	Izard *et al.* (1976, 1980)
	Fresh smoke	*Saccharomyces cerevisiae* D7	+	Gairola (1982)
Gene conversion	CSC	*Saccharomyces cerevisiae* D7	+	Hannan *et al.* (1980)
	Fresh smoke	*Saccharomyces cerevisiae* D7	+	Gairola (1982)
Petite mutations	Gas phase	*Saccharomyces cerevisiae* D3	+	Izard *et al.* (1976)
Mutation	CSC	*Saccharomyces cerevisiae* XV 185-14C	-	Hannan *et al.* (1980)
	Fresh smoke	*Saccharomyces cerevisiae* D7	+	Gairola (1982)
	CSC	*Neurospora crassa*	+	DeMarini (1981a,b)
PLANTS				
Chromosomal aberrations	Aqueous emulsion of CSC after ether extraction	*Allium cepa*	+	Venema (1959)
	Gas phase	*Allium sativum*	+	Pandey *et al.* (1978)
	Water-soluble fraction of CSC from filter and defiltered cigarettes	*Allium cepa*	+	Sabharwal *et al.* (1975)
INSECTS				
Sex-linked recessive lethal mutations	CSC and fresh smoke	*Drosophila melanogaster*	+	Pescitelli (1979)
	Fresh smoke	*Drosophila melanogaster*	+	Kale & Baum (1982)

Table 40 (contd)

Endpoint	Type of condensate or smoke	Test organism	Result	Reference
MAMMALIAN CELLS *IN VITRO*				
Mutation	CSC	L5178Y mouse lymphoma cells	+	Clive *et al.* (1979)
	CSC	L5178Y mouse lymphoma cells	+	Mitchell, A.D. *et al.* (1981)
Inhibition of metabolic cooperation	CSC	Chinese hamster V79 cells	+	Hartman & Rosen (1983)
SCEs	CSC	Chinese hamster ovary cells	+	De Raat (1979)
	CSC	Human lymphocytes	+	Hopkin & Evans (1979, 1980)
	CSC	Human lymphocytes	+	Madle *et al.* (1981)
	Gas phase	Human lymphocytes	+	Valadaud-Barrieu & Izard (1979)
	Gas phase	Human lymphocytes	+	Izard *et al.* (1980)
	CSC	Chinese hamster ovary cells and human lymphocytes	+	Hopkin & Perry (1980)
	CSC	Human lymphocytes	+	Sorsa *et al.* (1982)
	CSC	Human lymphocytes	+	Vijayalaxmi & Evans (1982)
	CSC	Chinese hamster ovary cells	+	Salomaa *et al.* (1985)
Cell transformation	CSC	Mouse L-cells and hamster lung fibroblasts	+	Inui & Takayama (1971a,b)
	CSC fractions	Syrian hamster embryo cells	+	Freeman *et al.* (1971)
	CSC (Basic, weak acidic and two neutral fractions)	Retrovirus-infected mouse and rat embryo cells; uninfected hamster embryo cells	+	Rhim & Huebner (1973)

Table 40 (contd)

Endpoint	Type of condensate or smoke	Test organism	Result	Reference
Cell transformation (contd)	Whole CSC and basic and weak acidic fractions from 1A1 cigarette	C3H 10T ½ cells	+	Benedict *et al.* (1975)
	CSC extracts	Syrian hamster embryo cells	+	Takayama *et al.* (1978)
	CSC ± benzo[*a*]pyrene	Syrian hamster embryo cells	+	Rivedal & Sanner (1980); Rivedal *et al.* (1980)
	Neutral fractions of CSC and hydrocarbon-enriched fraction of CSC	Human foetal lung	+	Lasnitzki (1958, 1968)
	Ethanol and ethyl acetate extracts of betel and tobacco	Syrian hamster embryo cells	+	Umezawa *et al.* (1978)
MAMMALS *IN VIVO*				
Cell transformation	CSC	Syrian hamster embryo cells (transplacental exposure followed by in-vitro culture)	+	Sabharwal *et al.* (1977)
SCEs (bone marrow)	CSC	Chinese hamster	-	Madle *et al.* (1981)
SCEs and chromosomal aberrations	Fresh smoke	Chinese hamster	-	Korte *et al.* (1981)
SCEs (lymphocytes)	Fresh smoke	Wistar rats	-	Basler (1982)
SCEs (bone marrow)	Fresh smoke	BC3F1/Cum mice	+	Benedict *et al.* (1984)
SCEs (bone marrow)	Fresh smoke	B6C3F1 mice	+	Putman *et al.* (1985)
Chromosomal aberrations	Fresh smoke	Chinese hamster	-	Korte *et al.* (1981)

[a]Abbreviation: SCE, sister chromatid exchange

No increase in the number of SCEs in bone marrow or of chromosomal aberrations was found in Chinese hamsters exposed to smoke from nonfilter commercial cigarettes for 1h/day for 9-12 weeks; addition of 20% ethanol to their drinking-water also had no effect on the frequency of SCEs or of chromosomal aberrations (Korte *et al.*, 1981). Exposure of female Wistar II rats to the smoke of 30 cigarettes/day for 28 days did not increase the frequency of SCEs in their cultured lymphocytes (Basler, 1982). [The Working Group considered that these negative results may have been due to inadequate exposure.] Recently, Benedict *et al.* (1984) demonstrated that exposure of female BC3F1/Cum mice to cigarette smoke daily for 1-46 weeks caused a two-fold increase in the frequency of SCEs in the bone marrow that persisted for at least one week after cessation of exposure. Putman *et al.* (1985) demonstrated dose-dependent increases in the frequency of SCEs in bone-marrow cells of B6C3F1 mice exposed to cigarette smoke on five days/week for two weeks. Rasmussen *et al.* (1981) reported that cigarette smoke inhibited DNA repair capacity in mice exposed to a test mutagen (methylmethanesulphonate), as evaluated by unscheduled DNA synthesis.

(ii) *Cigarette and other tobacco smoke condensates*

Tests with Salmonella typhimurium (Table 39)

CSC and its fractions have been tested extensively in *S. typhimurium* and shown to be mutagenic. Table 39 summarizes these studies, indicating the type of tobacco tested, the tissues and inducers used for metabolic activation, and the bacterial strains employed.

CSC was mutagenic primarily in strains TA1538 and TA98, which detect frameshift-type mutagens. Most of the activity was in the basic fractions; a small amount was found in the acidic fractions, and little was found in the neutral fractions (Kier *et al.*, 1974; Hutton & Hackney, 1975; Kouri *et al.*, 1979a; DeMarini, 1981a). The basic fractions may be the most mutagenic because the tester strain used, TA1538, is more sensitive to aromatic amines (present in the basic fractions) than to polynuclear aromatic hydrocarbons (present in the neutral fractions) (Kier *et al.*, 1974). Although most of the mutagenicity detected in *S. typhimurium* resides in the basic fractions, most of the carcinogenic activity detected in mouse skin assays has been found in the neutral fractions (Wynder & Hoffmann, 1967, 1968). Nitrate-treated cigarettes were mutagenic in strain TA1535, which detects mutagens that cause base-pair substitutions (Kier *et al.*, 1974).

Except for CSCs from nitrate-treated cigarettes, all tobacco smoke condensates required metabolic activation to be mutagenic in *S. typhimurium*. The mutation yields differed depending on the metabolic system used. Matsumoto *et al.* (1977) and Sugimura *et al.* (1977) demonstrated that the products of pyrolysis of amino acids and protein are mutagenic in the presence of a metabolic system. On the basis of this finding and of the relationship between nitrogen content of tobacco and mutagenicity of CSC, Mizusaki *et al.* (1977a) suggested that protein and amino acid pyrolysates are major contributors to the mutagenicity of CSC that is detected in *S. typhimurium*.

The mutagenic potency of CSC on a weight-to-weight basis was similar for low-tar and high-tar cigarettes (Sato *et al.*, 1977), and the presence of charcoal or other types of filters

had little effect on mutagenic activity (Kier *et al.*, 1974; Sato *et al.*, 1977). The mutagenic potency of CSCs collected from the first, middle and last third of cigarettes was similar; and the relative mutagenic potencies of tobacco smoke condensates were: cigars> cigarettes > pipe (Sato *et al.*, 1977). Neither the benzo[*a*]pyrene content nor the amount of *N*-nitroso compounds present accounts for much of the mutagenic activity of CSC (Kier *et al.*, 1974; Hutton & Hackney, 1975; Sato *et al.*, 1977).

Various characteristics of tobacco leaves may influence the mutagenic potency of CSC (Mizusaki *et al.*, 1977a). Total nitrogen, protein nitrogen and soluble nitrogen were positively associated with mutagenic potency; nicotine was not; CSC from old leaves (low on the stalk) was less mutagenic than that from young leaves (high on the stalk); CSC from tobacco with a high sugar content was less mutagenic than CSC from tobacco with a low sugar content. Sato *et al.* (1979) found that addition of sugars, such as fructose and sorbitol, to tobacco reduced the mutagenicity of the resulting CSC. Nitrate content increased the mutagenicity of CSC, and CSC from cigarettes with high draw resistance was more mutagenic than CSC from cigarettes with low draw resistance (Mizusaki *et al.*, 1977b).

CSC from Japanese domestic and burley tobaccos was more mutagenic (Mizusaki *et al.*, 1977b; Yoshida & Matsumoto, 1980) than CSC from flue-cured or blended tobaccos. [However, CSC from flue-cured tobacco was more carcinogenic to mouse skin than that from cigarettes composed of other types of tobacco (Wynder & Hoffmann, 1963, 1967, 1969; Hoffman & Wynder, 1972b). Burley tobacco cigarettes produce smaller amounts of polynuclear aromatic hydrocarbons than other cigarettes, resulting in lower carcinogenicity (Wynder & Hoffmann, 1969; Hoffmann & Wynder, 1972b). Possible reasons for this discrepancy between carcinogenicity and mutagenicity are discussed above.]

Tests in eukaryotic systems (Table 40)

Studies on the genetic effects of cigarette smoke and CSC in eukaryotic short-term tests are summarized in Table 40. CSC induced gene conversion in yeast (Hannan *et al.*, 1980) and mutation in *Neurospora crassa* (DeMarini, 1981a,b). CSC induced chromosomal aberrations in the root-tip cells of onion (Venema, 1959; Sabharwal *et al.*, 1975). It induced sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed as larvae (Pescitelli, 1979).

The neutral fraction of CSC was reported to inhibit DNA repair in normal human lymphocytes (Gaudin *et al.*, 1972). CSC was mutagenic to mammalian lymphoma cells *in vitro* (Clive *et al.*, 1979; Mitchell, A.D. *et al.*, 1981) and induced SCEs in Chinese hamster ovary cells (De Raat, 1979; Hopkin & Perry, 1980; Salomaa *et al.*, 1985) and in human lymphocytes (Hopkin & Evans, 1979, 1980; Madle *et al.*, 1981; Sorsa *et al.*, 1982). No difference was observed in the response of lymphocytes obtained from cigarettes smokers and from nonsmokers to the induction of SCEs by CSC (or by other mutagens) (Vijayalaxmi & Evans, 1982).

Whole CSC, organic solvent-soluble, acidic and water/methanol-soluble fractions and organic solvent eluates were reported to inhibit intercellular communication (measured by metabolic cooperation) between cultured HGPRT+ and HGRPT- V79 Chinese hamster cells (Hartman & Rosen, 1983).

CSC induced in-vitro transformation in a variety of mammalian cell systems (Lasnitzki, 1958, 1968; Freeman *et al.*, 1971; Inui & Takayama, 1971a,b; Rhim & Huebner, 1973; Benedict *et al.*, 1975; Takayama *et al.*, 1978; Umezawa *et al.*, 1978; Rivedal & Sanner, 1980; Rivedal *et al.*, 1980). Transforming activity has been found in basic, acidic and neutral fractions, and, similar to the results obtain in *S. typhimurium*, the basic and some of the acidic fractions were the most active (Benedict *et al.*, 1975).

CSC did not induce SCEs in bone marrow of Chinese hamsters *in vivo* (Madle *et al.*, 1981), but Sabharwal *et al.* (1977) demonstrated that transplacental exposure to CSC could transform Syrian hamster fetal cells.

3. Observations in humans

(*a*) *Methods of measuring intake of tobacco smoke*

Various methods have been used to measure the extent to which tobacco smoke is inhaled and taken into the human body. Most are designed to measure all phases of inhaling, while others make it possible to study specific phases only. The measurement of inhalation and factors influencing the extent of inhaling are discussed on pp. 170-179. This section discusses the methods employed in measuring intake of tobacco smoke.

(i) *Biochemical markers and biological measures of intake*

Three constituents of tobacco smoke are used routinely to measure exposure: carbon monoxide (CO), nicotine and hydrogen cyanide (HCN).

(1) *Carbon monoxide in blood.* CO can be measured in blood as carboxyhaemoglobin (COHb) or, rapidly and non-invasively, in end-expired air; the two measures have been found to be highly correlated (Jarvis *et al.*, 1980).

Analyses of COHb used to evaluate exposure to cigarette smoke are influenced by other environmental or occupational exposures to CO and to other compounds, such as methylene chloride (dichloromethane) (DiVicenzo & Kaplan, 1981). COHb can be used only as an indicator of recent exposure, since its half-life is relatively short — calculated to be 130 min for men during periods of activity and 220 min for seated men (Joumard *et al.*, 1981).

COHb levels in smokers are generally between 3 and 8% (see Table 41) but may occasionally reach 13% (Russell *et al.*, 1973a). According to Saloojee *et al.* (1982), a convenient cut-off point to discriminate between smokers and nonsmokers is a COHb value of 1.6%. Pojer *et al.* (1984) found that 97.8% of nonsmokers had COHb values below 2%.

EPIDEMIOLOGICAL STUDIES OF CANCER IN HUMANS

1. Introduction

Knowledge on the relationship between tobacco usage and a variety of human cancers depends primarily on epidemiological evidence. An immense amount of such evidence has been obtained, and, of necessity, only a small proportion can be referred to here. Cancers that are clearly related to smoking, described later in this monograph (i.e., cancers of the lung, upper respiratory and digestive tracts, lower urinary tract and pancreas) occur at lower rates of incidence (and mortality) in religious groups that proscribe smoking (particularly Seventh Day Adventists and Mormons) than in the corresponding national populations. Although many aspects of lifestyle differ in such populations, it seems probable that differences in smoking contribute substantially to the differences seen in smoking-related disease rates (Lyon *et al.*, 1978, 1980; Phillips *et al.*, 1980).

Case-control (retrospective) and cohort (prospective) studies first published in the early 1950s — though using different methodologies — are in qualitative, and approximately quantitative, agreement as to the risk among tobacco users for several types of cancer, among which lung cancer predominates.

The most readily comprehensible evidence, although often not the first nor the most detailed (which has commonly come from case-control studies), has been obtained in several large cohort studies, and they are, in consequence, referred to repeatedly in the sections that follow. Many of the case-control studies are described later in different sections of the monograph. To save unnecessary repetition, the large cohort studies are described and commented upon here:

Cohort studies on smoking and cancer

The first cohort studies to compare the risk of cancer among smokers and nonsmokers were begun in 1951. In most instances, smoking habits were ascertained through self-administered questionnaires. The cohorts studied were subsequently followed up to discover cancer deaths, or in some studies, incident cases of cancer. The design of those studies is summarized below and in Table 53.

American Cancer Society Nine-State Study (Hammond & Horn, 1958a,b)

Over 22 000 volunteers to the American Cancer Society were trained to have questionnaires filled out by 10 white men 50-69 years old whom he or she knew well. During 1952, a total of 204 547 smoking histories were collected in nine states. Several thousands were excluded for a variety of reasons. Follow-up of 187 783 men was conducted from 1952

Table 53. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size: initial samples; in brackets, population for follow-up	Source of information on smoking (proportion of respondents)	Duration of follow-up and no. of deaths	Completeness of follow-up for mortality
American Cancer Society Nine-State Study	1952	204 547 men [187 783]	Self-administered questionnaire	44 months 11 870 deaths	98.9%
Canadian Study	1955-1956	207 397 subjects (aged 30+) [92 000]	Self-administered questionnaire (57% respondents)	6 years 9491 deaths in men; 1794 deaths in women	NA[a]
British Doctors Study	1951	34 440 men (aged 20+)	Self-administered questionnaire (69% respondents	20 years 10 072 deaths	99.7%
		6194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1094 deaths	99%
American Cancer Society 25-State Study	1959-1960	1 078 894 subjects First follow-up: 440 558 men, 562 671 women (aged 35-84); second follow-up: 358 422 men, 483 519 women	Self-administered questionnaire	4.5 + 5 years 26 448 deaths in men; 16 773 deaths in women	97.4% in women 97.9% in men in first follow-up
US Veterans Study	1954	293 958 men (aged 31-84) [248 046]	Self-administered questionnaire (85% respondents	16 years 107 563 deaths	'Almost 100%' ascertainment of vital status; 97.6% of death certificates retrieved
Californian Study	1954-1957	68 153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4706 deaths	NA
Swedish Study	1963	27 342 men, 27 732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5655 deaths (2968 autopsies)	NA
Japanese Study	1965	122 261 men, 142 857 women (aged 40+)	Interview (95% of population in area)	16 years 51 422 deaths	Total

[a]NA, not available

through 1955 (average duration, 44 months), with losses of 1.1% and with 11 870 deaths (6.2%). Death certificates were collected for all deceased people, and, whenever cancer was mentioned, further information was collected from the physician, hospital or tumour registry. The distribution of smoking habits in the study population was in close agreement with that in a large survey on smoking habits in a sample of the US population (Haenszel *et al.*, 1956).

Canadian Study (Best *et al.*, 1961; Lossing *et al.*, 1966)

After a pilot study to validate questionnaires, in 1955-1956, 207 397 war veterans listed by the Canadian Pension Commission were mailed a questionnaire on smoking habits, principal occupations and residence history. Approximately 118 000 forms (57%) were returned; however, after removal of duplicates and unusable forms, only 92 000 (44%) remained. Follow-up was conducted from 1956 to 1962 through quarterly lists of deaths made available by the Department of Veterans Affairs. There were 9491 deaths among the male respondents and 1794 deaths among women; in most cases the cause of death was confirmed by autopsy.

British Doctors Study (Doll & Hill, 1964a,b; Doll & Peto, 1976; Doll *et al.*, 1980)

In 1951, a questionnaire on smoking habits was sent to all British doctors included in the Medical Register; 34 440 men and 6194 women responded (69% and 60%, respectively, of those who were alive). Further questionnaires about changes in smoking habits were sent in 1957, 1966 and 1972, with, on each occasion, about 97% of the survivors responding. Reports were published on cause-specific mortality from 1 November 1951 to 31 October 1971 (men) and to 31 October 1973 (women); 99.7% and 99% of the subjects were traced. Information on deaths was obtained principally from the Registrars General of the UK and from records of the General Medical Council and of the British Medical Association. There were 10 072 deaths among men and 1094 among women. Because the subjects in this study were themselves physicians, (i) they were a reasonably uniform socioeconomic group, and (ii) the causes of many of the deaths that occurred among them were certified more accurately than might have been the case among a sample of the general population. Whenever lung cancer was mentioned on the death certificate, details were reviewed centrally (by a chest physician who was unaware of the smoking history).

American Cancer Society 25-State Study (Hammond, 1966; Hammond & Seidman, 1980)

More than one million subjects were enrolled between October 1959 and February 1960 in 25 states. Enrollment was done through volunteers to the American Cancer Society and was by family; all family members over 30 years of age were requested to fill out detailed questionnaires. Each subject was traced annually and every two years had to fill in a brief questionnaire. Of the subjects originally enrolled, 1% could not be identified in the follow-up ascertainment, and for 2% the questionnaires were unusable. For the remaining 1 045 087 subjects, vital status was monitored by the volunteers up to September 1963, and was 97% complete. Death certificates were obtained from state or local authorities, and, when cancer was mentioned, further information was sought from physicians. For 483 519 white women

and 358 422 white men alive at the end of 1966, follow-up for mortality was extended to 31 December 1971. The proportion of these people who had been traced at the end of 1971 was about 99%. This is the largest of the cohort studies, and hence the one least subject to purely random error, even for quite rare causes of death. In particular, it gives the most reliable information that is currently available on lung cancer incidence rates among lifelong nonsmokers.

US Veterans Study (Kahn, 1966; Rogot & Murray, 1980)

Beginning in January 1954, 293 958 policy holders of US Government Life Insurance who had served in the armed forces at any time between 1917 and 1940 were sent a questionnaire on smoking habits; 198 834 (68%) responded, and 49 361 additional replies were obtained by a subsequent mailing in 1957 (total response rate, 85%). Policy holders were mainly white men of the middle and upper social classes. Follow-up of subjects occurred from 1954 through 1969. There were 107 563 deaths. Whenever a claim was filed for payment of a policy, a copy of the death certificate was sent routinely by the Veterans' Administration to the National Institutes of Health study office. 'Terminated' policies were also checked annually to ascertain if termination was due to death or to other reasons. Additional information was requested from a certifying physician or hospital for deceased people. The 16-year follow-up of cause and year of death was considered to be almost complete by Rogot and Murray (1980), with 97.6% of the death certificates having been obtained.

Californian Study (Weir & Dunn, 1970)

Self-administered questionnaires were collected in 1954-1957 from 68 153 labour union members (men aged 35-64) in California, USA; information on occupational exposures and smoking history was obtained. Follow-up for mortality was conducted up to December 1962 (average follow-up time, 7.1 years) through California death records; 4706 deaths occurred in the cohort. [The Working Group noted that the data available on smoking habits were less extensive than those in other studies.]

Swedish Study (Cederlöf *et al.*, 1975)

A sample drawn from the 1960 census of the Swedish population was stratified by sex, year of birth and urban-rural residence. A questionnaire was mailed in 1963, and, of 55 074 eligible subjects, 89% responded and some information was collected for another 5.3%. A 20% sub-sample were mailed a second questionnaire in 1969, with the aims of validating the accuracy of the replies and collecting information about changes in smoking patterns. Mortality in the cohort was ascertained through death certificates; an evaluation was made of the accuracy of registration and, for cancers at most sites, was found to be satisfactory. Between 1963 and 1972, 5655 deaths occurred in the cohort, and 2968 autopsies were performed; in addition, cancer incidence was ascertained from 1963 to 1970 through the Swedish Cancer Registry. Information is not available on the completeness of follow-up. This study is unusual in involving a population sample (stratified by place of residence), although the proportion of people with a *prolonged* history of smoking was low in Sweden in 1963, which will have affected some of the estimates of risk.

Japanese Study (Hirayama, 1967, 1975a,b, 1977a, 1978, 1982, 1985)

In 1965, 122 261 men and 142 857 women, aged 40 years and over (95% of the census population), were interviewed in 29 health centre districts in Japan. The main items studied were diet, smoking, drinking, occupation and marital status. A record linkage system was established for the annual follow-up. During 16 years of follow-up, 51 422 deaths occurred. This study is large and is unique in being of a non-Caucasian population and in being based on interviews rather than on self-completed questionnaires.

2. Cancer of the lung

The following section summarizes some of the epidemiological evidence on smoking-related factors that modify the incidence of lung cancer, assesses the proportion of lung cancer risk currently attributable to smoking in several different parts of the world, and shows how trends in the consumption of cigarette tobacco and changes from one type of cigarette to another relate to trends in the incidence of lung cancer in a few particular countries.

One factor that affects the estimate of relative risk in different studies is misdiagnosis of the disease. Although some patients with other disease may be misdiagnosed as having cancer of the lung (Heasman & Lipworth, 1966), these account for only a small proportion of cases nowadays. About 94% of deaths attributed to lung cancer were confirmed by hospital diagnosis in a study based on the Third National Cancer Survey in the USA (Percy *et al.*, 1981). Among nonsmokers, however, lung cancer is so rare that misdiagnoses may, in studies that are undertaken without careful histological evaluation, appreciably change the measured rates of lung cancer among nonsmokers, thereby biasing the relative (though not necessarily the absolute) excess risk of the disease among smokers. For this reason (and because the relative risks associated with smoking appear to be different for different histological categories of lung cancer, see below), histological characterization of the lung cancers that are studied is of substantial value.

(*a*) *Factors affecting risk*

(i) *Tobacco products smoked*

Evidence that the risk of lung cancer differs according to the tobacco product smoked was first obtained in case-control studies, such as those in the USA (Wynder & Graham, 1950) and in the UK (Doll & Hill, 1950). In these and other, similar studies, the estimated risk of lung cancer has usually been greatest among cigarette smokers (the largest and most recent study being that reported by Lubin *et al.*, 1984a), with the estimated risk in pipe and cigar smokers being intermediate between the risks in cigarette smokers and in nonsmokers. These findings have been fully corroborated in cohort studies, and the results are described in detail below. In contrast, adequate cohort studies are not yet available to assess whether changes in the composition of cigarettes (e.g., use of filters, 'tar' level reductions, etc.) have modified the risk of lung cancer conferred by *prolonged* use of such cigarettes. Therefore,

other types of evidence relating to this question are also described. The same is true for assessment of the health effects of *bidis*, which are the chief form in which tobacco is smoked in large parts of southern Asia.

(1) *Cigarettes, cigars and pipes.* In the American Cancer Society Nine-State study (Hammond & Horn, 1958a,b), there were 448 male deaths from lung cancer during the follow-up. The ratio of death rates (standardized for age), comparing people who smoked only cigarettes with lifelong nonsmokers, was 9.9 (Table 54); those who smoked only pipe and/or cigar tobacco had a relative risk of 2.3. A similar gradient was found between the death rates of nonsmokers, cigarette smokers and other smokers in each five-year age group. Thus, those who smoked cigarettes only had the highest lung cancer death rate, while pipe and cigar smokers experienced markedly lower excess risks of lung cancer death. Those smoking both cigarettes and some other type of tobacco had a risk intermediate between those people smoking 'cigarettes only' and 'cigars or pipe only' (Table 54).

In the Canadian Study (Lossing *et al.*, 1966), 343 lung cancer deaths occurred among current and ex-smokers, and seven in nonsmokers. The 325 current smokers of cigarettes only had a relative risk of 14.9 in relation to nonsmokers. The relative risks for cigar and pipe smokers were 2.9 and 4.4, respectively (Table 54).

In the American Cancer Society 25-State Study (Hammond, 1966), 1159 lung cancer deaths occurred among the 440 558 men in the cohort until 30 September 1963. The ratio of age-standardized death rates (or relative risks) for different smoking categories are given in Table 54. The rate for those who had smoked cigarettes only was 9.2 times the rate for those who had never smoked regularly, while those for men who smoked only cigars or only pipes were 1.8 and 2.2, respectively. The patterns in different age groups were roughly similar to that for the total group. Hammond and Seidman (1980) reported the results of follow-up of 358 422 white men and 483 519 white women in the same cohort during the five-year period 1967-1971. Those men who had smoked pipes or cigars only had an age-standardized mortality ratio (SMR) of 1.5 (nonsmokers, 1.0), while for those who had smoked cigarettes only the SMR was 8.5.

In the Swedish Study there were 116 lung cancer deaths in men and 28 in women (Cederlöf *et al.*, 1975). The relative risk for male cigarette smokers was 7.0; the highest relative risk, of 10.9, was found among those who smoked both cigarettes and a pipe (Table 54). An exceptionally high relative risk (9.2) was found for cigar smokers in this study. [The Working Group noted that this estimate was based on very small numbers.]

In the 20-year follow-up of the British Doctors Study (Doll & Peto, 1976), there were 441 male deaths that, after review, were attributed to lung cancer. The risks of lung cancer death in different smoking categories were expressed as death rates (indirectly standardized for age) per 100 000 person-years; these are shown as relative risks in Table 54. The relative risk for pipe and/or cigar smokers who had never previously smoked cigarettes was 5.8; that for pipe and/or cigar smokers who also smoked cigarettes, 8.2; and that for current cigarette smokers only, 14.0.

Table 54. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100 000	No. of cases
American Cancer Society Nine-State Study	Never smoked	1.0	12.8[a]	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	127.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian Study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
American Cancer Society 25-State Study	Never smoked	1.0[a]	12[a]	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish Study	Nonsmokers	1.0[a]		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12
British Doctors Study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
US Veterans Study	Nonsmokers	1.0[a]		
	Cigarettes	11.3		2609
	Cigarettes only	12.1		1095
	Cigars only	1.7		41
	Pipes only	2.1		32
	Ex-cigarette smokers	4.0		517
Norwegian Study	Nonsmokers	1.0[a]		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[a]Figures given in original report

There were 11 979 men and 13 998 women in a Norwegian cohort, 35-69 years of age, studied by Lund and Zeiner-Henriksen (1981); 120 male and 26 female lung cancer cases were identified from the files of the Cancer Registry of Norway. Table 54 gives the risks relative to that of nonsmokers for lung cancer in men; male cigarette smokers had a distinctly higher risk of lung cancer than smokers of other types of tobacco.

(2) *Bidis*. The association between lung cancer and the smoking of *bidis*, small hand-rolled Indian cigarettes, was investigated in two matched-pair, case-control studies conducted in Bombay, India. Notani and Sanghvi (1974) collected data on 520 patients with lung cancer seen at the Tata Memorial Hospital, Bombay, from 1963-1970 and on hospital controls matched for sex, age and community. Data on smoking habits were collected routinely from new patients coming to the hospital, irrespective of their ultimate diagnosis; 327 were *bidi* smokers. A matched-pairs analysis gave a relative risk of 2.6 for *bidi* smokers; the risk was 1.6 for those smoking <10 *bidis* per day, 2.8 for those smoking 10-19 per day, 2.8 for 20-29 per day, and 5.3 for 30 or more per day.

Jussawalla and Jain (1979) reported on 792 (i.e., 43%) of the male lung cancer patients diagnosed between 1964 and 1973 in the Greater Bombay area. Controls, randomly selected from a list of registered voters, were subsequently matched with cases for age and community and were interviewed at home by medical social workers. Of the patients, 451 were *bidi* smokers. The relative risk was found to be 19.3 for *bidi* smokers (12.3 for those smoking <20 *bidis* per day and 56.7 for those smoking 20 or more *bidis* per day).

[The Working Group noted the substantially different estimates of relative risk derived from these two studies, even though they were based largely on the same cases of lung cancer; the control series were different (hospital *versus* community), the latter risking some confounding by socioeconomic status, as all cases may not have been on the lists of registered voters.]

(ii) *Duration of smoking*

One of the key features of the relationship between cigarette smoking and lung cancer is the relevance of duration of regular cigarette smoking to lung cancer onset rates. For example, using a statistical model fitted to data from the British male doctors study, Doll and Peto (1978) estimated that the excess annual incidence rates of lung cancer after about 45, 30 and 15 years of cigarette smoking were in the approximate ratio 100:20:1 to each other (Table 55).

Thus, according to the model fitted, a three-fold increase in the duration of regular tobacco use would increase the annual incidence of lung cancer by about a hundred-fold. This particular relationship, derived from one detailed epidemiological study, may apply elsewhere, even though the additional evidence from cohort studies is sparse (Table 56). However, in the entire adult male population of England and Wales in the 1970s, the proportions of smokers at various different ages were not very different (Lee, P.N., 1976), yet the lung cancer death rate at 80 years of age was about 100 times that at 40 years of age (Office of Population Censuses and Surveys, 1984b). [The Working Group considered that the most likely explanation is that the 80-year-old smokers had been smoking cigarettes for about three times as long as the 40-year-old smokers.]

Table 55. Approximate[a] effects of various durations of cigarette smoking on annual excess incidence of lung cancer

Years of cigarette smoking	Annual excess incidence	
	Moderate smokers (%)	Heavy smokers (%)
15	0.005	0.01
30	0.1	0.2
45	0.5	1

[a]Estimated by Peto and Doll (1984) from the model reported by Doll and Peto (1978) fitted to incidence data for male UK doctors

Table 56. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

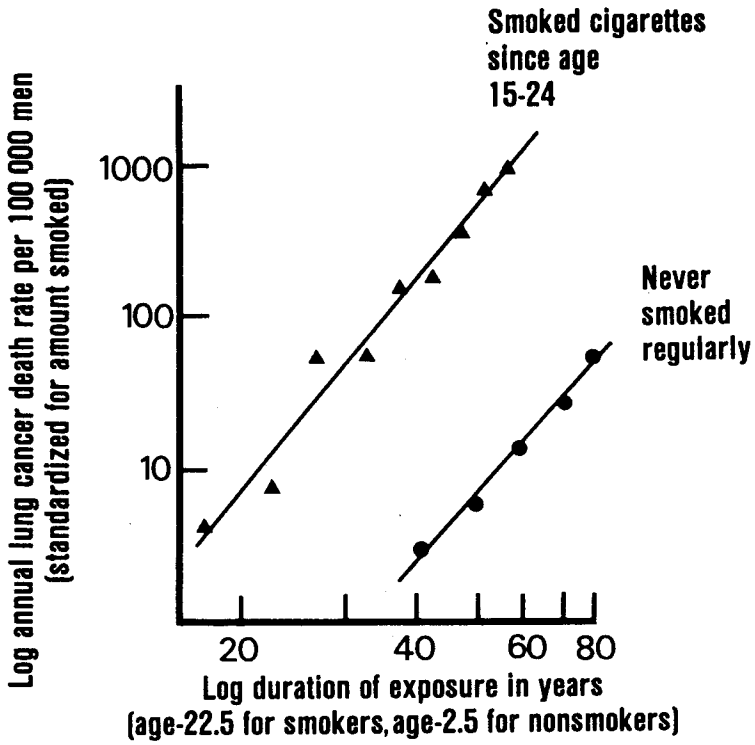
Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)[a]
Weir & Dunn (1970)	1-9	1.13 (total observed deaths, 368)	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	nonsmokers	1.0	0
Cederlöf *et al.* (1975)	1-29	1.8 (5)	0.01 (0.008)
	⩾30	7.4 (23)	0.1 (0.06)
	nonsmokers	1.0 (7)	0

[a]The mortality rate among nonsmokers was assumed to be 15.6/100 000 per year, as in the American Cancer Society study (see p. 230). Figures in parentheses were computed by the Working Group applying the British doctors' mortality rate among nonsmokers (10.0/100 000 per year) (see p. 230).

(1) *Nature of the relationship with duration.* The annual lung cancer incidence among regular cigarette smokers can be separated arithmetically into the 'background' (non-smoker) rate, which, like the onset rates of many other types of carcinoma, depends strongly on age (Garfinkel, 1981), plus an 'excess' rate, which depends strongly on the duration of regular exposure (Doll, 1971; Doll & Peto, 1978, 1981). Examples of background and excess rates for males are given in Figure 8, while those for females might be about two-thirds as great (Doll *et al.*, 1980).

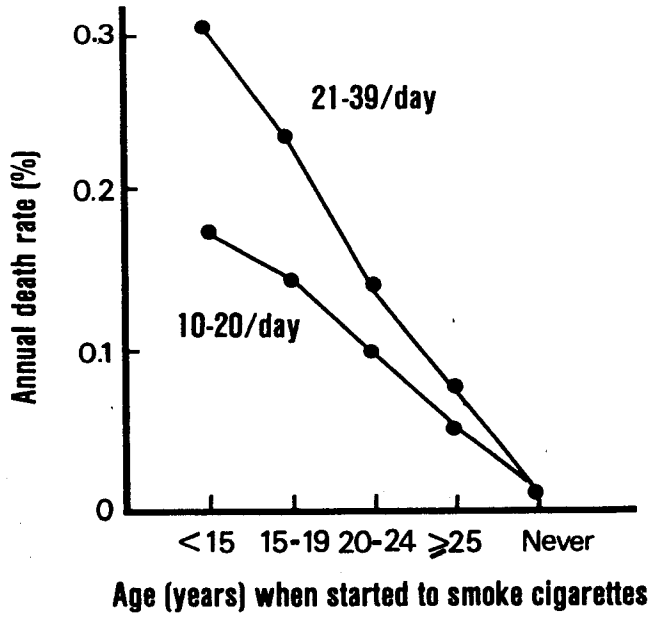
One feature of the effects of the duration of smoking is illustrated in Figure 9, which shows how the annual excess risk of lung cancer at age 60 in the US Veterans Study depended on whether men started to smoke at 15 or at 25 years of age (i.e., on whether, by the age of 60, they had smoked for 45, or for only 35, years). Some of the cohort studies of smoking and lung cancer have not produced differences

Fig. 8. Background and excess risks: lung cancer death rates among nonsmokers in relation to age (lower line) and among regular cigarette smokers, in relation to approximate years of smoking (upper line)[a]



[a]From Doll (1971) and Peto and Doll (1984)

Fig. 9. Relationship between age of starting regular cigarette smoking in early adult life and lung cancer death rates at age 55-64 (mean, 60) for US men. Data presented separately for heavy and for moderate smokers[a]



[a]From Doll and Peto (1981)

as marked as these (Table 57); however, the ratios in the Swedish Study were based on small numbers of deaths. The long delay that is commonly seen between an increase in cigarette usage and emergence of its full effects on national lung cancer rates in old age (Doll & Peto, 1981) shows that it is *prolonged* cigarette smoking that produces large lung cancer risks.

Table 57. Relationship between risk of lung cancer and age at start of cigarette smoking in men, based on available information from cohort studies

Reference	Age at start of smoking (years)	Mortality ratio (no. of observed deaths
American Cancer Society 25-State Study (Hammond, 1966)	25+	3.21 (20)
	20-24	9.72 (110)
	15-19	12.81 (315)
	<15	15.10 (101)
	nonsmoker	1.0 (49)
Japanese Study (Hirayama, 1975a)	25+	2.87 (NA)
	20-24	3.85 (NA)
	<20	4.44 (NA)
	nonsmoker	1.0 (NA)
Swedish Study (Cederlöf *et al.*, 1975)	⩾19	6.5 (11)
	17-18	9.8 (10)
	⩽16	6.4 (7)
	nonsmoker	1.0 (7)

Current patterns of mortality from lung cancer in late middle age or in old age therefore depend not only on current patterns of cigarette use, but also on the patterns of cigarette use among young adults perhaps half a century ago. Current trends, current urban-rural differences, and current international differences in lung cancer rates reflect, among other things, past trends, past urban-rural differences, and past international differences in cigarette usage by young adults.

For example, Doll and Peto (1981) pointed out that, in 1930, US cigarette consumption was increasing rapidly among young men, and national sales rose from <2 cigarettes per adult a day in 1920 to about 10 per adult a day in 1950 (Lee, P.N., 1975). However, the effects on the lung cancer incidence rate of those increases are only now becoming fully apparent, and, largely as a very long delayed result, US male lung cancer rates in late middle and old age are still rising steeply, despite the fact that cigarette sales per adult have remained at approximately 10-12 a day since 1950 (Doll & Peto, 1981).

Doll and Peto (1981) noted that when the national lung cancer rates for one generation are related to national cigarette consumption rates when that generation were young adults, a moderately close relationship emerges. They concluded that it is wrong to suggest that the poor international correlation between current smoking habits and current lung cancer rates indicates that smoking is not the chief determinant of worldwide lung cancer mortality.

(2) *Effects of age.* The effects of the duration of smoking are so strong, and so closely correlated with age, that it is virtually impossible to determine exactly whether ageing *per se* has any independent effect on excess lung cancer rates among people of different ages who have all smoked similarly for a similar number of years. If age has any independent effect, however, this would seem to be small compared with the cumulative effect of duration of smoking (Peto *et al.*, 1975, 1985; see also Likhachev *et al.*, 1985).

(3) *Time course of the effects of stopping smoking.* When smoking ceases, the annual excess risk of lung cancer appears to remain roughly (perhaps to within a factor of two) constant for many years thereafter (Doll & Peto, 1976). It is not consistently apparent that the annual absolute excess risk decreases substantially (Table 58). Two cohort studies have suggested that it decreases to zero after 10 years (Hammond, 1966; Cederlöf *et al.*, 1975), but others do not (Doll & Peto, 1976; Rogot & Murray, 1980). Hirayama (1975b) reported a rate ratio of 1.35 between people who had stopped smoking for 10 or more years and nonsmokers. Table 55 shows that the annual excess risk after 30 years of smoking is about 0.1% (1 per 1000). If a smoker stops after 30 years, for example, 15 years later the annual excess risk may still be about 0.1% instead of the 0.5% that it would have been had smoking continued. Therefore, about 80% of the excess risk that would have accrued with continuation of smoking has been avoided.

(4) *Time course of the effects of changes in smoking that fall short of complete cessation.* In the mid-1950s, the 'tar' level[1] per manufactured cigarette was high throughout the world, and in several developing countries (e.g., China, India, Indonesia, Pakistan, the Philippines and Zaire) and some developed ones (e.g., Denmark, eastern European countries, France, Italy and the USSR) it still is high (Lee, P.N., 1984; Jenkins, R.A. *et al.*, 1986; see pp. 60-65). In some developing countries (e.g., Chile, Kenya, Nicaragua and Papua New Guinea), 'tar' levels were greatly reduced by the end of the 1970s, and in several developed countries (e.g., Canada, Finland, the UK and the USA), 'tar' levels had already been greatly reduced by the end of the 1960s (Lee, P.N., 1976; US Department of Health and Human Services, 1981; Lee, P.N., 1984). In the latter countries, therefore, the 'tar' level per manufactured cigarette has been much lower than it was in the mid-1950s for the past 15 years.

[The Working Group considered that this period may, depending on the time course of any effects such changes may have on lung cancer rates, be long enough to evaluate whether lifelong exposure to such cigarettes is likely to be different from lifelong exposure to the types of cigarettes that were ubiquitous 30 years ago. One particular source of difficulty in answering this question epidemiologically, which affects both the usual cohort studies and the usual case-control studies of individuals, is that in many countries it is impossible to

[1][The Working Group noted that many changes have occurred in cigarette design and smoke composition, including the introduction of filters, porous paper and changes in types of tobacco. These changes affect the tar yield of smoke. For convenience, therefore, in the following pages the term 'tar' levels is used to describe all these changes in cigarette design.]

Table 58. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
American Cancer Society 25-State Study (Hammond, 1966)	**1-19 cigarettes/day**	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cigarettes/day	
	Current smokers	13.7 (351)
	<1	29.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish Study (Cederlöf *et al.*, 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British Doctors Study (Doll & Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot & Murray (1980)	Current smokers	11.3 (2609)
	<5	18.8 (47)
	5-9	~ 7.5 (86)
	10-14	~ 5.0 (100)
	15-19	~ 5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA, not available

compare prolonged smoking of high-tar cigarettes with prolonged smoking of low-tar cigarettes directly, simply because they have never coexisted: in the early 1950s there were no really low-tar cigarettes, while now in many countries there are no really high-tar ones. Moreover, the 'tar' level of the cigarettes smoked by many individuals may not remain consistently higher than average or consistently lower than average. Another source of difficulty, which affects not only studies of individuals but also studies of national trends, is

that it is not possible to predict reliably whether any effect of changing 'tar' levels would be rapid or slow to emerge. If such changes had analogous effects to those of cessation of smoking, then within 10-15 years of 'tar'-level decreases, changes in lung cancer might emerge. In view, however, of the great importance (see Fig. 9) of cigarette smoking in early adult life, it is possible that 'tar' levels in early adult life might be relevant to lung cancer risks many decades later, in which case the full effects of any changes in 'tar' levels might take many decades to emerge.]

Among UK men, decreases in lung cancer incidence are occurring at all ages, with the largest in the youngest age groups (Table 59). Although decreases in UK cigarette consumption have recently begun to be seen (particularly in men, but also in women: Royal College of Physicians, 1983), these did not start until 1975, and did not start to be rapid until after 1980 (average per-caput consumption by men of 10-11/day in 1940-1975; 9/day in 1980; 8/day in 1981; 7/day in 1982) (Wald, 1985). In men, including those under the age of 40, increases in cigarette usage were seen in the period 1950-1973 (Lee, P.N., 1976; and see Table 60). Changes in cigarette usage could account, therefore, for only a small part of the large decrease in lung cancer that was seen by 1978 and that has continued thereafter. Since no large improvement in the curability of the disease has taken place since the 1950s, it seems that for people in early middle age the lung cancer risk per cigarette is now substantially lower than it was more than 25 years ago. The interpretation of these trends is also discussed below (pp. 235-242). The percentage change in early middle age may provide the first clear indication of what can ultimately be expected throughout adult life, even though only a small minority of cancer deaths take place in early middle age.

Table 59. Trends in lung cancer death certification rates (per million) in middle-aged UK men (average of five years around each date)[a]

Age range (years)	1953[b]	1958[b]	1963[b]	1968[c]	1973[c]	1978[d]	1983[d,e]	Change over past 25 years (%)
30-34	37	36	33	25	24	17	14	—62
35-39	100	94	90	76	58	56	44	—53
40-44	250	253	225	218	177	139	122	—52
45-49	584	594	565	532	504	402	321	—46
50-54	1232	1254	1225	1162	1073	999	765	—39
55-59	2018	2326	2288	2203	2076	1897	1705	—27

[a]Calculated by the Working Group from Office of Population Censuses and Surveys, 1975 (numerators, 1951-1970; denominators, 1951-1960), 1980a (numerators, 1971-1978), 1980b,c, 1982, 1983b, 1984a,b, 1984c (denominators, 1961-1981), 1984d (denominators, 1981-1983), 1985a (numerators, 1979-1984; denominators, 1984)

[b]ICD6 162-164

[c]ICD8 162, 163

[d]ICD9 162-165

[e]1982-1984

Table 60. Cigarette consumption in the UK, 1943-1975[a]

Parameter	1943	1953	1963	1973	1975
No. of cigarettes/adult male per year	3930	3690	3820	3980	3730
Mean tar level (mg/cigarette)	ND	ND	31.4 (1965)	18.7	17.9
Proportion of never smokers (%)	ND	ND	16.9	18.4	20.3
Proportion of ex-smokers (%)	ND	ND	15.1	16.0	18.2
Proportion of nonsmokers by age group (%)					
16-19	ND	ND	39	42	43
20-24			26	26	29
25-29			20	26	27
30-34			20	20	23
35-49			13	16	19
50-59			11	10	10
60+			11	9	12

[a]From Lee, P.N. (1976)
ND, no data

(iii) *Intensity of smoking*

(1) *Effects on observed dose-response relationships.* In view of the importance of duration of smoking, the prospective studies undertaken in Sweden (Cederlöf *et al.*, 1975) and Japan (Hirayama, 1977a), in which cigarette smoking in early adult life was not widely prevalent among the smokers who were studied, greatly underestimate both the absolute and the relative risks that are to be expected from lifelong cigarette smoking in those countries. Similar problems exist in the USA, for the first generation of US men who had really heavy exposure to cigarettes in early adult life was that reaching adulthood just after the Second World War (i.e., those born after 1925) (Beese, 1972). Consequently, the relative risks observed among male cigarette smokers in the US cohort studies of the 1950s and 1960s may be substantially lower than those that may be observed in the 1980s, the 1990s and beyond, and this bias would be even greater for US women, although changes in 'tar' levels may complicate the picture.

Even in the UK, where cigarette smoking among men has been widespread for much longer than in most other parts of the world, similar problems affected the interpretation of the risks observed in both cohort (Doll & Peto, 1976) and case-control (Doll & Hill, 1950, 1952) studies. For British men born in the previous century, the relationships observed between lung cancer risks and daily cigarette dose-rates were probably underestimates, and this is even more true for British women. Indeed, in all countries, the widespread adoption of cigarette smoking by women is so recent that no adequate study of the full effects of lifelong smoking on female mortality is yet available.

(2) *Changes in relative risk with age.* A related difficulty is that (as reviewed by Doll, 1971; see also Fig. 8), even among people who have smoked cigarettes regularly since early adult life, the relative risk (i.e., the ratio of the annual lung cancer risk among regular smokers to that among lifelong nonsmokers) is not constant — indeed, it may be about three or four times as large in old age as in early middle age (Doll & Peto, 1978). [The Working Group considered, therefore, that no single (age-independent) relative risk can strictly or adequately characterize a particular smoking habit, and even the relative risks derived from epidemiological studies of lifelong cigarette smokers are hybrid mixtures of various different age-specific relative risks.]

(3) *Relationships observed in cohort studies with average daily amount of tobacco* (Table 61). In the American Cancer Society Nine-State Study (Hammond & Horn, 1958a,b), four categories of cigarette smokers were formed: <0.5 pack; 0.5-1 pack; 1-2 packs; and more than 2 packs per day. A consistent increase was found in the relative risk of lung cancer with increase in amount smoked per day (Table 61).

In the Canadian Study (Lossing *et al.*, 1966), the relative risk of lung cancer among men, compared with nonsmokers, was 10.0 for smokers of 1-9 cigarettes/day and 17.3 for smokers of ⩾21 cigarettes/day (Table 61).

In the American Cancer Society 25-State Study reported by Hammond (1966), the relative risk of lung cancer (compared to nonsmokers) in men was 4.6 among smokers of 1-9 cigarettes per day and 16.6 among those smoking 40 or more cigarettes per day; a consistent dose-response relationship was seen (Table 61). Among women, the risk was 1.1 for those smoking 1-19 cigarettes per day and 4.8 for those smoking 20 or more cigarettes per day. [The Working Group considered that the findings for men and, especially, for women probably underestimate the relative risks that prolonged cigarette use will cause.]

In the Californian Study (Weir & Dunn, 1970), the category 'nonsmokers' included (in contrast with the practice in other studies) those cigar and pipe smokers who had never smoked cigarettes. The relative risk for lung cancer increased with increasing amount smoked daily (see Table 61).

In the Japanese Study (Hirayama, 1985), 1324 male lung cancer deaths were observed during a 16-year follow up (1966-1981). The relative risks for those who smoked different amounts of cigarettes are given in Table 61. Although, again, these relative risks may grossly underestimate what will eventually be seen with the prolonged use of cigarettes, a consistent correlation was found between the amount smoked and the relative risk of lung cancer.

A dose-response relationship in the relative risk of lung cancer was found in the Swedish Study (Cederlöf *et al.*, 1975) by the amount of cigarettes smoked daily and, also, by the amount of pipe tobacco used (Table 61).

In the British Doctors Study (Doll & Peto, 1976), the indirectly standardized death rate per 100 000 was calculated for three groups of male current smokers (any tobacco): 1-14, 15-24 and 25+ g tobacco/day. A consistent gradient in the death rate was found: 52, 106 and 224 per 100 000, respectively. The rate for nonsmokers was 10. A separate analysis was made for those current smokers who smoked cigarettes only: the death rates were somewhat higher than those among current smokers of any tobacco (see Table 61). On the basis of the

Table 61. Dose-response relationship between the amount smoked and risk of lung cancer in men in some cohort studies

Study	Smoking category	Relative risk	Death rate per 100 000	No. of cases
American Cancer Society Nine-State Study (Hammond & Horn, 1958b)	(No. of packs/day)		*a*	
	0	1.0	12.8	15
	<0.5	7.4	95.2	24
	0.5-1	8.4	107.8	84
	1-2	17.9	229.2	90
	> 2	20.6	264.2	27
Canadian Study (Lossing *et al.*, 1966)	(No. of cigarettes/day)	*a*		
	0	1.0		
	1-9	10.0		57
	10-20	16.4		204
	21+	17.3		63
American Cancer Society 25-State Study (Hammond, 1966)	(No. of cigarettes/day)	*a*	*a*	
	0	1.0	12	49
	1-9	4.6	56	26
	10-19	7.5	90	82
	20-39	13.1	159	381
	40+	16.6	201	82
Californian Study (Weir & Dunn, 1970)	(No. of packs/day)	*a*		
	0	1.0		
	about ½ or less	3.7		
	about 1	9.1		
	about 1½ or more	9.6		
Japanese Study 16-year follow-up (Hirayama, 1985)	(No. of cigarettes/day)	*a*		
	0	1.0	23.0	80
	1-9	2.3	49.6	74
	10-19	4.0	93.2	486
	20-29	5.9	137.0	464
	30-39	6.1	141.3	52
	40-49	7.2	170.0	28
	50+	15.2	352.6	12
Swedish Study (Cederlöf *et al.*, 1975)		*a*		
	Nonsmokers	1.0		7
	Cigarettes only			
	1-7/day	2.3		4
	8-15/day	8.8		11
	16+/day	13.9		13
	Pipe tobacco only			
	<6 g/day	2.9		4
	>6 g/day	9.1		27

Table 61 (contd)

Study	Smoking category	Relative risk	Death rate per 100 000	No. of cases
British Doctors Study (Doll & Peto, 1976)	(No. of cigarettes/day)		*a*	
	0	1.0	10	
	1-14	7.8	78	
	15-24	12.7	127	
	25+	25.1	251	
US Veterans Study (Rogot & Murray, 1980)	(No. of cigarettes/day)	*a*		
	0	1.0		
	1-9	3.9		
	10-20	9.6		
	21-39	16.7		
	40+	23.7		
Norwegian Study (Lund & Zeiner-Henriksen, 1981)	(No. of cigarettes/day)	*a*		
	0	1.0		7
	1-9	6.0		19
	10-19	9.9		31
	20+	18.2		20

[a]Figures given in original report

data obtained in this study, Doll and Peto (1978) made a more detailed analysis of the relationship between the number of cigarettes smoked regularly and the risk of dying from lung cancer. They fitted a model indicating an upward curvature of the dose-response relationship in the range 0-40 cigarettes per day.

The results of the British Doctors Study for women were reported by Doll *et al.* (1980). There were only 27 lung cancer deaths during the entire 22-year follow-up period. The death rates were standardized for age to the age distribution of the person-years experienced by the male part of the cohort (Doll & Peto, 1976). The rate for nonsmokers was 7 (men, 10). Among current cigarette smokers, the groups smoking 1-14, 15-24 and 25 or more cigarettes per day had death rates of 9, 45 and 208, respectively (men: 78, 127 and 251, respectively). It was noted that the women who were light and moderate smokers had started later than men and also inhaled less. [The Working Group noted that, as with all studies of female smoking, the observed rates probably greatly underestimate the rates that will eventually be produced by prolonged tobacco use.]

The relative risks of those smoking different numbers of cigarettes per day in the US Veterans Study reported by Rogot and Murray (1980) are given in Table 61. Among men

who smoked <10 cigarettes per day, the relative risk was 3.9, while among men who smoked 40 or more cigarettes per day it was 23.7. A similar gradient, although less prominent, was found among ex-cigarette smokers: an increase in the risk from 1.2 to 7.8 as the number of cigarettes smoked before stopping increased from <10 to 40 or more per day.

In the Norwegian Study of Lund and Zeiner-Henriksen (1981), the relative risk of lung cancer also increased with increasing amount of cigarettes smoked per day (Table 61).

(4) *Comparison of effects of prolonged use of different types of cigarette (e.g., filter/nonfilter, high/medium/low 'tar', etc.)* (see footnote, p. 210). The most serious difficulties arise when comparing the effects of prolonged (i.e., lifelong) use of various different types of cigarette, for substantial changes in cigarette composition are so recent that prolonged use of the 'modern types' introduced in western countries in the late 1950s and early 1960s has not yet taken place. Therefore, epidemiological studies dating from the 1960s or early 1970s may underestimate the differences in risk that may exist between lifelong use of different types of cigarette. Lee, P.N. and Garfinkel (1981) noted the consistent reduction in mortality from lung cancer in early epidemiological studies with use of the more 'modern' cigarette. They also noted their limitations, imposed by the short duration of use of 'modern' cigarettes. [The Working Group noted that these studies related chiefly to comparisons between filter and nonfilter cigarettes; this distinction does not correspond fully to changes in tar delivery per cigarette.] Since then, a case-control study has been reported (Lubin *et al.*, 1984b) which is unusually large (involving the study of 23 000 people, one-third of whom were lung cancer cases and two-thirds controls) and involves longer exposure to the 'modern' types of cigarettes (because it took place in the late 1970s). Because of its large size and late date, the results from this study are perhaps more informative than those from the earlier and smaller studies.

Because the effects only of short-term use of 'modern' cigarettes could be assessed in the early studies, only two (in addition to that of Lubin *et al.*, 1984b) are reviewed here in detail (Hammond *et al.*, 1976; Wynder & Stellman, 1979). The results of the others are summarized in Table 62.

Hammond *et al.* (1976) reported the results obtained in the American Cancer Society 25-State Study with regard to the association between 'tar' content of cigarettes and risk of lung cancer. The subjects in this part of the study were those 40 years of age or older in July 1960 and who then said that they were currently smoking cigarettes regularly and had never smoked pipes or cigars regularly (first period — follow-up July 1960 to June 1966), or who in a later contact in 1965-1966 said that they were currently smoking cigarettes (second period — July 1966 to June 1972). Cigarettes containing 25.8-35.7 mg tar were classified into the 'high-tar' category, those with 17.6-25.7 mg into the 'medium-tar' category, and those with <17.6 mg into the 'low-tar' category. [Note that this terminology differs from that proposed on p. 61 of this monograph.] Those who reported use of the high-tar cigarettes experienced the highest risk of lung cancer death. The results were similar for men and women and for the two periods under study. Those who never had smoked cigarettes, pipes or cigars regularly had a distinctly lower risk of lung cancer than those who had smoked low-tar cigarettes (Table 63).

Table 62. Relative risk for lung cancer by type of cigarette smoked (filter *vs.* nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne & Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross & Gibson (1968)	Case-control	0.6
Wynder *et al.* (1970)	Case-control	0.6
Dean *et al.* (1977)	Case-control	0.5

Table 63. Age-standardized mortality ratio of lung cancer in two time periods, by tar content of cigarettes usually smoked, by sex[a]

Sex	Period	Mortality ratio			
		Tar content (mg/cigarette)			
		25.8 - 35.7	17.6 - 25.7	< 17.6	Never smoked
Male	1 July 1960-30 June 1966	1.0	0.96	0.83	0.07
	1 July 1966-30 June 1972	1.0	0.94	0.79	0.07
Female	1 July 1960-30 June 1966	1.0	0.86	0.57	0.25
	1 July 1966-30 June 1972	1.0	0.73	0.62	0.14

[a]From Hammond *et al.* (1976)

Wynder and Stellman (1979) calculated the risk of lung cancer among those who had been filter-cigarette smokers for more than ten years and compared it with the risk among nonfilter-cigarette smokers. The risk among filter-cigarette smokers, both men and women, was smaller in all categories defined by the amount smoked, except for women who smoked 31 or more cigarettes per day (Table 64).

Lubin *et al.* (1984b) reported on a comparison of 7804 lung cancer cases with 15 207 hospital-based controls in five European countries or territories (Austria, Federal Republic of Germany, France, Italy and Scotland). Results of a standard analysis of the data from the entire study suggest that lifelong use of filter, as opposed to nonfilter, cigarettes is associated

Table 64. Relative risk of lung cancer for current smokers who had used filter cigarettes for ≥10 years to that among current smokers whose present brand was nonfilter[a]

No. of cigarettes smoked	Relative risk of lung cancer (filter for 10+ years: current nonfilter)	
	Men	Women
1 - 10	0.6	0.4
11 - 20	0.9	0.7
21 - 30	0.7	0.8
31 - 40	0.7	-
31+	-	1.0
41+	0.9	-

[a]From Wynder and Stellman (1979)

with avoidance of 40-50% (Table 65) of lung cancer cases. Because of the large numbers involved, this finding is highly statistically significant ($p<0.001$). Data are also provided on different risks according to 'tar levels' of different brands (Table 66).

One part of this study (on Austria) has been presented separately (Kunze & Vutuc, 1980) in a report that claims a very large (about 80%) protective effect of 'tar-level' reductions. [The Working Group noted that this analysis depends upon the inappropriate use of a cumulative tar exposure index that appears to confuse the number of cigarettes smoked, the number of years for which they have been smoked, and their tar content in such a way that none can be informatively assessed.]

An analysis of another subset of this study (in France) (Benhamou *et al.*, 1985) showed findings similar to those of Lubin *et al.* (1984b), although when adjusting for daily cigarette consumption and type of cigarette, the relative risk associated with the use of nonfilter compared to filter cigarettes was 1.3 (not statistically significant).

[The Working Group noted that, in the report of Lubin *et al.* (1984b), lifelong filter-cigarette smoking is considered, whereas many of the smokers could have been expected to have commenced smoking before filter cigarettes became available. In addition, the reported relative risks for different proportions of 'low-tar' and 'high-tar' brands smoked were not adjusted for other characteristics of cigarette design such as use of filters. The latter consideration makes it difficult to determine which of the changes in cigarette design (filter or lower tar yield) were responsible for the reduction in risk.]

Table 65. Relative risk of lung cancer by proportion of years of use of nonfilter cigarettes[a]

Proportion of years nonfilter cigarettes smoked[b]	Relative risk[c]	
	Men	Women
0.0 (all filter)	1.0	1.0
0.01 - 0.49	1.5	1.8
0.50 - 0.69	1.4	1.7
0.70 - 0.83	1.7	1.9
0.84 - 0.99	1.7	2.1
1.0 (all nonfilter)	1.7	2.0

[a]From Lubin *et al.* (1984b)
[b]Apart from 0 and 1, these groups represent quartiles of the reported duration of use of filters
[c]Adjusted for years of cigarette use, number smoked/day and years since cessation. Test for linear trend: $p < 0.001$

Table 66. Relative risk of lung cancer by proportion of smoking history during which brands with different 'tar' levels were used[a]

Brand	Relative risk[b]	
	Men	Women
Low-tar brands (100%)	1.0	1.0
Low-tar brands (> 75%)	1.2	-
Other mixed brands	1.5	5.9
High-tar brands (> 75%)	1.8	4.0
High-tar brands (100%)	1.7	7.7

[a]From Lubin *et al.* (1984b)
[b]Adjusted for years of cigarette use, number smoked/day and years since cessation

While the 'low-tar' cigarette appears to reduce the risk for lung cancer, a recent report by Kauffmann *et al.* (1983) indicated that it has no protective effect against myocardial infarction. [The Working Group considered that possible differences in the effect of cigarette smoke in the pathogenesis of lung cancer and myocardial infarction may explain these findings.]

(*b*) *Histological types and association with smoking*

The association between smoking and different histological types of lung cancer has been analysed in many different ways. The problems related to the interpretation of the results obtained in epidemiological studies in which the histology of lung cancer is considered include variation in the nomenclature and criteria of classification of the tumours, inadequacy of the specimens that have been made available for histological classification in patients who are not subjected to operation, and the small size of many of the patient series, resulting in unstable risk estimates, particularly in women. Kreyberg (1962) divided epithelial lung cancers into two groups on the basis of the histological appearance of the tumour. Group I, squamous-cell (epidermoid) carcinoma and small (oat)-cell carcinoma; Group II, the rest, i.e., adenocarcinoma, large-cell undifferentiated carcinoma, combined squamous-cell and adenocarcinoma, bronchiolo-alveolar carcinoma, carcinoid tumours and tumours of mucous glands. Quite often, these two broad categories, referred to as Kreyberg Groups I and II, have been applied without more detailed description. Moreover, in many areas, a substantial proportion of lung cancer cases are not verified histologically; cases diagnosed by other means (cytology, X-ray, etc.) do not constitute a random sample of the total material.

In the study of Doll *et al.* (1957), there were 878 male and 76 female lung cancer patients with histological verification of diagnosis, and 1357 male and 108 female 'matched-control' patients of the same age distribution with other diseases. A substantial part of the material was histologically reclassified into Kreyberg Groups I and II. The risks of developing different histological types of lung cancer relative to nonsmokers are given in Table 67. There was a consistent increase in the relative risk for Kreyberg Group I tumours in both men and women, and for Kreyberg Group II tumours only in women (based on only eight cases in smokers).

The relative risk of lung cancer among cigarette smokers compared to nonsmokers was 4.3 for adenocarcinoma and 31.0 for cancers other than adenocarcinoma in the study of Hammond and Horn (1958b). For those smoking other types of tobacco, the corresponding relative risks were 1.3 and 3.7, respectively. The dose-response relationship among cigarette smokers between the amount smoked and risk of adenocarcinoma or other types of lung cancer is given in Table 67. An increase in the relative risk with increasing amount of cigarettes smoked was seen for both groups, the slope being, however, much steeper for types other than adenocarcinoma.

Doll and Hill (1964a) analysed the death rate ascribed to different histological types of lung cancer in groups with different smoking habits within the cohort of male British doctors (Table 67). A consistent increase in the death rate by increasing amount smoked was found for epidermoid, oat-cell and anaplastic carcinomas but not for adenocarcinoma. However, in a later analysis of the cohort for the years 1951-1971, a statistically significant trend was observed with respect to the number of cigarettes smoked in the age-standardized incidence of all four major histological types, i.e., squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma and undifferentiated carcinoma (Doll & Peto, 1978).

Table 67. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments	
Doll *et al.* (1957)		Sex	No. of cases	Relative risk				Nonsmokers, 1.0 (RR)	No. observed
				Amount of tobacco smoked (g)					
				<5	5-14	15-24	25+		
	Kreyberg I	M	829	4.7	10.6	14.3	25.4		3
		F	32	1.0	1.7	8.3			16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1		2
		F	8	1.1	2.3	4.1			5
Hammond & Horn (1958b)		Relative risk						Nonsmokers, 1.0	
		No. of packs/day						Only regular smokers considered	
		<½		½-1		1+			
	Adenocarcinoma	2.0		2.5		7.0			
	Other types	16.3		25.5		88.0			
Doll & Hill (1964a)		Death rate/1000						Men only	
		Amount of tobacco smoked							
		Ex-smokers	1-14 g	15-24 g	25+ g				
	Squamous-cell carcinoma	0.09	0.22	0.33	0.45				
	Small-cell and anaplastic carcinoma	0.05	0.10	0.20	0.38				
	Adenocarcinoma	0.03	0.03	0.12	0.07				

Table 67 (contd)

Reference	Histological type	Results					Comments
Haenszel & Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratios; total group, 1.00
		Never smoked	Ex-smokers	Occasional cigarette smokers	Regular cigarette smokers		
					<1 pack/day	>1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.78	
Hanbury (1964)		No. of cases (%)					Women only
		'Heavy' and 'medium' smokers			Nonsmokers and 'remainder'		
	Small-cell carcinoma	18 (47)			21 (34)		
	Undifferentiated carcinoma	9 (24)			14 (23)		
	Squamous-cell carcinoma	9 (24)			12 (19)		
	Adenocarcinoma	2 (5)			15 (24)		

Vincent, T.N. *et al.* (1965)		Total no. of cases	Number of cigarettes smoked/day										Women only
			None		1-20		21-40		41+		Unknown		
			No.	%	No.	%	No.	%	No.	%	No.	%	
	Squamous-cell carcinoma	19	10	53	3	16	2	10	2	10	2	10	
	Small-cell carcinoma	17	2	12	7	41	6	35	2	12	0	0	
	Adenocarcinoma	64	51	80	6	9	4	6	0	0	3	5	
	Undifferentiated	22	12	54	4	18	6	27	0	0	0	0	
	Others	41	32	78	8	20	1	2	0	0	0	0	
	Total	163	107	66	28	17	19	12	4	2	5	3	

Table 67 (contd)

Reference	Histological type	Results			Comments
Deaner & Trummer (1970)		Pack-years	Number of tumours	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Epidermoid carcinoma	52	9	9 (100%)	
Wynder *et al.* (1970)		Sex	No. (%)		Heavy = 41+ cigarettes/day
			Cigarette smokers	Heavy smokers	
	Kreyberg I	M	191 (91.0)	59 (29.9)	
		F	24 (80.0)	3 (12.0)	
	Kreyberg II	M	61 (82.4)	9 (14.1)	
		F	21 (58.3)	1 (4.8)	
	Controls	M	199 (47.4)	26 (9.8)	
		F	53 (40.2)	3 (5.4)	
Weiss, W. *et al.* (1972)		Death rate per 1000 man-years of observation (adjusted for age and race)			
		No. of cigarettes/day			
		1 - 10	10 - 19	20+	
	Squamous-cell carcinoma				
	Well differentiated	-	0.8	2.1	
	Poorly differentiated	0.7	0.4	1.0	
	Small-cell carcinoma	-	0.3	0.7	
	Adenocarcinoma	-	0.6	1.0	

Table 67 (contd)

Reference	Histological type	Results					Comments
Vincent, R.G. *et al.* (1977)		No. of cigarettes smoked/day					
		0	1-20	21-40	41+	Other	
	Squamous-cell carcinoma	14	219	110	120	16	
	Adenocarcinoma	28	101	66	53	7	
	Small-cell carcinoma	4	103	62	56	6	
	Large-cell carcinoma	2	40	32	33	1	
	Bronchiolo-alveolar carcinoma	6	20	9	6	0	
	Mixed	0	9	5	5	0	
	Other	6	30	18	17	4	

Reference	Histological type	Smoking category (kg tobacco smoked during lifetime)							Comments
		Non-smokers	<100		100-199		>200		
			Manufactured	All	Manufactured	All	Manufactured	All	
Chan *et al.* (1979)	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1	Women only
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7	

Reference	Histological type	Relative risk by duration of smoking (years)								Comments
		Men				Women				
		1-29	30-39	40-49	50+	1-29	30-39	40-49	50+	
Joly, O.G. *et al.* (1983)	Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9	Nonsmokers, 1.0
	Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0	
	Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3	
	Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.4	13.1	

Haenszel and Taeuber (1964) estimated the standardized mortality ratio of different types of lung cancer in groups defined by smoking habits among women in the USA. In each category, a sizeable smoking-class gradient was found (Table 67), and no clear difference between adenocarcinoma and other histological types was discernible.

One hundred consecutive female lung cancer cases diagnosed in a hospital in London were classified by smoking habit and cell type of the tumour in the study of Hanbury (1964). Five per cent of the tumours among heavy and medium smokers were adenocarcinomas (2/38) compared to 24% among nonsmokers and others (15/62) (Table 67).

Vincent, T.N. *et al.* (1965) classified 163 lung cancers in women by histological type and smoking habits. Of Kreyberg Group I tumours (squamous-cell and small-cell carcinomas), 65% (22/34) were among cigarette smokers; but only 19% (19/102) of Kreyberg Group II tumours (adenocarcinoma, carcinoma with mucus production, bronchiolo-alveolar carcinoma, carcinoid tumour and adenoid cystic carcinoma) were in smokers. Four cancers were diagnosed among heavy smokers (41 or more cigarettes a day); all had Kreyberg Group I tumours (Table 67).

In a series of female lung cancer cases from California, USA (Deaner & Trummer, 1970), all patients with epidermoid carcinoma (9) and those with undifferentiated carcinoma (40) were cigarette smokers. The average number of pack-years was 52 for epidermoid and 40 for undifferentiated carcinoma. Among patients with adenocarcinoma, 13/19 were cigarette smokers, the average number of pack-years being 12.

Wynder *et al.* (1970) interviewed a hospital series of 210 men and 30 women with Kreyberg Group I (squamous- and small-cell carcinomas) and 74 men and 36 women with Kreyberg Group II tumours ('glandular') of the lung. A control group from the same hospital, twice the size of the cancer group, was matched by age to the male Kreyberg Group I patients and to all female patients; these individuals had no tobacco-related disease. In male cases, there was a significantly higher percentage of cigarette smokers and of heavy cigarette smokers in both histological groups than in the controls, and the percentage was even higher in Kreyberg Group I than in Kreyberg Group II cases (Table 67). In women, the difference between lung cancer patients and controls was similar to that in men for Kreyberg Group I; but for Kreyberg Group II the difference was small and not significant.

In a study by Weiss, W. *et al.* (1972), a US male cohort of 2580 men who regularly smoked cigarettes and 830 nonsmokers was followed up for 10 years for risk of lung cancer of different histological types. No lung cancer developed among nonsmokers, but there were 67 among smokers. The death rates from well-differentiated squamous-cell carcinoma, small-cell carcinoma and adenocarcinoma showed a dose-response relationship to cigarette smoking, but poorly differentiated squamous-cell carcinoma did not (Table 67).

Smoking histories were obtained from the clinical records of 112 female lung cancer patients at the Sheffield Royal Infirmary in the UK diagnosed in 1955-1971 (Kennedy, 1973). The tumours were histologically reclassified. The proportion of nonsmokers was 25% among 87 patients with Kreyberg Group I tumour and 40% among 25 patients with Kreyberg Group II tumour. The difference was not statistically significant.

Beamis *et al.* (1975) reclassified histological specimens of 142 female lung cancer cases seen in one hospital in the USA in 1957-1972. Data on smoking habits were obtained from clinical records. Among those with Kreyberg Group I tumour (squamous-cell, small-cell, large-cell and undifferentiated carcinomas), 25/86 (29%) were nonsmokers compared to 35/56 (63%) among cases with Kreyberg Group II tumours (adenocarcinoma and bronchiolo-alveolar-cell carcinomas).

Vincent, R.G. *et al.* (1977) analysed the histology of lung cancer in a series of 1208 male and female lung cancer cases in different smoking categories in the Roswell Park Memorial Institute in the USA. The proportion of adenocarcinomas among nonsmoking patients was 46.7% compared to 19.8% among cigarette smokers (without much variation between different numbers of cigarettes smoked a day). The proportions of squamous-cell and small-cell carcinomas among nonsmokers were 23.3 and 6.7%, respectively, compared to 40.5 and 19.8% among cigarette smokers (again, without much variation between numbers of cigarettes smoked a day).

A case-control study was carried out in Hong Kong in 1976-1977 in order to analyse the relationship between smoking and lung cancer by histological type (Chan *et al.*, 1979). There were 208 male and 189 female patients and 204 male and 189 female controls; the controls were orthopaedic patients in the same hospitals as the lung cancer patients. Data on smoking habits were obtained through interviews of patients. Histological specimens were reclassified. The risk of lung cancer among smokers was greater than that in nonsmokers, both in men and women, but there was little evidence of a dose-response relationship. The risk was greater for squamous-cell and small-cell carcinomas (combined) than for adenocarcinoma. These findings were similar for manufactured cigarettes and for all forms of tobacco (Table 67).

In a case-control study carried out in Cuba in 1978-1980 (Joly, O.G., *et al.*, 1983), there were 607 male and 219 female patients, and 979 hospital and 539 neighbourhood controls. The histological specimens were reclassified (all patients had a histological and/or cytological verification of tumour). Cigarette smoking was associated with all major histological types of lung cancer, although the relative risk for adenocarcinoma was lower than that for the other types. The risk of lung cancer increased significantly with longer duration of cigarette smoking for all histological types (Table 67).

Shimizu *et al.* (1982) analysed a series of 14 946 lung cancer cases diagnosed in 1972-1976 in Los Angeles County, USA. A specific histological diagnosis was available for 76% of the cases; no reclassification was performed. Data (relative risks on the relationship between the amount smoked and risk of total lung cancer, adenocarcinoma and squamous-cell carcinoma) were obtained from a previous case-control study (Pike *et al.*, 1979). Using this information, the authors calculated 'residual' incidence rates of different histological types of lung cancer, i.e., rates as they would be if the total population were nonsmokers. The observed and 'residual' incidence rates per 100 000 for squamous-cell carcinoma were 117.3 and 12.2 in men, and 22.3 and 2.5 in women, whereas the corresponding figures for adenocarcinoma were 47.5 and 9.8 in men and 20.2 and 10.9 in women. In other words, the male:female ratio of the observed rates for squamous-cell carcinoma (5.3) was close to that of the 'residual' rates (5.0), while the ratio of the observed rates for adenocarcinoma (2.3)

disappeared (0.9 for the 'residual' rates). Smoking could explain 90% of the squamous-cell carcinoma cases in both men and women but only 79% of male and 46% of female cases with adenocarcinoma.

In a study from Hong Kong reported by Lam, W.K. *et al.* (1983), there were 267 male and 140 female lung cancer cases diagnosed in 1976-1980 with known smoking habits. The 204 male and 189 female controls were the same individuals as in the study of Chan *et al.* (1979). The relative risks in men of different types of lung cancer in relation to the risk among nonsmokers were 6.9 for squamous-cell carcinoma, 10.4 for small-cell carcinoma, 3.2 for large-cell carcinoma and 0.9 for adenocarcinoma. Among women, the relative risks were 6.5 for squamous-cell carcinoma, 8.3 for small-cell carcinoma, 1.1 for large-cell carcinoma and 1.8 for adenocarcinoma.

Auerbach *et al.* (1979) studied autopsy specimens from the bronchi of US men who died in 1955-1960 or 1970-1977. Changes in the bronchial epithelium, such as basal-cell hyperplasia, loss of cilia and occurrence of cells with atypical nuclei, were recorded for smokers and nonsmokers separately. In both periods studied, these histological changes occurred far less frequently in nonsmokers than in cigarette smokers and increased in frequency with amount of smoking, adjusted for age. The frequencies of epithelial changes in each of the smoking categories in 1970-1977 were much lower than those in 1955-1960. [The Working Group noted that, although the changes recorded are not necessarily direct indicators of cancer risk, they illustrate the dose-response effect between smoking and epithelial changes in the bronchi, possibly related to squamous-cell carcinoma, and reduction in the frequency of these changes with time, at least partly attributable to changes in the smoke content and design of the cigarettes consumed.]

In certain populations, the risk of adenocarcinoma is exceptionally high, even when exposure to tobacco smoke has been low and short in duration. These populations include Chinese women in some regions (Law *et al.*, 1976; MacLennan *et al.*, 1977; Gao, 1986). It is possible that in these populations the etiological factors involved are not related to smoking but to other cultural and environmental exposures, e.g., ways of cooking (MacLennan *et al.*, 1977).

There have been some reports that the proportion of adenocarcinoma may be increasing, particularly in Japan (Hanai *et al.*, 1982) and in the USA (Vincent, R.G. *et al.*, 1977). [The Working Group noted that trends in the relative frequency of histological type must be interpreted very cautiously, since, in addition to real increases in incidence, many other reasons, such as changes in the criteria for histological diagnosis, in the diagnostic facilities available and in the extent to which resections are performed, may have an effect on these trends.]

(*c*) *Proportion of risk currently attributable to smoking*

Very few attempts have been made to quantify the proportion of cases of lung cancer attributable to tobacco smoking in well-defined populations (Hammond & Seidman, 1980; Davies, J.M., 1981; Doll & Peto, 1981; US Department of Health and Human Services, 1982).

The number of cases attributable to tobacco smoking in a given population is the number that would have been avoided had the individuals of that population not smoked. The simplest way of counting them is to assume that the risk in smokers would have been that in nonsmokers if the former had never smoked, and to consider that the number of person-years of observation would not have been affected to any meaningful extent by such a change in population behaviour. On the basis of these hypotheses, the number of cases attributable to smoking (AC) can be calculated from:

$$AC = (N \times \lambda) - (N \times \lambda_0)$$

and the attributable proportion (AP) from:

$$AP = \frac{\lambda - \lambda_0}{\lambda}$$

where N, λ, λ_0 are, respectively, the number of person-years of observation, the actual observed rate in the total population and the rate in nonsmokers.

The attributable proportion can also be calculated from case-control studies (Miettinen, 1974; Whittemore, 1983).

In addition to tobacco, various occupational and other factors are known to affect lung cancer risks (Merletti *et al.*, 1984), and others may await discovery. Since little is known about the correlation between smoking and such other factors, some uncertainty will remain in the estimates of the exact risks attributable to tobacco smoking. The uncertainty is not, however, so large as to hinder reasonable estimations in many populations.

The best data for calculating the number of lung cancer cases attributable to smoking would be the nonsmoker rate in each category of confounding variable for a representative sample of the population (Table 68). At present, the most reliable such data are those of the American Cancer Society (ACS) for the nonsmoking population of the USA. Table 68 indicates that this rate applies to other populations. The rates are fairly stable over time (Garfinkel, 1981).

Stevens and Moolgavkar (1984) suggested that there may have been a small decrease in the rate of lung cancer for British nonsmoking men in recent years. This result was obtained by fitting a statistical model to population data, partitioning the observed rate between smokers and nonsmokers as described by their proportion and their consumption by birth cohort. [The Working Group noted that residual artefact of the procedure cannot be completely excluded.]

The mortality rates in nonsmokers by age group are shown in Table 69 and Figure 10. The good linearity of the data suggests that a smoothing of the rate could be used in estimating the attributable number of cases and attributable proportion. The results of a weighted linear regression for re-estimating age-group rates from the ACS study are shown in Table 70.

Since there is no indication of differences in rates in nonsmokers in the various countries for which it has been looked at, one can use the previously estimated rates to calculate the number of lung cancer deaths attributable to tobacco smoking in those countries, using vital statistics and the formulae given above. The results are shown in Table 71 for the last year for which deaths are available from the Global Epidemiological Surveillance and Health Situation Assessment data bank of the WHO. In Canada, the USA and England and Wales

Table 68. Lung cancer mortality in nonsmokers

Study	Reference	Start of study	Length of follow-up (years)	Age range (years)	Person-years in nonsmokers		No. of lung cancer death in nonsmokers		Rate/100 000/year[a]	
					Males	Females	Males	Females	Males	Females
ACS 25-state	Garfinkel (1980, 1981)	1959	12	30+	961 975	3 950 186	189 (195)	503 (564)	19.6 (15.6)	12.7 (13.3)
British Doctors	Doll & Hill (1966)	1951	M; 10 F: 11	20+	54 660	32 075	3	1	<15.9[b]	<17.5[b]
	Doll & Peto (1976); Doll *et al.* (1980)		M: 20 F: 22	20+	NA	NA	7	NA	(10)	(7)
US Veterans	Kahn (1966)	1954	8.5 (up to 1962)	35-84	443 856	-	78	-	17.6[b] (17.1)[b]	-
	Garfinkel (1981)		16		NA	-	168[c]	-	NA	-
Japanese study	Hirayama (1967)	1965	1.25	40+	29 188	148 920	3	9	<29[b]	<11.4[b]
	Hirayama (1975b)		8		NA	NA	NA	NA	(14.8)	NA
	Hirayama (1982)		13		248 155	1 431 798	NA	NA	(20.7)	(15.8)
Swedish study	Cederlöf *et al.* (1975)	1963	10	18-69	63 520	176 790	7	19	11.0[b]	10.7[b]
Canadian study	Lossing *et al.* (1966)	1955-1956	6	30+	398 328	-	7	-	16.6[b]	

[a]Crude or standardized (in parentheses) rates; since the latter are usually standardized internally, they do not allow strict comparison between countries. <, upper limit of two-sided 95% confidence interval

[b]Calculated by the Working Group

[c]78 included in 168

Table 69. Lung cancer mortality (rates per 100 000 per year) in nonsmokers, by age group[a]

Reference	Population	Age group (years)				
		35-44	45-54	55-64	65-74	75+
Garfinkel (1980)[b]	ACS men	4 (1.0-9.7)	5 (3.1-7.8)	14 (9.9-19.3)	27 (29.3-37.7)	60 (36.1-94.4)
	ACS women	1 (0.4-2.1)	4 (3.0-5.2)	9 (7.3-10.9)	17 (13.7-20.8)	38 (28.6-49.9)
Kahn (1966)	American veterans[c]	0 (0-10.5)	0 (0-24.4)	10 (7.6-17.3)	30 (21.2-37.8)	46 (13.0-120.2)
Hirayama (1985)	Japanese men	-	3.5[d] (0.4-12.4)	17.6[d] (10.5-27.9)	43.8[d] (10.5-27.9)	54.9[d] (32.5-86.8)

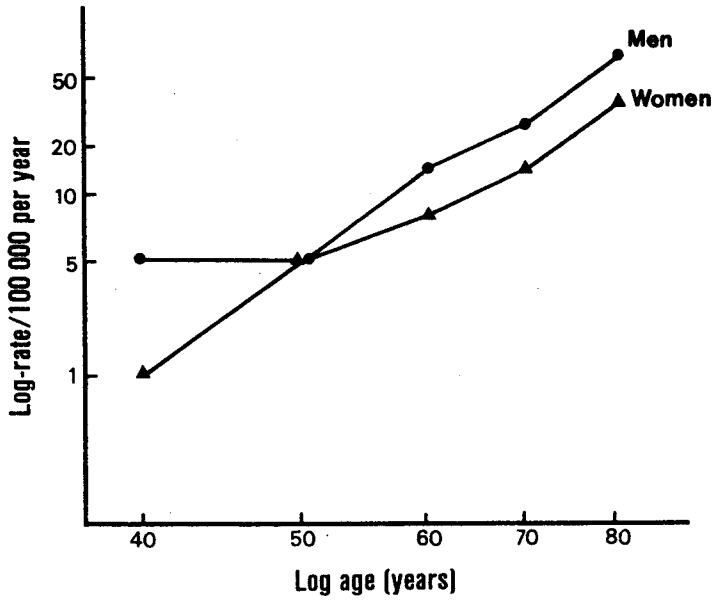
[a]In parentheses, confidence intervals calculated by the Working Group from published rates and person-years

[b]Way in which rates were standardized was not specified, and the numbers of cases by age group were not given.

[c]16-year follow-up rates calculated by Rogot and Murray (1980), but data not given

[d]Calculated by the Working Group

Fig. 10. Lung cancer mortality in nonsmokers, by age[a]



[a]Adapted by the Working Group from Garfinkel (1981)

Table 70. 'Best' estimate[a] of lung cancer mortality rates per 100 000 population per year by age group in nonsmokers

	Age group (years)				
	35-44	45-54	55-64	65-74	75+
Men	2.48	6.23	13.20	25.10	43.50
Women	1.17	3.58	8.92	19.32	37.71

[a]Smoothing the American Cancer Society rate (Garfinkel, 1981) by fitting a linear model on a double logarithmic scale, weighting each of five points according to the corresponding period × years of observations

the results are very similar. In Sweden (Cederlöf *et al.*, 1975), where there is a moderate risk for lung cancer, it is worth comparing the estimate of the attributable proportion with the estimate obtainable directly from the cohort, using percentage of smokers and risk estimates. In men, 6352 out of 25 444 persons who answered the questionnaire were nonsmokers, and the relative risk for smokers was 7. From these figures, an attributable proportion equal to 82% can be calculated. In women, 17 679 out of 26 467 persons who answered were nonsmokers, and the risk for smokers was 4.5, giving an attributable

Table 71. Lung cancer deaths attributable to tobacco smoking in certain countries

Country	Year	No. of deaths[a]	Expected deaths in nonsmokers[b]	Crude rate in persons aged 35+		AC[c]	AP[d]
				Observed	In non-smokers		
Canada							
Men	1978	6 435	556	142.8	11.8	5 762	0.9
Women	1978	1 681	487	34.0	9.9	1 194	0.71
England & Wales							
Men	1981	26 297	1 576	228.5	13.3	24 720	0.94
Women	1981	8 430	1 663	63.3	12.4	6 767	0.80
Japan							
Men	1981	16 638	2 868	64.8	10.7	13 184	0.83
Women	1981	6 161	2 593	21.0	8.9	3 568	0.58
Sweden							
Men	1981	1 777	301	85.0	14.0	1 476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72 803	5 778	166.7	12.7	67 024	0.92
Women	1979	25 648	5 736	50.0	11.1	19 912	0.78

[a]From Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO

[b]Rate given in Table 70 extrapolated down to 20 and 30 years for calculating rate in age groups 0-24 and 25-34 years. This procedure slightly overestimates the number of expected deaths.

[c]AC, number of cases attributable to smoking

[d]AP, proportion of cases attributable to smoking

proportion equal to 54%. [These figures are remarkably close to that obtained from applying the smoothed ACS rate to the Swedish population, and it suggests that the method could also be used for many of the countries not listed in Table 71, but perhaps not for those with substantial Chinese populations; see pp. 234-235.]

In France, a large hospital-based case-control study conducted between 1976 and 1980 mainly in the Paris area assembled 1217 cases of histologically confirmed lung cancer cases of Kreyberg Groups I and II. Among 1098 cases of the first group, 24 were in nonsmokers, and the relative risk for smoking was 17.2. Of the 119 cases of the second histological type, nine were in nonsmokers and the relative risk was 3.6 for smoking (Benhamou *et al.*, 1985). [Attributable proportions of 96% and 66%, respectively, can be calculated, giving an attributable proportion of 89% for lung cancer of any type. Using the ACS rate, one can calculate that 14 019 male lung cancer deaths out of the 15 635 observed in the French population in 1981 were due to smoking, giving an attributable proportion of 90%, a figure

again in remarkable agreement with that obtained from the case-control study. The low figure of 17% obtained for women is a composite of very different rates for different age groups; e.g., 40% in 45-54-year-old women and 3% in 75+-year-old women. It would, however, be unwise to use this (ACS-based) method for some populations; for example, in some heavily occupationally exposed populations, the rate for nonsmokers may be higher than that in the ACS study.]

In Italy, a population-based case-control study was conducted in the Lombardy region, which is covered by a cancer registry (Berrino *et al.*, 1982). Among the 204 male cases reported in the analysis, 194 were in smokers; and the relative risk for smoking, adjusted for occupational exposure, was found to be 7.1. An attributable proportion of 81% was due to smoking (Pastorino *et al.*, 1984). [The ACS-based method for the whole male Italian population would give 89% for 1979. Although the difference between these two figures is not statistically significant, the existence of a real difference cannot be excluded.]

Attributable risks reported in one part of Japan by Hirayama (1982) were 69% and 13% for men and women, respectively, over the period 1965-1978. [The proportions calculated using the ACS-based method for the whole of Japan in 1981, i.e., about ten years later, are 83% in men and 58% in women.]

Data for estimating attributable proportions are available for only a few other countries. For example, in Havana, Cuba, a case-control study was conducted between 1978 and 1980 (Joly, O.G. *et al.*, 1983), including all incident cases, one hospital control and one neighbourhood control per case; 595 of the 607 men were smokers, and a relative risk of 12.4 was reported. [An attributable proportion of 90% can thus be calculated.] Among the 219 female cases, 167 were in smokers, and a relative risk of 5.1 was reported [giving an attributable proportion of 61%].

In Bombay, India, a hospital-based case-control study was conducted between 1963 and 1970 (Notani & Sanghvi, 1974). The study participants were matched for sex, community and age, but the results are reported for the two sexes combined. [It is thus impossible to calculate attributable proportions in men and women separately. Since 80% of the cases were in smokers and the relative risk was 2.5, however, the attributable proportion would be somewhat lower (about 50%) than those calculated in Table 71.] Jussawalla and Jain (1979) later reported a much higher relative risk (16.8) for male smokers in the same town. In the latter study, 43% of the male incident cases were compared to a random sample of Bombay residents taken from the voters' list. The proportions of smokers in cases and controls were 81% and 21%, respectively. [If the cases interviewed are a representative sample of cases arising in this population, in which 21% of individuals are smokers, the proportion of male cases attributable to smoking (either *bidis* or cigarettes) would be about 75%, a fairly high proportion in view of the low observed lung cancer rate found in Bombay (truncated rate of 22.6 in men; Waterhouse *et al.*, 1982).]

A hospital-based case-control study was conducted in Singapore between January 1972 and June 1973, including 147 male Chinese lung cancer cases, of whom 142 were smokers. A relative risk of 3.8 for smoking was reported. In women, 21/39 Cantonese lung cancer cases and 21/44 non-Cantonese lung cancer cases were in smokers; relative risks of 1.6 and 3.6, respectively, were calculated. Despite the small number of cases, it is clear that tobacco

smoking explains very little of the relatively high rate of lung cancer in Cantonese women. In this study, a relatively high proportion of adenocarcinomas was found (30% in 54 Cantonese female cases for whom histological typing was possible), and this tendency could explain the result (MacLennan *et al.*, 1977). A similar study was carried out in Hong Kong (Chan *et al.*, 1979). Two histological groups were examined separately: squamous-cell carcinoma + small-cell carcinoma and adenocarcinoma + large-cell carcinoma; relative risks of 3.9 and 1.6 were found for female current smokers, with proportions of 30% and 59%, respectively, of nonsmokers among female cases. In Los Angeles County, USA, Shimizu *et al.* (1982) found that only 46% of female adenocarcinomas were due to smoking; they also reported a high rate of adenocarcinomas in Chinese women in that county.

Hinds, M.W. *et al.* (1981) compared the smoking histories of 375 female lung cancer cases obtained from medical records between 1968 and 1978 in Hawaii with that of 2404 sex- and race-matched controls. After controlling for socioeconomic status, very different relative risks for smoking were found according to ethnic origin (10.5 for Hawaiians, 4.9 for Japanese, 1.8 for Chinese). This finding is largely explained by the proportion of adenocarcinomas in each group. Using the above relative risk estimate, the authors calculated attributable proportions of 79%, 44% and 11%, respectively, for the three ethnic groups. The incidence was greater, however, in Chinese than in Japanese women.

[Attributable proportions must be interpreted with caution. If an attributable proportion is 90%, it does not mean that, if smoking is given up tomorrow, 90% of lung cancer deaths will be eliminated immediately; this will happen only in the course of time. The calculated proportion applies to a population as a whole and cannot be extrapolated to smaller populations among which an occupational hazard exists. Low attributable proportions may be interpreted differently and should be examined in conjunction with incidence rates. Because of the combined effect of smoking and occupational exposure, a figure of 90% for tobacco smoking does not imply that the effect of an occupation is less than 10%; nor does it mean that an occupationally exposed smoker with lung cancer has a 90% probability that the cancer was caused by smoking.]

(*d*) *Trends in lung cancer incidence in relation to cigarette usage*

(i) *Introduction*

In the world as a whole, the overall pattern for lung cancer is one of rapid increase. About 600 000 new cases of the disease were estimated for 1975 (Parkin *et al.*, 1984), and this number will have increased since then. Three factors contribute to this continuing increase. First, especially in old people, increased access to diagnosis and progressive improvements in the accuracy of certification of cause of death mean that an increasing proportion of fatal lung cancers are recognized as such (Waterhouse *et al.*, 1976; Doll & Peto, 1981). Second, the absolute size of the world population of adults old enough to be at risk of developing the disease is increasing rapidly. Finally, and most importantly, large increases in the numbers of people smoking cigarettes have produced — and are producing — large, real increases in age-specific lung cancer rates (Doll & Peto, 1981).

Indeed, although lung cancer is believed to be the commonest fatal neoplastic disease in the world today (on the basis of knowledge of the worldwide trends of lung and stomach cancer and the data of Parkin *et al.*, 1984), most of the increase that has thus far materialized has been the delayed result of increases in cigarette smoking by young adults that took place in the first half of this century (US Deparment of Health and Human Services, 1982). Little has yet been seen of the increase in lung cancer rates that will be produced over the next few decades as a delayed result of the large increases in cigarette smoking by young adults that have been (and still are) taking place during the second half of the century, not only in the developed but also, now, in the developing world (Royal College of Physicians, 1983). [Reliable predictions are not yet available, but it is plausible that by the year 2000 the 1975 total of 600 000 lung cancer deaths a year worldwide will have increased to about two million, the large majority of which will be due to tobacco.]

Rather than present tabulations of past and present lung cancer rates in many countries, the Working Group chose to present (after a review of some general methodological considerations) the patterns of increase for six countries — five developed and one developing — selected to illustrate different types of evolution of the disease onset rates.

The first two (Finland and the UK) are countries where cigarette smoking by young men appears to have become widespread in the first quarter of the century and increased slowly up to 1975 (Lee, P.N., 1976). In the UK, extensive changes to cigarettes that lowered 'tar' yields were implemented in the third quarter (Lee, P.N., 1976; Wald *et al.*, 1981a). Consequently, any effects that these changes in cigarette composition may have on lung cancer can be assessed against a background rate of lung cancer that had, at least in early middle age, already approximately stabilized (at a very high level) (Doll & Peto, 1981; Teppo, 1984).

The third (the USA) is a country where cigarette smoking by men increased substantially in the second quarter of the century (Lee, P.N., 1975), and where 'tar'-level reductions were also implemented in the third quarter (US Department of Health and Human Services, 1982). Consequently, any effects of these reductions on lung cancer rates have to be assessed against a background of the rapid rises in lung cancer produced by the delayed effects of the earlier increase in cigarette usage (Doll & Peto, 1981).

An example of a country where smoking by women became common only in the third quarter of the century is France (Hill, C. & Flamant, 1986). The large increases in lung cancer that this will eventually produce have not yet really begun to materialize, as discussed on p. 213.

The fifth example, the USSR, differs not so much in timing but in 'tar' trends. The USSR is a country where cigarette smoking by young men appears to have become widespread during the first half of the century [Actual data were not available to the Working Group.], but where 'tar' levels still remain much higher than they currently are in the first three countries (see Table 10, p. 64), and where the absolute lung cancer rates in early middle age appear to be remaining as high as those in the UK before 'tar' levels were reduced (Napalkov *et al.*, 1983).

The final example presented in this section is a city (Shanghai, China) in a developing country, which is unusual among developing parts of the world in that cigarette consumption among men has been widespread for many decades (see Table 13, p. 69), and in which 'tar levels' remain high (see Table 10, p. 64). Once due allowance has been made for various methodological problems in assessing rates and trends in developing parts of the world (Waterhouse *et al.*, 1976), the high lung cancer rates in Shanghai (Shanghai Cancer Institute, Shanghai Sanitary Antiepidemic Centre, 1982) illustrate what can be expected elsewhere in China — and, indeed in other developing countries — when the delayed health effects materialize of the large changes in cigarette consumption that have already taken place in many such areas.

(ii) *Methodology*

(1) *Sources of data on history of cigarette usage.* In developed countries, where cigarette sales are monitored quite closely, data on actual cigarette sales per head (Lee, P.N., 1975) are usually reasonably reliable. Data from questionnaires on the proportion of smokers or on the total numbers of cigarettes smoked may be biased, as antismoking propaganda may have a larger effect on people's self-reported smoking than on their actual smoking, as seen by recent divergences between the trends in self-reported smoking and sales in the USA (Warner, 1978) and France (Hill, C. & Flamant, 1986).

(2) *Assessment of separate age-specific trends.* Throughout this section, 'age' is used to mean age in years, while 'time' is used to mean calendar year. 'Age' is conventionally divided into five-year age groups (10 for the USSR), but, because lung cancer is so rare in childhood and early adult life, the present analyses are of lung cancer trends only at ages 30-34 and upwards (to 80-84 and finally 85+ — a total of 12 different age groups). When, in one country, the trends in certain age groups are downwards but those in certain others are upwards, these are examined separately.

(3) *Miscertification of cause of death.* Due to errors in death certification procedures, lung cancer rates derived from death certificates may not reflect the true lung cancer death rate, particularly in old people, and progressive rectification can cause large, purely artefactual increases in the age-specific death certification rates in older age groups (Doll & Peto, 1981). Such artefactual errors were large in all people of all ages, even in developed countries, during the first half of the century and may still be so in many developing countries. Since 1950, however, such increases may have been important in most developed countries only for old people.

(4) *Misregistration of incident cases.* Related problems may also affect the use of lung cancer incidence rates to assess the real trends in disease onset rates: discrepancies between the two may exist, due generally to progressive improvement in disease registration techniques. Nevertheless, for certain areas, only incidence trends are usable, either because mortality trends are unavailable or because they are completely unreliable (Doll & Peto, 1981).

(iii) *Effects of nationwide adoption of cigarette usage*

Cigarettes cause a far greater risk of lung cancer than other forms of tobacco do. So, when a nation adopts widespread cigarette usage, large, real increases in lung cancer rates

will eventually follow, whether the switch is from no tobacco use to cigarettes or from use of other forms of tobacco to cigarettes. These large increases in lung cancer rates may, however, appear many decades after the large increases in cigarette usage, because it is those who start to smoke in early adult life who are at greatest risk in middle and old age (Doll & Peto, 1981). Thirty years separate the late teenage years from the age range 45-49, while 60 years separate the late teenage years from the age range 75-79. For 30 years after cigarette smoking among teenagers finally becomes maximal, lung cancer rates in people aged 45-49 may continue to rise. Thereafter, they will, other things being equal, become stable, while lung cancer rates in people of the age range 65-69 may continue to rise for another 20 years before they too stabilize. Hence, it will probably not be until about 20, 30, 40, 50 and 60 years after cigarette smoking in people in their late teens or early twenties approaches a maximum that lung cancer rates in people aged 35-39, 45-49, 55-59, 65-69 and 75-79 can be expected to do so.

This possibility is exemplified by UK male lung cancer death certification rates (Table 72). Those rates in italics are for men born in about 1900 and are approximately maximal. The general pattern in each age group is one of sharp increases preceding this maximum, followed by an approximate stability that is disturbed only by the recent decreases that have begun to take place in early middle age. These decreases were examined in more detail on pp. 210-212, where they were attributed to changes in 'tar' delivery per cigarette.

Similar decreases are beginning to emerge in Finland (Fig. 11), where 'tar' levels have probably decreased slightly more sharply than in the UK, due in part to progressive abandonment of the 'Russian-style' *papirossi* cigarettes that used to be favoured in Finland (Lee, P.N., 1975). Due to the use of a log scale, the decreases over the past 15 years (i.e., 1963-1978) at ages 45-49, 40-44 and 35-39 may not look important, yet they would, respectively, represent avoidance of about 31%, 41% and 53% of the lung cancer deaths at these ages in 1963. Except for a temporary decrease during the Second World War, cigarette consumption per Finnish adult has been fairly steady for more than 50 years, averaging about four/day and five/day, respectively, in the second and third quarters of the present century (Lee, P.N., 1975).

It is interesting to contrast these figures from countries where substantial changes in cigarette composition have occurred with the corresponding figures from a country such as the USSR, where they have not (Table 73). In the USSR, typical 'tar' deliveries per cigarette are still about 20-30 mg (see Table 10, p. 64), with a mean of about 25 mg. This is nearly as high as the 'tar' deliveries of UK and US cigarettes in the 1950s, before they were halved, together with other changes in cigarette design and smoke composition (Wald *et al.*, 1981a; US Department of Health and Human Services, 1982), and it may be noteworthy that the USSR lung cancer incidence rates in middle age (Table 73) appear to be converging towards the high UK lung cancer rates of the 1950s and not towards the lower rates that now obtain in both the UK (Table 72) and Finland (Fig. 11).

The increases between 1960 and 1970 of about 50% (Table 73), suggested by the incidence data, are larger than the corresponding increases suggested by the mortality data — indeed, the crude male lung cancer death certification rate rose by only about 25% between 1961 and 1970 in the USSR (Cooper, 1982). Recent mortality data are not available, but there was by 1970 a reasonable correspondence between the mortality and the incidence data (Napalkov *et al.*, 1983), so the recent incidence data (Table 73) may suffice.

Table 72. Annual number of death certifications from respiratory cancer (per 100 000) in UK men, 1943-1983 (average of five years around each date)[a]

Age range (years)	1943[b]	1953[c]	1963[d]	1973[e]	1983[f]
30-34	4	4	3	2	1
40-44	*20*[g]	25	22	18	12
50-54	63	*123*	122	107	77
60-64	107	258	*367*	354	299
70-74	80	265	497	*678*	640
80-84	-[h]	144	342	602	*834*
No. of cigarettes/man per day in preceding year	10.7	9.9	10.6	10.6	7.1

[a]Calculated by the Working Group from Office of Population Censuses (1975, 1980a,b,c, 1982, 1983b, 1984a,b,c,d, 1985a) (see footnote *a* to Table 59)

[b]ICD5 47b

[c]ICD6 162-164

[d]ICD7 162-164

[e]ICD8 162, 163

[f]ICD9 162-165

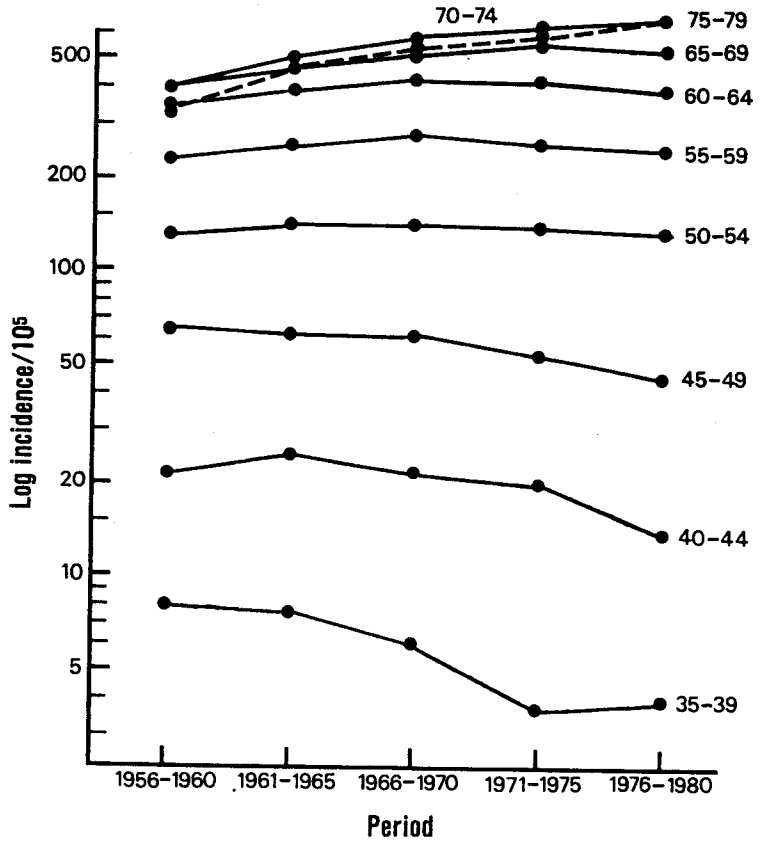
[g]Figures in italics, rates for men born in about 1900

[h]Subject to gross undercertification

If the hypothesis is true that 'tar' level decreases and other changes in cigarette design and smoke composition are largely responsible for the recent decreases in lung cancer mortality among people in early middle age in the UK and Finland (see Table 72 and Fig. 11), then it may be asked why corresponding decreases are not seen in other countries. They may, however, be occurring but being swamped by the large increases in lung cancer mortality due to the delayed effects of past changes in cigarette usage (Doll & Peto, 1981; Peto & Doll, 1984). Finland and the UK provide an opportunity to observe the effects of 'tar' level changes because they are probably the only two countries in the world (Lee, P.N., 1975) where cigarette smoking by young adults became established so long ago that the lung cancer rates in early middle age had stabilized by the late 1950s, i.e., before the large 'tar' level reductions began.

In the USA (Table 74), cigarette sales increased between the First and Second World Wars from two (in 1920) up to five (in 1939) cigarettes per adult per day; during the Second World War, the number doubled and has remained thereafter at 10-12 per adult per day (US Department of Agriculture, 1965; Lee, P.N., 1975). A delayed effect of this large increase in cigarette usage was the large increases in male lung cancer death rates that took place throughout the 1950s and 1960s, the maximal rate in any age group being seen among those

Fig. 11. Lung cancer incidence in Finnish men, 1956-1980[a]



[a]From Finnish Cancer Registry (1963-1983)

Table 73. Annual lung cancer incidence registration rates per 100 000 men in the USSR 1960-1980[a] compared with corresponding rates in the UK, 1958[b] and 1983[c]

Age range (years)	USSR Incidence					England & Wales Mortality × 1.1[d]	
	1960	1965	1970	1975	1980	1958	1983
30-39	3	5	6	7	6	7	3
40-49	24	29	35	46	47	47	24
50-59	85	127	142	153	176	197	136

[a]From Napalkov *et al.* (1980, 1982); incidence data for 1960 are published for people aged 60 years and over, without subdivision

[b]From Doll and Peto (1981)

[c]From Office of Population Censuses and Surveys (1984b)

[d]By 1958, UK mortality rates at ages 30-59 had reached their maxima and had stabilized. Rates for 10-year age groups are estimated as averages of the rates for the two corresponding five-year age groups. Multiplication by 1.1 provides an approximate estimate of the ratio of incidence to mortality (Waterhouse *et al.*, 1976, 1982).

who reached adulthood in the late 1940s. Thus, at ages 30-34, 35-39, 40-44 and 45-49, the maximal lung cancer rate has been reached (Doll & Peto, 1981); and at 50-54 it should recently have been reached (Table 74). Within each age group, the large increases before the maxima are clearly seen; in addition, however, there does appear to be a slight decrease after the maximum is attained (especially at ages 30-34).

Table 74. Annual number of deaths from respiratory cancer (per 100 000) among US men, 1940-1980[a]

Age range (years)	1940	1950	1960	1970	1980[b]
30-34	1.5	1.7	*2.4*[c]	2.1	1.1
40-44	7	11	15	*22*	17
50-54	24	47	67	87	*91*
60-64	41	97	166	225	236
70-74	38	103	211	355	422
80-84	30	77	152	291	460
Actual period studied	1938-1942	1948-1952	1958-1962	1968-1972	1978-1981
No. of cigarette/adult per day in preceding year[d]	5	9	10	10	11[e]

[a]From Doll and Peto (1981), except where otherwise stated

[b]From Horm *et al.* (1984)

[c]Figures in italics, rates for men born in about 1920

[d]From Lee, P.N. (1975)

[e]From Peto and Doll (1984)

Shanghai was, before the establishment of the People's Republic of China in 1949, one of the larger oriental markets for western cigarette manufacturers, and still about half the men in Shanghai smoke cigarettes, the 'tar' levels in many of which appear to be 'very high' (Gao, 1986; see Table 10, p. 64). Men in the municipal area of Shanghai had, in the early 1970s, lung cancer rates that were the highest of any municipal area or province in China (Li *et al.*, 1979); and, indeed, they exceed the absolute rates seen in many developed countries (Table 75).

Comparison of the earlier with the more recent figures (Table 75 and Shanghai Cancer Institute, Shanghai Sanitary Antiepidemic Centre, 1982) suggests the age dependence of the trends. Very few middle-aged or older women in Shanghai have smoked cigarettes regularly for any substantial length of time, and no clear trend in the age-specific lung cancer incidence rates among women aged 30-54 is seen. Among women aged 55-64, however, a moderate upward trend is apparent, while among older women a vast upward 'trend' is in progress. [In principle, real increases could be in progress only in old age, but the lack of any

Table 75. Trends in lung cancer incidence rates in Shanghai city, 1963-1965 to 1972-1979[a]

Age (years)	Men			Women		
	1963-1965	1972-1979	Increase (%)	1963-1965	1972-1979	Increase (%)
30-	2	2	31	2	2	7
35-	4	5		2	4	
40-	11	14		7	7	
45-	24	32		13	12	
50-	51	75	45	26	27	4
55-	98	157	60	38	45	16
60-	157	272	73	62	82	31
65	177	391	121	61	125	105
70-	210	475	126	65	155	138
75-	213	436	104	74	153	107
80-	141	375	~150	38	138	~200
85+		334			108	

[a]Shanghai Cancer Registry (1970); Shanghai Cancer Institute, Shanghai Sanitary Antiepidemic Centre (1982)

trend in early middle age (and the lack of much tobacco use among Shanghai women) suggests that there may be no real trend at any age, and that apparent female trends are due to changes in diagnostic practices, especially in old people.] In contrast, there does seem to be a substantial trend in lung cancer onset rates in men in early middle age in Shanghai. [The Working Group considered that the lack of any such trend among women of comparable age makes it plausible that this trend among men in early middle age is mostly real. However, the trends among older women suggest that much of the upward trend in lung cancer in older men may also be artefactual.] The current rates in middle-aged men in Shanghai (Table 75) are already similar to those in the UK (Table 72), but the rates in old men are much lower in Shanghai. [The Working Group noted that this may reflect the slowness with which the effects of smoking (or whatever other causes underly the increase among men in early middle age) extend themselves into old age. In either case, the rates recorded in old age will probably continue to rise at least throughout this century.]

(*e*) *Summary*

Lung cancer is believed now to be the commonest fatal neoplastic disease in the world, and rapid increases in its incidence are still in progress in many developed and developing countries. Tobacco smoking causes most cases of lung cancer, and where prolonged cigarette smoking is widespread the habit generally accounts for more than 80% of the disease. In populations in which the effect of smoking has not yet reached its peak —including most female populations — the proportion may be lower.

The three principal types of lung cancer are squamous-cell, small-cell and adenocarcinoma. All of these types are caused by smoking, although the relative risk is least extreme for adenocarcinoma.

The observed incidence of lung cancer may depend on four factors:

(i) *The daily dose of tobacco*

It is consistently found that, among otherwise similar cigarette smokers, there is a direct relationship between the daily dose and the excess risk of lung cancer in both men and women. The observed relationship is, in many studies, one of approximate linear proportionality.

(ii) *The duration of regular smoking*

Because damage to the lung accumulates with continuous smoking, the incidence of lung cancer depends strongly on the duration of smoking. So,

(1) those who start to smoke in adolescence and continue to smoke are at the greatest risk of developing lung cancer in adult life;

(2) there is a delay of several decades between the widespread adoption of cigarette smoking by young adults and emergence of the full effects on national lung cancer rates;

(3) even among people who have been smoking for many years, those who have not already developed lung cancer (or some other disease) can, by ceasing to smoke, avoid most of their subsequent lifelong risk of tobacco-induced lung cancer.

(iii) *The form in which tobacco is smoked (cigarettes, cigars, pipes and* bidis*)*

It is generally found that, among otherwise similar smokers, those who have used only cigarettes have lung cancer risks much higher than those who have used only pipes and/or cigars, although the latter materials do cause some appreciable risk.

In large parts of Asia, the chief form in which tobacco is smoked is the *bidi*, and there is evidence that regular use of *bidis* also increases the risk for lung cancer.

(iv) *The type of cigarette*

Soon after the lung cancer risks from smoking, especially of cigarettes, were first established during the 1950s, substantial modifications of cigarette manufacture were introduced in some countries. At present, only about 20 years after their introduction, no direct comparison of the health effects of lifelong use of modified and unmodified cigarettes is possible, but:

(1) In one large cohort study, cigarettes delivering less than 17.6 mg 'tar' were associated with a lower lung cancer risk than were those delivering more than 25.7 mg 'tar'. In other epidemiological studies — mostly case-control — there was a fairly consistent tendency for lung cancer risks to be lower among users of filter than of nonfilter cigarettes. The reduction in the largest and most recent such study was about 40-50%, which was highly significant; in that study, 'tar' yields were also recorded and were positively associated with lung cancer risk.

(2) In a few countries where changes in cigarette design and composition began to be made in the late 1950s or early 1960s, cigarette smoking by young men had been established so many years previously that some of the lung cancer rates in men in early middle age had largely or wholly completed their rise by 1960, and might have been expected to remain

approximately constant thereafter if the risk per cigarette had remained constant. A few years after the changes in cigarettes (associated with reductions in 'tar' levels) became substantial, however, substantial decreases in lung cancer rates began to appear in these particular age groups, without a corresponding reduction in the number of cigarettes smoked.

3. Cancer of the urinary tract

(*a*) *Geographic and temporal correlation studies*

(i) *Lower urinary tract*

Lea (1966), on the assumption that death rates from cancer of the bladder are correlated with death rates from cancer of the lung if these two neoplasms are both related to cigarette smoking, compared such rates in 20 countries. The correlation coefficient (0.6) was highly statistically significant for males but not for females. Fraumeni (1968) compared variation in bladder cancer mortality between men and women in the USA with the per-caput cigarette sales, estimated from tax revenues; a correlation coefficient of 0.73 was found and persisted when adjusted for urbanization. Hoover and Cole (1971) examined trends in smoking habits and bladder cancer incidence or mortality for successive birth cohorts in the USA, Denmark, and England and Wales; an association, consistent in both sexes, was found between increase in smoking and increased occurrence of the disease. Similarly, Armstrong and Doll (1974) attributed an increase in bladder cancer mortality rates in UK male cohorts born since 1870 to an increase in cigarette smoking since 1890. A cohort analysis of bladder cancer mortality (1951-1970) in England and Wales in relation to cigarette consumption has been reported by Stevens and Moolgavkar (1979); the relative risk due to smoking of 20 cigarettes/day for 20 years was estimated to be around 3.0. The same estimate has been obtained from an extension of the analysis to 1941-1970 (Moolgavkar & Stevens, 1981).

(ii) *Kidney*

Fraumeni (1968) also reported a correlation coefficient of 0.49 between cigarette consumption and kidney cancer mortality in the USA, independent of level of urbanization.

(*b*) *Analytical studies*

(i) *Study designs*

Cohort studies on smokers have been reported from the UK (Doll & Hill, 1964a,b; Doll & Peto, 1976; Doll *et al.*, 1980), the USA (Hammond & Horn, 1958a,b; Hammond, 1966; Kahn, 1966; Weir & Dunn, 1970; Hammond & Seidman, 1980; Rogot & Murray, 1980), Canada (Lossing *et al.*, 1966), Japan (Hirayama, 1967, 1975a,b, 1977, 1985) and Sweden (Cederlöf *et al.*, 1975). The design of these studies is described on pp. 199-203.

The study designs of available case-control investigations are summarized in Table 76.

Table 76. Case-control studies on smoking and urinary-tract cancer: main characteristics of study design

Reference (place and years of study)	Numbers of cases and controls	Criteria of eligibility and comments
Lower urinary tract		
Lilienfeld *et al.* (1956) (USA, 1945-1955)	Men: 321 cases and 663 controls; women: 118 cases and 1205 controls	Hospital-based study; male controls: 287 prostate cancers, 39 benign bladder conditions and 337 healthy men; women: 776 breast cancers, 110 benign bladder conditions and 319 healthy women
Lockwood (1961) (Denmark, 1956-)	Men: 282 cases and 282 controls; women: 87 cases and 87 controls	Population-based study; living cases from the Danish Cancer Registry (1956-1957); controls selected from Population Registry
Schwartz *et al.* (1961) (France, 1954-)	Men: 214 cases and 214 controls	Hospital-based study; age-matched controls were subjects admitted to hospitals for accidents
Wynder *et al.* (1963a) (USA, 1960-1961)	Men: 300 cases and 300 controls; women: 70 cases and 70 controls	Hospital-based study; sex- and age-matched controls; papillomas excluded; controls: cancers of respiratory system, upper alimentary tract and myocardial infarction excluded
Cobb & Ansell (1965) (USA, 1951-1961)	Men and women: 136 cases and 342 controls	Hospital-based study; 120 colon cancer controls + 222 controls with 'pulmonary problems'; data on smoking available for 131
Staszewski (1966) (Poland, 1958-1964)	Men: 150 cases and 750 controls	Hospital-based study; age-matched controls with cancer or other diseases
Dunham *et al.* (1968) (USA, 1958-1964)	Men: 334 cases and 350 controls; women: 159 cases and 177 controls	402 incidence cases in New Orleans and 91 prevalent cases or cases not living in the city; hospital controls, including unspecified numbers of bronchitis, emphysema, mycocardial infarction; 162 (29%) of eligible cases not interviewed
Anthony & Thomas (1970) (UK, 1958-1967)	Men: 381 cases and 275 controls	Hospital-based study; surgical controls (excluding chest, genitourinary and malignant disease) in 1955-1958
Cole *et al.* (1971) (USA, 1967-1968)	Men: 360 cases and 381 controls; women: 108 cases and 117 controls	Cases randomly selected among all (668) eligible incident cases occurring in 1967-1968 in 87 cities of the Boston area (20-89-years old); controls: random sample of 20-89-year-old residents, matched for sex and age; interviews of 140/470 cases and 78/500 controls obtained from spouse or next-of-kin

Table 76 (contd)

Reference (place and years of study)	Numbers of cases and controls	Criteria of eligibility and comments
Tyrrell *et al.* (1971) (Ireland, 1967-1968)	Men: 200 cases and 200 controls; women: 50 cases and 50 controls	Hospital-based study; age- and sex-matched urological controls
Makhyoun (1974) (Egypt, 1966-1971)	Men: 365 cases and 365 controls	Hospital-based study; age-matched non-cancer controls; 278 cases and 278 matched controls had previous urinary bilharziasis
Morgan & Jain (1974) (Canada)	Men: 158 cases and 158 controls; women: 74 cases and 74 controls	Hospital-based study; controls matched for sex and age; postal questionnaires: responses were 67% (cases) and 57% (controls) among men; 73% (cases) and 57% (controls) among women
Schmauz & Cole (1974) (USA)	Men: 18 cases renal pelvis and ureter cancer (1:8) and 376 controls	Population-based study of cancer of the renal pelvis and ureter (see Cole *et al.*, 1971, for design)
Wynder & Goldsmith (1977) (USA, 1969-1974)	Men: 574 cases and 574 controls; women: 158 cases and 158 controls	Hospital-based study on 40-80+-year-old cases and sex-, ethnic group-, hospital- and age-matched controls; controls had no 'tobacco-related condition'
Miller, C.T. *et al.* (1978) (Canada)	Men: 188 cases and 564 controls; women: 77 cases and 231 controls	Hospital-based study; two sex- and age-matched controls (only subjects over 40 years) for each case; self-completed questionnaires
Sadeghi *et al.* (1979) (Iran, 1969-1976)	Men: 88 cases and 88 controls	Hospital-based study; sex- and age-matched hospital controls excluding cancer, pulmonary and bladder disease (23/122 cases discarded due to poor information)
Howe *et al.* (1980) (Canada, 1974-1976)	Men: 480 cases and 480 controls; women: 152 cases and 152 controls	Population-based study; eligible cases: all patients with newly diagnosed bladder cancer in 3 Canadian provinces (77% interviewed); controls matched for sex, age and neighbourhood (refusals were 20%, 4% and none in the 3 provinces; refusing controls were substituted); male cases had higher education and income than controls
Tola *et al.* (1980) (Finland, 1975-1976)	Men: 134 cases and 134 controls; women: 46 cases and 46 controls	Originally eligible cases were all (274) those reported to the Finnish Cancer Registry for 5 Finnish provinces; postal questionnaires sent to 269 cases and 271 sex- and age-matched hospital controls or their relatives; responses were 80% (cases) and 81% (controls); source of information was a relative for 39% (cases) and 12% (controls)

Table 76 (contd)

Reference (place and years of study)	Numbers of cases and controls	Criteria of eligibility and comments
McCredie *et al.* (1982) (Australia, 1977-1980)	Men: 27 cases and 70 controls; women: 40 cases and 110 controls	Cancer registry and hospital-based study; renal pelvis cancer cases; friends or relatives of other patients (1st control group), plus additional controls attending a screening clinic (2nd control group); 37% of cases and 16% of controls interviewed at home; 24 cases and no controls interviewed by their doctors; higher socio-economic status among screening clinic controls
Najem *et al.* (1982) (USA, 1978)	Men: 65 cases and 123 controls; women: 10 cases and 19 controls	Hospital-based study; prevalent cases only; 2 controls per case matched for sex, age, ethnic group, place of birth and place of residence (cancer and tobacco-related heart disease excluded)
Cartwright *et al.* (1983) (UK, 1978-1981)	Men: 932 cases and 1402 controls; women: 327 cases and 579 controls	90% of incidence cases in West Yorkshire (1978-1981) and prevalent cases included; sex- and age-matched hospital controls (25% arterial disease; 60% accident, minor surgery; 10% chest conditions)
McCredie *et al.* (1983) (Australia, 1977-1982 [ureter], 1980-1982 [renal pelvis])	Men: 36 (ureter) and 29 (pelvis) cases; 307 controls	Population-based (cancer registry) study; cancers of the ureter and renal pelvis only; controls were a random sample of the general population; questionnaires mailed to cases and controls (no. of non-respondents not given); higher educational level among controls
McLaughlin *et al.* (1983) (USA, 1974-1979)	Men: 50 cases and 428 controls; women: 24 cases and 269 controls	Population-based study on cancer of the renal pelvis (71/74 were transitional-cell carcinomas); controls were (1) a random sample of the general population and (2) a group of deceased individuals matched to the deceased cases
Møller-Jensen *et al.* (1983) (Denmark, 1979-1981)	Men: 286 cases and 574 controls; women: 95 cases and 193 controls	Cases, 2/3 of all incident cases in Greater Copenhagen (under age 75); controls, a random sample of the general population (out of 1052 controls approached, 109 refused, 114 were not located and 39 were too ill)
Mommsen & Aagaard (1983) (Denmark, 1977-1979 [men], 1977-1980 [women])	Men: 165 cases and 165 controls; women: 47 cases and 94 controls	Population-based study; controls: random sample of general population; cases interviewed at hospital, controls by phone

Table 76 (contd)

Reference (place and years of study)	Numbers of cases and controls	Criteria of eligibility and comments
Morrison *et al.* (1984) (UK and Japan, 1976-1978; USA, 1976-1977)	Men: Greater Manchester, 398 cases and 490 controls; Nagoya (Japan), 224 cases and 442 controls; Boston area, 427 cases and 391 controls Women: Greater Manchester, 155 cases and 241 controls; Nagoya, 66 cases and 146 controls; Boston area, 165 cases and 142 controls	Population-based study in USA, Japan, UK; 96% (Manchester), 84% (Nagoya) and 81% (Boston) of all incident cases (aged 21-89) were interviewed; controls were randomly selected from electoral registers; in Nagoya most cases were interviewed in hospital, all other groups at home; 95% of tumours were of the bladder
Vineis *et al.* (1984) (Italy, 1978-1983)	Men: 512 cases and 596 controls	Hospital-based study; 210/512 prevalent cases and 225 age-matched pairs (with urological controls); 287 cases and 371 unmatched controls from surgical departments (87 hernias, 41 peripheral arteriopathies and other diagnoses)
Kidney		
Schwartz *et al.* (1961) (France, 1954-)	Men: 69 cases and 69 controls	See Schwartz *et al.* (1961) above
Bennington & Laubscher (1968) (USA, 1951-1966)	Men: 88 cases and 170 controls; women: 12 cases and 20 controls	Hospital-based study; information on smoking habits retrieved from clinical records; information lacking for 22/122 cases and 70/190 controls (the latter were replaced)
Wynder *et al.* (1974) (USA, 1965-1973)	Men: 129 cases and 256 controls; women: 73 cases and 138 controls	Hospital-based study; controls were patients admitted for conditions not related to smoking (75% of which were malignant neoplasms) and age-matched to the cases
Armstrong *et al.* (1976) (UK, 1972-1974)	Parenchyma: men: 74 cases and 74 controls; women: 32 cases and 32 controls Renal pelvis: men: 22 cases and 22 controls; women: 11 cases and 11 controls	Hospital-based study; age- and sex-matched hospital controls (tobacco-related diseases not excluded); 48% of eligible cases in Oxford area and 44% in London could not be interviewed (mostly because of death); 19 lost controls replaced
McLaughlin *et al.* (1984) (USA, 1974-1979)	Men: 313 cases and 428 controls; women 182 cases and 269 controls	Population-based study; all newly diagnosed cases in the Minneapolis-St Paul area; controls: age- and sex-stratified random sample of the population and 495 randomly selected deceased individuals matched (for age, sex and year of death) to deceased cases

(ii) *Cancer of the lower urinary tract: men*

The denomination 'lower urinary tract' comprises the renal pelvis, ureter, bladder and urethra. Cancers originating in the urothelium at these sites are mostly transitional-cell carcinomas. These cancers are discussed together, unless a distinction is expressly made in the studies that are considered.

(1) *Dose-response relationship and duration of cigarette smoking.* Table 77 gives the relative risks according to average daily number of cigarettes smoked. With the exception of the study by Anthony and Thomas (1970), in Leeds, UK, all the others show an association between cancer of the lower urinary tract and cigarette smoking in men. Another case-control study conducted in Leeds (Cartwright *et al.*, 1983) failed to show a clear-cut dose-response relationship in men, although a statistically significant overall relative risk of 1.6 was found. [The Working Group noted that the control group used in this study included patients with tobacco-related diseases, a choice that could have biased the result.] Considerable variations in the relationship between relative risks and average daily amount of cigarettes smoked are evident (Table 77). For male smokers of more than 20 cigarettes/day, the relative risk is around 5.0 in one study in the USA (Wynder *et al.*, 1963a), in two studies in Canada (Morgan & Jain, 1974; Howe *et al.*, 1980) and in one study in Denmark (Møller-Jensen *et al.*, 1983); but other studies in the USA (Dunham *et al.*, 1968; Cole *et al.*, 1971; Wynder & Goldsmith, 1977), France (Schwartz *et al.*, 1961) and Japan (Morrison *et al.*, 1984) report lower relative risks, between 2.0 and 3.0, for the same category of smokers. Intermediate values have been reported from Boston, USA, and Manchester, UK (Morrison *et al.*, 1984). Estimates of around 2.0 for all smokers have been published from Denmark (Mommsen & Aagaard, 1983), the USA (Najem *et al.*, 1982), Poland (Staszewski, 1966) and Finland (Tola *et al.*, 1980). Higher estimates have been reported in Denmark (Lockwood, 1961) and Italy (Vineis *et al.*, 1984), although, in the latter study, relative risks are around 2.0 when only blond (flue-cured tobacco) cigarettes are considered.

Several of the studies report a levelling-off of the dose-response curve (Dunham *et al.*, 1968; Cole *et al.*, 1971; Cartwright *et al.*, 1983; Møller-Jensen *et al.*, 1983). [The Working Group noted that the wide variations in the dose-response relationship could be explained by a number of factors, namely, different study designs, different ways of smoking, or different types of tobacco smoked. It was noted that the apparent levelling-off of the dose-response curve could reflect an artefact in data collection, due to underestimation of levels of consumption by the interviewees.] A clear-cut dose-response was observed in other studies (Lockwood, 1961; Schwartz *et al.*, 1961; Morgan & Jain, 1974; Howe *et al.*, 1980; Morrison *et al.*, 1984; Vineis *et al.*, 1984).

Duration of cigarette smoking shows a direct relationship with relative risks for bladder cancer in men in a few studies that have examined it. Tyrrell *et al.* (1971) reported relative risks of 3.6 (based on 21 exposed cases) for 1-19 years of smoking, 4.2 (32) for 20-29, 2.8 (31) for 30-39, 3.9 (38) for 40-49 and 4.4 (40) for 50-59 years [calculated by the Working Group]. Wynder and Goldsmith (1977) in the USA reported the following estimates: 0.9 (95% confidence limits, 0.4-2.1) for 1-10 years, 1.1 (0.6-2.1) for 11-20, 1.9 (1.3-2.9) for 21-30, 2.5 (1.8-3.5) for 31-40, and 2.8 (2.1-3.9) for 41 years and more. Howe *et al.* (1980) in Canada reported estimates of 1.8 (1.1-3.3) for 1-20 years, 3.9 (2.6-6.4) for 21-40 and 4.8 (3.3-7.7) for

Table 77. Cancer of the lower urinary tract and average daily number of cigarettes smoked

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Case-control studies				
Lilienfeld *et al.* (1956)	Men	Nonsmokers	1.0 (51)	Crude risks calculated by the Working Group; unadjusted
		Smokers	2.1 (151)	
	Women	Nonsmokers	1.0 (108)	
		Smokers	0.4 (10)	
Lockwood (1961)	Men	Nonsmokers	1.0 (24)	Crude risks calculated by the Working Group
		(g tobacco/day)		
		1-10 g/day	1.3 (16)	
		11-20	3.3 (40)	
		21-30	9.5 (18)	
		31+	15.8 (10)	
	Women	Nonsmokers	1.0 (49)	
		(g tobacco/day)		
		1-10 g/day	0.9 (8)	
		11-20	4.6 (4)	
		21+	no cases or controls	
Schwartz *et al.* (1961)	Men	Nonsmokers	1.0 (24)	Crude risks calculated by the Working Group
		1-9	1.4 (31)	
		10-19	2.1 (69)	
		20-29	2.6 (63)	
		30+	3.8 (15)	
Wynder *et al.* (1963a)	Men	Nonsmokers	1.0 (21)	Crude risks calculated by the Working Group
		1-9	2.1 (12)	
		10-15	1.5 (15)	
		16-20	2.8 (86)	
		21-34	5.2 (63)	
		35+	5.7 (78)	
	Women	Nonsmokers	1.0 (43)	
		1-9	3.1 (9)	
		10-20	3.3 (14)	
		21+	4 cases, 0 controls	
Cobb & Ansell (1965)	Men and women	Nonsmokers	1.0 (6)	Age-adjusted relative risks computed by the Working Group; hospital controls with colon cancer only; heavy smokers smoked > 1 pack of cigarettes/day for 30+ years
		Light and medium smokers	3.0 (21)	
		Heavy smokers	10.3 (104)	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Staszewski (1966)	Men	Nonsmokers	1.0 (10)	Nonsmokers include smokers of <1 g tobacco per day for <1 year.
		Smokers	2.7 (140)	
Dunham *et al.* (1968)	Men			
	White	Nonsmokers	1.0 (55)	Crude risks calculated by the Working Group
		<10	1.2 (19)	
		10-19	2.1 (76)	
		20+	1.1 (114)	
	Black	Nonsmokers	1.0 (14)	
		<10	0.9 (9)	
		10-19	2.7 (25)	
		20+	1.9 (21)	
	Women			
	White	Nonsmokers	1.0 (77)	
		<10	0.7 (6)	
		10-19	1.0 (12)	
		20+	1.9 (17)	
	Black	Nonsmokers	1.0 (28)	
		<10	1.0 (8)	
		10-19	1.0 (5)	
		20+	1.9 (6)	
Anthony & Thomas (1970)	Men (aged 40-69)	Nonsmokers	1.0 (18)	Age-adjusted relative risks computed by the Working Group; only surgical controls considered
		< 15 g/day	0.7 (81)	
		15+	1.1 (104	
Cole *et al.* (1971)	Men (aged 20-89)	Nonsmokers	1.0 (70)	Smoker defined as smoking at least 100 cigarettes in life; amount considered is maximum amount smoked per day during life
		⩽ ½ pack/day	1.0 (36)	
		½-1½ packs/day	2.0 (140)	
		1½-2½ packs/day	2.2 (85)	
		> 2 ½ packs/day	1.8 (25)	
	Women (aged 20-89)	Nonsmokers	1.0 (50)	
		⩽ ½ pack/day	1.5 (13)	
		½-1½ packs/day	2.0 (30)	
		> 1½ packs/day	3.8 (12)	
Tyrrell *et al.* (1971)	Men	Nonsmokers	1.0 (7)	Crude relative risks computed by the Working Group
		Smokers	3.7 (163)	
		Nonsmokers		
		Smokers		
	Women	Nonsmokers	1.0 (31)	
		Smokers	0.8 (19)	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Makhyoun (1974)	Men with urinary bilharziasis	Nonsmokers	1.0 (66)	Crude relative risks computed by the Working Group; moderate smokers: (average number of cigarettes per day × duration of smoking) = 300-600; heavy smokers: > 600
		Moderate smokers	1.5 (42)	
		Heavy smokers	1.4 (21)	
	Men without urinary bilharziasis	Nonsmokers	.0 (15)	
		Moderate smokers	2.3 (41)	
		Heavy smokers	3.3 (28)	
Morgan & Jain (1974)	Men	Nonsmokers	1.0 (22)	
		1-14	2.6 (57)	
		15-24	2.7 (42)	
		25+	6.4 (37)	
	Women	Nonsmokers	1.0 (45)	
		1-14	1.2 (16)	
		15-24	1.1 (9)	
		25+	4.4 (4)	
Schmauz & Cole (1974)	Men (cancer of the renal pelvis and ureter)	Nonsmokers	1.0 (4)	
		≤½ pack/day	1.2 (2)	
		½-1½ pack/day	1.3 (5)	
		1½-2½ packs/day	1.1 (2)	
		>2½ packs/day	10.0 (5)	
Wynder & Goldsmith (1977)	Men	Nonsmokers	1.0 (65)	
		1-10	1.4 (0.9-2.2)	(338)
		11-20	2.4 (1.7-3.3)	
		21-30	2.7 (1.8-4.1)	
		31-40	2.3 (1.5-3.4)	
		41+	3.3 (2.1-5.3)	
	Women	Nonsmokers	1.0 (67)	
		1-10	1.7 (0.9-3.3) (28)	
		11-20	2.3 (1.3-4.2) (39)	
		21+	2.4 (1.1-5.1) (20)	
Miller, C.T. *et al.* (1978)	Men	Nonsmokers	1.0	
		Ever smoked	1.6	
	Women	Nonsmokers	1.0	
		Ever smoked	0.8	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Sadeghi *et al.* (1979)	Men	Nonsmokers	1.0 (17)	
		Smokers	2.0 (27)	
Howe *et al.* (1980)	Men	Nonsmokers	1.0	
		<10	2.6 (1.7-4.4)	
		10-20	3.8 (2.6-6.0)	
		>20	5.1 (3.5-8.6)	
	Women	Nonsmokers	1.0	
		≤15	2.3 (1.3-4.6)	
		>15	2.6 (1.4-6.9)	
Tola *et al.* (1980)	Men	Nonsmokers	1.0 (19)	Crude relative risks computed by the Working Group
		Ever smoked	1.9 (114)	
	Women	Nonsmokers	1.0 (25)	
		Ever smoked	5.4 (17)	
McCredie *et al.* (1982)	Men (cancer of renal pelvis)	Nonsmokers	1.0	Relative risks adjusted for consumption of analgesics; first set of controls, 'contacts'; second set of controls, 'screening clinic'
		Smokers	1.0 (0.2-4.3)	
	Women (cancer of renal pelvis)	Nonsmokers	1.0	
		Smokers	2.2 (0.8-5.9)	
			7.0 (2.5-19.7)	
Najem *et al.* (1982)	Men and women	Nonsmokers	1.0	Data not given separately
		Smokers	2.0 (1.1-3.7) (36)	

Cartwright *et al.* (1983) — Reference category includes nonsmokers (<1000 cigarettes in life) and smokers up to 5 years; incident and prevalent cases considered together

Men	Duration of cigarette smoking (years)					
	≤5	6-15	16-25	26-35	36-45	46+
<10	1.0	0.85	1.3	1.6	1.3	1.9
10-20	1.0	1.8	1.8	1.5	1.7	1.8
21+	1.0	1.4	1.1	1.3	1.5	0.85

Women	Duration of cigarette smoking (years)					
	≤5	6-15	16-25	26-35	36-45	46+
<10	1.0	2.4	1.2	1.4	1.4	1.6
10-20	1.0	1.0	2.0	1.5	1.6	1.5
21+	not enough data					

McCredie *et al.* (1983)	Men (ureter cancer)	Nonsmokers	1.0	Relative risks adjusted for phenacetin consumption and age
		1-249 kg tobacco in life	1.9	
		≥250 kg tobacco in life	4.6	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
McCredie *et al.* (contd)	Men (cancer of renal pelvis)	Nonsmokers	1.0	
		1-249 kg tobacco in life	1.3	
		≥250 kg tobacco in life	4.2	
McLaughlin *et al.* (1983)	Men (cancer of renal pelvis)	Nonsmokers	1.0 (3)	Light, ≤32 pack-years of cigarettes; moderate, 33-57; heavy, ≥58; relative risks adjusted for age and type of respondent (living case/control or next of kin)
		Light smokers	5.5 (1.4-25.5) (15)	
		Moderate smokers	9.6 (2.5-43.4) (17)	
		Heavy smokers	10.7 (2.7-48.9) (15)	
	Women (cancer of renal pelvis)	Nonsmokers	1.0 (8)	
		Light smokers	4.9 (1.2-20.2) (7)	
		Moderate smokers	7.6 (1.9-31.3) (6)	
		Heavy smokers	11.1 (1.8-68.7) (3)	
Møller-Jensen *et al.* (1983)	Men	Nonsmokers	1.0 (9)	Crude relative risks computed by the Working Group
		1-14	4.2 (82)	
		15-24	4.9 (112)	
		25+	4.3 (54)	
	Women	Nonsmokers	1.0 (23)	
		1-14	2.0 (30)	
		15+	2.5 (42)	
Mommsen & Aagaard (1983); Mommsen *et al.* (1982, 1983)	Men	Nonsmokers	1.0	Figure 1 in Mommsen & Aagaard (1983) suggests that relative risks are around 6.5 for smokers of 201-300 and 9.5 for smokers of 301-400 (years × no. of cigarettes/day) during life
		Smokers	1.9 (crude) (1.2-3.0) (122)	
	Women	Nonsmokers	1.0	
		Smokers	1.9 (crude) (0.9-3.9) (22)	
Morrison *et al.* (1984)	Boston area men	Nonsmokers	1.0 (53)	
		Current smokers		
		< 1 pack/day	1.4 (25)	
		1 pack/day	3.2 (91)	
		≥2 packs/day	4.7 (67)	
		Ex- and current smokers	1.9 (1.3-2.8)	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Morrison *et al.* (contd)	Women	Nonsmokers	1.0 (49)	
		Current smokers		
		<1 pack/day	4.3 (18)	
		⩾ 1 pack/day	6.2 (48)	
		Ex- and current smokers	4.2 (2.5-7.1)	
	Manchester area Men	Nonsmokers	1.0 (28)	
		Current smokers		
		<1 pack/day	1.9 (85)	
		1 pack/day	3.2 (104)	
		⩾2 packs/day	4.0 (31)	
		Ex- and current smokers	2.2 (1.4-3.5)	
	Women	Nonsmokers	1.0 (63)	
		Current smokers		
		<1 pack/day	2.1 (40)	
		⩾1 pack/day	2.2 (26)	
		Ex- and current smokers	1.3 (0.8-2.0)	
	Nagoya area Men	Nonsmokers	1.0 (24)	
		Current smokers		
		<1 pack/day	1.6 (47)	
		1 pack/day	2.1 (92)	
		⩽2 packs/day	2.8 (33)	
		Ex- and current smokers	1.7 (1.1-2.9)	
	Women	Nonsmokers	1.0 (45)	
		Current smokers		
		<1 pack/day)	4.4 (11)	
		⩾1 pack/day)	4.2 (7)	
		Ex- and current smokers	4.3 (2.0-9.2)	
Vineis *et al.* (1984)	Men	Nonsmokers	1.0 (19)	
		1-14	4.0 (2.4-6.8) (181)	
		15-29	5.7 (3.5-9.3) (261)	
		30+	10.1 (4.9-20.7) (47)	
Cohort studies				
Hammond & Horn (1958b)	187 783 men, aged 50-69	Nonsmokers	1.0 (38)	In parentheses, observed no. of deaths in each category
		<½ pack/day	2.0 (14)	Microscopically verified cancer of the genitourinary system
		½-1 pack/day	2.0 (42)	
		>1 pack/day	3.4 (41)	
		Smokers	2.2 (59)	Bladder only, microscopically verified

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Hammond (1966)	440 558 men and 562 671 women aged ⩾ 30			Relative risks computed by the Working Group as ratios of age-adjusted annual death rates
	Men (aged 45-64)	Nonsmokers	1.0 (10)	
		Smokers	1.8 (59)	
	Men (aged 65-79)	Nonsmokers	1.0 (13)	
		Smokers	2.9 (56)	
Kahn (1966)	293 658 men aged 35-84 followed up 1954-1962	Nonsmokers	1.0 (52)	
		<10	1.0 (11)	
		10-20	2.3 (71)	
		21-39	3.1 (51)	
		40+	3.0 (9)	
Lossing *et al.* (1966)	78 000 men, aged ⩾ 30	Nonsmokers	1.0	Genitourinary cancers
		<10/day	1.3 (29)	
		10-20/day	1.4 (57)	
		>20 day	1.4 (15)	
Weir & Dunn (1970)	68 153 men aged 35-64	Nonsmokers	1.0	Total observed deaths from bladder cancer, 27
		< ½ pack/day	1.5	
		½—1 pack/day	2.8	
		> 1 pack/day	5.4	
Cederlöf *et al.* (1975)	Men	Nonsmokers	1.1 (16)	
		1-7	1.5 (6)	
		8-15	1.6 (6)	
		⩾16	2.7 (6)	
	Women	Nonsmokers	1.1 (24)	
		1-7	1.2 (2)	
		8-15	2.1 (4)	
		⩾16	0.8 (1)	
Doll & Peto (1976)	34 440 male British doctors	Nonsmokers	1.0	Relative risks, calculated by the Working Group, are ratios of age-adjusted annual death rates; total observed deaths from bladder cancer, 80
		1-14	2.2	
		15-24	2.2	
		>25	1.4	
Hirayama (1977b, 1985)	122 261 men aged 40+	Nonsmokers	1.0	
		Smokers	1.4 (59)	

Table 77 (contd)

Reference	Subjects	Average consumption (cigarettes/day)	Relative risk[a]	Comments
Doll *et al.* (1980)	6194 female British doctors	Nonsmokers Smokers	1 0.6	Total deaths from bladder cancer, 5
Rogot & Murray (1980)	293 958 men aged 31-84; same cohort as described by Kahn (1966), but followed up 1954-1969	Smokers	2.16 (326)	Standardized mortality ratio

[a]In parentheses, absolute number of cases or deaths or 95% confidence limits

more than 40 years. Cartwright *et al.* (1983) reported relative risks in relation to both average daily consumption of cigarettes and duration.

When cancers of the renal pelvis and of the ureter are considered separately (Schmauz & Cole, 1974; McCredie *et al.*, 1982; McLaughlin *et al.*, 1983), a dose-response relationship with daily or cumulative consumption of tobacco is found, and relative risks are generally higher than those reported for the bladder. In the population-based study by McLaughlin *et al.* (1983), the overall relative risk for men who had ever smoked was 7.6.

Cohort studies consistently show an excess of deaths from bladder cancer among male smokers, with relative risks of between 3.0 and 5.4 for smokers of 20 or more cigarettes/day in the US studies (Hammond & Horn, 1958b; Kahn, 1966; Weir & Dunn, 1970). The cohort study on British male doctors failed to show a dose-response relationship (Doll & Peto, 1976) (see Table 77).

(2) *Type of cigarette, effect of inhaling.* In only one study (Vineis *et al.*, 1984) are estimates reported of the relative risks for lower urinary tract cancers separately for smokers of black (air-cured) and blond (flue-cured) tobacco, although the assignment of brands to these classifications is reported by the authors to be tentative. Relative risks for smokers of black tobacco were more than twice those for smokers of blond tobacco, adjusted for age, occupation, average daily consumption of cigarettes, years since stopping and use of a filter tip.

The use of filter-tip cigarettes has been analysed in several studies, with conflicting results (Table 78). A weaker effect of filter cigarettes was reported by Howe *et al.* (1980) and Cartwright *et al.* (1983), whereas no difference between filter and nonfilter cigarettes was

found in the study by Wynder and Goldsmith (1977) or in the investigation by Morrison *et al.* (1984). In Italy (Vineis *et al.*, 1984), the relative risk for lifelong smokers of filter-tip cigarettes was 0.3 in comparison with the risk for smokers of less than 50% filter cigarettes smoked throughout life (adjusted for age, type of tobacco, number of cigarettes smoked, years since stopping and high-risk occupation).

A slight effect of inhaling has been reported by Cole *et al.* (1971), Howe *et al.* (1980) and Morrison *et al.* (1984), but not by Lockwood (1961) (Table 78).

(3) *Effect of stopping and of age at starting cigarette smoking.* A lowering of risk in men after stopping cigarette smoking (Table 79) is evident from studies conducted in the USA (Kahn, 1966; Wynder & Goldsmith, 1977; Rogot & Murray, 1980; Morrison *et al.*, 1984), in Canada (Howe *et al.*, 1980), in the UK (Doll & Peto, 1976; Cartwright *et al.*, 1983; Morrison *et al.*, 1984), in Japan (Morrison *et al.*, 1984) and in Italy (Vineis *et al.*, 1984). The risk for ex-smokers approximates that of nonsmokers more than 15 years after cessation (Wynder & Goldsmith, 1977). At least one study does not, however, show a clear-cut decreasing trend of risk (Tyrrell *et al.*, 1971).

The role played by age at starting to smoke was considered by Cole *et al.* (1971), who reported a lower mean age among cases than among controls (at a statistically significant *p* value). Tyrrell *et al.* (1971) reported relative risks of 4.7 (based on 11 exposed cases) for age at starting <10 years, 4.9 (51) for 10-14, 3.5 (60) for 15-19, 3.7 (28) for 20-24, 3.0 (7) for 25-29 and 1.2 (5) for 30+ [calculated by the Working Group]. Morrison *et al.* (1984) reported the following relative risks for age at start of 15-19 and 20+ years, respectively (reference category, less than 15 years; relative risks adjusted for intensity of smoking): 1.1 (based on 89 cases) and 1.0 (36) in Boston; 1.3 (92) and 0.9 (39) in Manchester; and 0.7 (109) for ⩾20 years in Nagoya (*versus* <20 years). In the study reported by Vineis *et al.* (1984), relative risks were 7.9 (95% confidence limits, 2.4-25.2), 8.0 (3.5-18.5) and 7.3 (3.1-17.0) for cases under the age of 50 and 8.5 (2.7-26.8), 6.3 (2.6-15.3) and 8.2 (3.7-17.9) in the age group 50-59 for age at start of <13, 13-16 and ⩾17, respectively, in relation to nonsmokers.

(4) *Other types of smoking (cigar, pipe).* Conflicting evidence is available on the role of pipe smoking in the etiology of bladder cancer in men (Table 80). Relative risks of about 1.0 were reported by Hammond and Horn (1958b), Kahn (1966), Cole *et al.* (1971), Wynder and Goldsmith (1977) and Mommsen and Aagaard (1983). However, an association was found by Wynder *et al.* (1963a; based on six cases), by Dunham *et al.* (1968; only among black men; based on three cases), by Howe *et al.* (1980; with a statistically significant relative risk of 8.8 for men heavily inhaling pipe smoke, adjusted for cigarette smoking) and by Morrison *et al.* (1984; particularly in the Manchester area). In the Danish study, by Mommsen and Aagaard (1983), the relative risk for current pipe smokers was 6.2 (95% confidence limits, 1.1-36.6).

Risks in men associated with the smoking of cigars and cigarillos vary from about 1.0 (Wynder *et al.*, 1963a; Dunham *et al.*, 1968, in black men; Cole *et al.*, 1971; Wynder & Goldsmith, 1977) to 1.4 (Mommsen & Aagaard, 1983) or 1.6 (Dunham *et al.*, 1968, in white men). In Denmark, Møller-Jensen *et al.* (1983) detected a crude relative risk of 2.4 (based on 29 cases) for smokers of products other than cigarettes. A second Danish study (Mommsen & Aagaard, 1983) reported a relative risk of 2.3 for current cigar/cigarillo smokers (see Table 80).

Table 78. Cancer of the lower urinary tract and use of filter-tip cigarettes and effect of inhaling. Relative risks (RR) in relation to nonsmokers, unless otherwise specified

Reference	Subjects	Use of filter-tip cigarettes	Relative risk[a]	Inhalation pattern	Relative risk[a]	Comments
Lockwood (1961)	Men	-		Inhaling *vs.* noninhaling	0.7 (65)	Age-adjusted relative risks computed by the Working Group from Table 52 of the reference
Cole *et al.* (1971)	Men	-		'Somewhat inhaling'	1.0	
				'Deeply inhaling' (*vs.* not inhaling)	1.4	
	Women	-		'Somewhat inhaling'	1.8	
				'Deeply inhaling' (*vs.* not inhaling)	2.5	
Wynder & Goldsmith (1977)	Men	Filter > 10 years	3.0 (2.1-4.3)			
		Non-filter > 10 years	3.1 (2.1-4.7)			
Howe *et al.* (1980)	Men	Nonfilter	1.1	Inhale nonfilter moderately	0.7	Computed by the Working Group from regression coefficients; reference category, all other smokers of the same amount
		Filter	1.0	Inhale nonfilter heavily	1.1	
				Inhale filter moderately	1.2	
				Inhale filter heavily	1.1	

Table 78 (contd)

Reference	Subjects	Use of filter-tip cigarettes	Relative risk[a]	Inhalation pattern	Relative risk[a]	Comments
Howe *et al.* (1980) (contd)	Women	Nonfilter	1.1	Inhale nonfilter moderately	1.1	
		Filter	1.0	Inhale nonfilter heavily	0.8	
				Inhale filter moderately	1.1	
				Inhale filter heavily	2.4	
Cartwright *et al.* (1983)	Women and men	Nonfilter cigarettes only	1.4 (1.1-1.7)			Adjusted for age and sex
		Filter cigarettes only	1.05(0.7-1.5)			
		Both types	1.6 (1.3-2.0)			
Morrison *et al.* (1984)[b]	Men					RRs are for deep inhalers *vs.* inhaling somewhat or not at all and adjusted for current intensity of smoking
	Boston area	Users *vs.* nonusers	1.3 (0.7-2.3)	Inhaling *vs.* noninhaling	1.4 (0.8-2.3)	
	Manchester area	Users *vs.* nonusers	1.2 (0.8-1.8)	Inhaling *vs.* noninhaling	1.3 (0.8-1.9)	
	Nagoya area	Users *vs.* nonusers	1.0 (0.5-1.9)	Inhaling *vs.* noninhaling	1.4 (1.0-2.1)	

Table 78 (contd)

Reference	Subjects	Use of filter-tip cigarettes	Relative risk[a]	Inhalation pattern	Relative risk[a]	Comments
Morrison *et al.* (contd)	Women					
	Boston area			Inhaling *vs.* noninhaling	2.4 (0.7-7.8)	
	Manchester area			Inhaling *vs.* noninhaling	0.7 (0.3-1.8)	
Vineis *et al.* (1984)	Men	50% filter-tip cigarettes	1.0			Relative risks adjusted for age, high-risk occupation, average daily amount, years since stopping and type of tobacco
		50-74%	1.1			
		75-99%	0.5			
		100%	0.3			

[a]In parentheses, no. of exposed cases or 95% confidence limits

Table 79. Cancer of the lower urinary tract and effect of stopping cigarette smoking. Relative risks (RR) in relation to nonsmokers

Reference	Subjects	Smoking status	Relative risk[a]	Comments
Case-control studies				
Anthony & Thomas (1970)	Men	Current pure cigarette smokers	0.9 (185)	Age-adjusted relative risks computed by the Working Group
		Ex-pure cigarette smokers	1.2 (43)	
Tyrrell *et al.* (1971)	Men	0 years since stopping	3.9 (129)	Crude relative risks computed by the Working Group
		0.1-3.9	1.5 (3)	
		4.0-6.9	2.9 (5)	
		7.0-12.9	4.1 (6)	
		13.0-21.9	6.2 (9)	
		22.0+	2.7 (11)	
		Nonsmokers	1.0 (7)	
Wynder & Goldsmith (1977)	Men	1-3 years since stopping	2.6 (1.6-4.5)	
		4-6	2.9 (1.7-5.2)	
		7-9	1.5 (0.8-3.0)	
		10-12	1.6 (0.8-3.1)	
		13-15	1.2 (0.6-2.5)	
		16+	1.1 (0.7-1.8)	
	Women	1-6 years since stopping	2.5 (1.0-6.2)	
		7+	1.2 (0.5-2.9)	
Howe *et al.* (1980)	Men	2-15 years since stopping	0.6 (0.4-0.9)	Relative risks computed by the Working Group from logistic regression coefficients; reference category, current smokers
		>15	0.5 (0.4-0.8)	
	Women	Ex-smokers	0.2 (0.1-0.5)	

Table 79 (contd)

Reference	Subjects	Smoking status	Relative risk[a]	Comments
Cartwright *et al.* (1983)	Men (current and ex-smokers)	Smoking for ⩽ 5 years	1.7	Reference category, never smokers, and those with >35 years since stopping
		6-15 years since stopping	1.0	
		16-25	1.1	
		26-35	0.9	
	Women (current and ex-smokers)	Smoking for ⩽ 5 years	1.4	
		6-15 years since stopping	0.5	
		16+	0.5	
McLaughlin *et al.* (1983)	Men	Current and ex-smokers	7.6 (47)	Renal pelvic cancer
		⩾ 10 years since stopping	4.3	
	Women	Current and ex-smokers	5.8 (16)	
		⩾ 10 years since stopping	3.9	
Morrison *et al.* (1984)	Men, ex-smokers			Relative risks adjusted for intensity of smoking; those for ex-smokers calculated using nonsmokers and current smokers as reference category, respectively
	Boston area	*vs.* nonsmokers	1.5 (191)	
		vs. current smokers	0.5 (0.4-0.8)	
	Manchester area	*vs.* nonsmokers	1.8 (150)	
		vs. current smokers	0.7 (0.5-0.9)	
	Nagoya area	*vs.* nonsmokers	1.0 (28)	
		vs. current smokers	0.5 (0.3-0.8)	
	Women, ex-smokers			
	Boston area	*vs.* nonsmokers	3.4 (50)	
	Manchester area	*vs.* nonsmokers	0.7 (26)	
	Nagoya area	*vs.* nonsmokers	Not given (3)	

Table 79 (contd)

Reference	Subjects	Smoking status	Relative risk[a]	Comments
Vineis *et al.* (1984)	Men aged < 60	0-2 years since stopping	10.2 (5.0-21.2)	
		3-9	3.3 (1.2-9.2)	
		10-14	1.6 (0.3-8.2)	
		15+	1.9 (0.5-7.9)	
	Men aged >60	0-2 years since stopping	3.8 (2.0-7.2)	
		3-9	2.8 (1.2-6.6)	
		10-14	2.4 (0.9-6.3)	
		15+	2.5 (1.0-5.8)	
Cohort studies				
Kahn (1966)	Men	Nonsmokers	1.0	
		Current smokers	2.2 (82)	Relative risks statistically significant (p <0.01)
		Ex-smokers	1.6 (51)	
Doll & Peto (1976)	Men	Current smokers	2.1	Ratio of annual death rates × 10^5 men; total number of deaths, 80; calculated by the Working Group
		Ex-smokers	1.2	
Rogot & Murray (1980)	Men	Current smokers	2.16 (326)	Standardized mortality ratio
		Ex-smokers	1.41 (126)	

[a]In parentheses, no. of exposed cases or 95% confidence limits

Table 80. Cancer of the lower urinary tract and smoking of products other than cigarettes: Relative risks in relation to nonsmokers

Reference	Subjects	Product smoked	Relative risk[a]	Comments
Case-control studies				
Lockwood (1961)	Men	Preferring cigars Preferring cigarillos Preferring pipe	1.7 (50) 1.2 (52) 1.4 (70)	Age-adjusted relative risks computed by the Working Group
	Women	Cigarillos only	1.5 (25)	
Schwartz *et al.* (1961)	Men	Pipe only	0.5 (2)	Crude relative risk computed by the Working Group
Wynder *et al.* (1963a)	Men	Pipe only Cigar only	2.2 (6) 0.8 (9)	Crude relative risks computed by the Working Group
Dunham *et al.* (1968)	White men	Cigar only Pipe only	1.6 (8) 0.4 (1)	Crude relative risks computed by the Working Group
	Black men	Cigar only Pipe only	1.0 (2) 3.0 (3)	
Anthony & Thomas (1970)	Men	Pipe and cigar Pipe only	1.6 (18) 0.7 (39)	Age-adjusted relative risks computed by the Working Group
Cole *et al.* (1971)	Men	Pipe Cigar	1.1 1.2	Adjusted for cigarettes
Tyrrell *et al.* (1971)	Men	Pipe only	3.9 (30)	Crude relative risk computed by the Working Group

Table 80 (contd)

Reference	Subjects	Product smoked	Relative risk[a]	Comments
Wynder & Goldsmith (1977)	Men	Pipe only	0.7 (7) (0.3-1.9)	
		Cigar only	0.9 (19) (0.5-1.7)	
Howe *et al.* (1980)	Men	Pipe		Adjusted for cigarettes
		<50 000 pipefuls	1.3 (0.7-2.1)	
		>50 000 pipefuls	2.0 (1.2-3.5)	
		Inhale pipe moderately	1.1 (0.6-2.1)	Adjusted for amount of tobacco smoked
		Inhale pipe heavily	8.8 (1.1-71.7)	
Mommsen & Aagaard (1983)	Men	Cigars/cigarillos only	1.4 (0.9-2.2)	RR for current cigar/cigarillo smokers, 2.3 (0.7-7.4)
		Pipe only	1.3 (0.9-2.1)	RR for current pipe smokers, 6.2 (1.1-36.6)
	Women	Cigar/cigarillos	3.3 (1.3-8.5)	
Møller-Jensen *et al.* (1983)	Men	Ever smoked other than cigarettes only	2.4 (29)	Crude relative risk computed by the Working Group
Morrison *et al.* (1984)	Men			Ever smoked pipe
	Boston area	Pipe only	1.7 (0.8-3.6)	
	Manchester area	Pipe only	3.9 (1.3-11.8)	
	Nagoya area	Pipe only (*kizami* type)	1.3 (0.5-3.5)	
Cohort studies				
Hammond & Horn (1958b)	Men	Pipe only	1.2 (21)	Genitourinary system
		Cigar only	1.1 (19)	

Table 80 (contd)

Reference	Subjects	Product smoked	Relative risk[a]	Comments
Kahn (1966)	Men	Cigar only, current smokers Pipe only, current smokers	0.9 (10 1.2 (8)	
Lossing *et al.* (1966)	Men	Cigar only <3/day 3-10/day Pipe only	 1.1 (2) 1.7 (1) 0.6 (10)	Genitourinary system
Cederlöf *et al.* (1975)	Men	Pipe, ≤5 g/day Pipe, ≥6 g/day	0.6 (2) 1.9 (15)	No cigarette smoking after 1953 (pipe smoked at least 10 years)
Doll & Peto (1976)	Men	Pipe and/or cigar only	1.5	Ratio of annual death rates × 10^{-5} men; absolute numbers not given

[a]In parentheses, no. of exposed cases or 95% confidence limits

(iii) *Cancer of the lower urinary tract: women*

Most published studies (Table 77) report a positive association between cigarette smoking and cancer of the lower urinary tract in women. In one study, the relative risk was about 1.0 (Miller, C.T. *et al.*, 1978), and, in another, no clear-cut dose-response relationship was seen (Cartwright *et al.*, 1983). The relative risks for women are sometimes lower (Tyrrell *et al.*, 1971; Morgan & Jain, 1974; Howe *et al.*, 1980; Møller-Jensen *et al.*, 1983; Morrison *et al.*, 1984, in the Manchester area) and sometimes higher than those for men (Cole *et al.*, 1971 and Morrison *et al.*, 1984, both in the Boston and Nagoya areas; McCredie *et al.*, 1982, for cancer of the renal pelvis). [On the basis of the available data, it is not possible to establish whether such variations reflect different types of tobacco smoked by people of the two sexes in different countries, different susceptibilities of the two sexes, or random fluctuations due to small numbers.]

The reported relative risk in ex-smokers was lower in women (Wynder & Goldsmith, 1977; Howe *et al.*, 1980; Cartwright *et al.*, 1983), except in one study (Morrison *et al.*, 1984, in the Boston area) (see Table 79). Information on risks associated with tobacco products other than cigarettes is available only for men, with the exception of two studies in Denmark, reporting relative risks of 1.5 for use of cigarillos (Lockwood, 1961) and 3.3 for use of cigars/cigarillos in women (Mommsen & Aagaard, 1983) (see Table 80).

(iv) *Kidney (adenocarcinoma)*

(1) *Case-control studies.* A study described by Schwartz *et al.* (1961) reported that 69 cases and 69 matched controls smoked the same average number of cigarettes per day, suggesting the absence of an association between adenocarcinoma of the kidney and cigarette smoking. In a study by Bennington and Laubscher (1968), however, the age-adjusted relative risk for male smokers of more than 10 cigarettes/day was 5.1 (based on 60 cases); for pipe smokers, the corresponding figure was 10.3 (based on 8 cases); and for cigar smokers, 12.9 (55 cases). For ex-smokers and women the numbers were too small to calculate risks.

Wynder *et al.* (1974) reported the following relative risks for adenocarcinoma and cigarette smoking in men: 1-9 cigarettes/day, 1.5 (based on 12 cases); 10-20, 1.9 (45 cases); ⩾21, 2.2 (37 cases). Among women, the corresponding figures were 1.1 (9 cases), 1.5 (18 cases) and 2.2 (8 cases). Male cigar smokers had a relative risk of 1.3 (8 cases), and pipe smokers one of 1.5 (3 cases). When only men under 50 years old were considered, cigarette smokers had relative risks of 3.3 (1-20 cigarettes/day) and 8.0 (⩾21 cigarettes/day).

Armstrong *et al.* (1976) reported from their hospital-based study relative risks for adenocarcinoma of 1.1 for current male cigarette smokers (95% confidence limits, 0.5-2.2) and 1.0 for women (0.3-3.4). The corresponding estimate for transitional-cell carcinoma of the renal pelvis was 1.8 (0.5-6.8) in men. There was no excess of cases compared with controls who smoked tobacco in forms other than cigarettes. [The Working Group noted that almost 50% of eligible cases could not be interviewed, whereas this proportion was much lower in the controls; in addition, people with 'tobacco-related diseases' were not expressly excluded from the hospital-control group.]

McLaughlin *et al.* (1984) reported from a large case-control study a statistically significant association between renal-cell carcinoma (adenocarcinoma) and cigarette smoking, both in men and women, with a dose-response relationship: relative risks in men were 1.2 for light smokers, 1.3 for moderate smokers and 2.3 for heavy smokers; the corresponding figures in women were 1.8, 1.9 and 2.1. All relative risks were adjusted for respondent type (i.e., living case/control or next-of-kin). These risks remained virtually the same after adjustment for potential confounders such as phenacetin abuse and body weight. The relative risk for male cigar smokers was 0.6 (95% confidence limits, 0.2-2.0) and for pipe smokers 2.2 (0.7-6.9). The relative risk was 1.1 for men who had stopped smoking >10 years prior to diagnosis, 1.7 for those who had stopped ≤10 years before and 1.8 for continuing smokers (relative to nonsmokers). Among women, the corresponding figures were 1.6, 1.7 and 2.0.

(2) *Cohort studies* (see Table 77 for numbers of subjects). Hammond and Horn (1958b) reported a ratio of 1.6 between 35 deaths from histologically proved cancer of the kidney observed among regular cigarette smokers and the expected value based on nonsmokers (men only).

Kahn (1966) estimated a mortality ratio of 0.7 for current male smokers of <10 cigarettes/day (6 deaths), 1.6 for 10-20 cigarettes/day (39 deaths), 2.0 for 21-39 (28 deaths) and 2.7 for ≥40 (7 deaths). For cigar smoking, the estimate was 0.8, and that for pipe smoking, 1.3 (both based on 6 deaths). Among ex-cigarette smokers, the relative risk was 1.7 (based on 40 deaths).

Hammond (1966) reported mortality ratios of 1.4 (ages 45-64, based on 54 deaths in smokers) and of 1.6 (ages 65-79, based on 28 deaths) for cigarette smoking in men.

Weir and Dunn (1970) reported a relative risk for 35-64-year-old men of 2.5; the risk was 0.9 for smokers of one-half a pack/day or less; 3.3 for smokers of about one pack; and 2.6 for one to one-and-a-half packs or more; a total of 27 deaths was observed.

In the study on male British doctors (Doll & Peto, 1976), although the absolute numbers of deaths from kidney cancer (46) was small for comparisons, the annual death rate ($\times 10^{-5}$ men, age-adjusted) was 8 among current smokers or ex-smokers (any tobacco), 9 among ex-smokers, and 3 among nonsmokers.

Hirayama (1977b), in a cohort study on 122 261 men followed up from 1966 to 1975, found 24 deaths from cancer of the kidney among smokers, corresponding to a standardized mortality ratio of 1.2.

In the study of US veterans (Rogot & Murray, 1980), a standardized mortality ratio for kidney cancer of 1.4 (based on 175 observed deaths) was reported for current cigarette smokers and of 1.2 (82 deaths) for ex-cigarette smokers.

[The Working Group did not consider studies based only on death certificates, since these cannot distinguish between adenocarcinoma of the kidney and carcinoma of the renal pelvis.]

(*c*) *Estimates of risk attributable to smoking*

The proportion of bladder cancers occurring in the general population due to cigarette smoking has been estimated in a few population-based studies from different countries. In men, the estimated proportions were 39% (Cole *et al.*, 1971) and 44% (Morrison *et al.*, 1984) in the Boston, USA, area; 61% in a Canadian population (Howe *et al.*, 1980); 32% in a rural population in Denmark (Mommsen & Aaagard, 1983); 46% in the Manchester, UK, area and 34% in Nagoya, Japan (Morrison *et al.*, 1984). Among women, the following estimates have been given: 29% (Cole *et al.*, 1971), 26% (Howe *et al.*, 1980), 22% (Mommsen & Aagaard, 1983), 56% (Boston), 14% (Manchester) and 24% (Nagoya) (Morrison *et al.*, 1984). Attributable risks of 31% for men and 15% for women have been estimated from the large cohort study conducted in Japan by Hirayama (1982). Moolgavkar and Stevens (1981) computed estimates of 73% among men and 14% among women in England and Wales (1941-1970).

A few estimates are available for cancers of the renal pelvis and ureter: 39% (Schmauz & Cole, 1974; Boston area) and 82% in men, and 61% in women (McLaughlin *et al.*, 1983; Minneapolis-St Paul area).

Only one estimate has been given for renal adenocarcinoma from a population-based study: 30% among men and 24% among women (McLaughlin *et al.*, 1984; Minneapolis-St Paul area).

(*d*) *Summary*

Cancers of the bladder and renal pelvis have been associated consistently with cigarette smoking in many cohort and case-control studies conducted in various parts of the world. These studies have generally shown a dose-response relationship, with risks for heaviest cigarette smokers being about five times those for nonsmokers. Relative risks in women are usually lower, although the risk estimates for women were often based on much smaller numbers and less prolonged smoking. No other factor (e.g., occupation) has been shown to confound this association. It can be concluded that cigarette smoking is an important cause of bladder cancer, and that 50% of male cases and 25% of female cases in some populations are attributable to smoking.

Several studies have shown an association between renal adenocarcinoma and cigarette smoking.

4. Cancers in other organs

(*a*) *Cancers of the upper respiratory and upper digestive tracts*

The sites considered here are the lip, oral cavity, pharynx, larynx and oesophagus, cancers that share a common feature — they are usually studied in relation to smoking and to some other factor, such as alcohol in western countries, chewing of betel quid in south-east Asia (IARC, 1985a) and other factors elsewhere. Thus, it is possible to assess the role of tobacco only on the basis of studies that address both tobacco and other factors suspected to be of importance.

The oral use of snuff has been implicated in the etiology of cancer of the oral cavity and, to a lesser extent, of the pharynx. While one case-control study has suggested that the oral use of snuff may be associated with certain types of cancer of the nasal sinus, in other case-control studies no association was evident between snuff and cancer of the oesophagus. Four case-control studies indicated that use of unspecified smokeless-tobacco products is moderately to strongly associated with the occurrence of oral cancer, although smoking habits were not controlled for in three of the studies; a dose-response relationship was found in one large case-control study. In one cohort study, there were two- to three-fold increased risks of death from oral, pharyngeal and oesophageal cancer in users of unspecified smokeless-tobacco products; in another study, an increased mortality from oesophageal cancer was seen (IARC, 1985a).

Cancers of the oral cavity and pharynx occur at relatively high frequency in countries of south-east Asia, where smoking is commonly associated with betel-quid chewing. The role of the latter was reviewed in detail in a monograph (IARC, 1985a) which described three case-control studies in which various combinations of the two habits were analysed. The relative risk among nonchewing male smokers was found to be 5.7 for oral cancer in Pakistan (Jafarey *et al.*, 1977), 2.1 for oral cancer and 28.5 for cancer of the oropharynx in India and Sri Lanka (Hirayama, 1966) and 1.2 for oral cancer in Calcutta, India (Chandra, 1962). There is *sufficient evidence* that the combined habits of smoking tobacco and chewing betel quid that does not contain tobacco cause oral and pharyngeal cancer, although the evidence considered did not allow an assessment of the possible contribution of betel quid without tobacco to this carcinogenic risk (IARC, 1985a).

Although most cohort studies showed an increased risk among smokers for cancers of the lip, oral cavity, pharynx, larynx and oesophagus, only one made a distinction between smokers who drink and those who do not. Hirayama (1978) found an excess of cancers at each site among daily cigarette smokers; the excesses of cancers of the mouth, pharynx and oesophagus, however, were lower among smokers 'only' as compared with 'drinking' smokers (Table 81).

In the US Veterans Study (Kahn, 1966), cited as an example of other cohort studies (Table 82), a dose-response relationship was seen for cancer at each site among cigarette smokers; the standardized mortality ratio was greater for cancers of the larynx and pharynx than for those at other sites. For cigar smokers, there was a contrast between the slightly elevated risk for lung cancer (see pp. 204-206) and the higher relative risks for cancers of the mouth, oesophagus and larynx.

Table 81. Mortality ratios for cancers at various sites in men in a Japanese cohort study[a]

Site	Buccal cavity	Pharynx	Oesophagus	Larynx
No. of deaths	23	12	172	35
Daily smoking plus daily drinking[b]	5.26	3.01	2.26	4.51
Daily smoking only[b]	2.46	0.82	1.18	4.93

[a]From Hirayama (1978)

[b]In relation to those who neither smoke nor drink

Table 82. Mortality ratios for cancers of the upper respiratory and digestive tracts in a US prospective study[a]

Smoking category	No. of person-years of observation	Buccal cavity (ICD 140-144)		Pharynx (ICD 145-148)		Oesophagus (ICD 150)		Larynx (ICD 161)	
		No. of deaths	Mortality ratio	No. of deaths	Mortality ratio	No. of deaths	Mortality ratio	No. of deaths	Mortality ratio
Never smoked	443 856	11	1.00	4	1.00	11	1.00	3	1.00
Current cigarette smokers (all levels)	701 768	56	3.75	48	9.60	77	5.87	40	9.45
1 - 9/day	95 462	5	2.12	4	4.60	6	2.53	3	4.53
10 - 20/day	333 619	18	2.56	21	8.72	24	3.83	16	8.33
21-39/day	207 821	24	5.90	18	14.35	38	11.88	16	13.26
> 39/day	34 738	7	9.26	5	21.71	5	8.38	5	21.17
Current smokers of cigars only	82 912	9	4.11	-	-	12	5.33	6	10.33
Current smokers of pipe only	49 545	4	3.12	1	1.98	3	1.99	-	-

[a]From Kahn (1966)

(i) *Cancer of the lip*

Lip cancer cases are included in many studies of oral cancer, but when findings for this subsite are reported separately the number of lip cancer cases is usually small. Three large case-control studies of lip cancer, however, do provide information on the relationship with tobacco smoking.

Keller (1970) studied 314 male cases, representing a 20% sample of patients discharged from all Veterans' Administration hospitals in the USA from 1958 through 1962. Two control groups were identified by sampling — one of patients with cancers of the mucous membrane of the mouth and pharynx, the other of patients discharged during the same period with no oral or pharyngeal cancer. The authors concluded that smoking of pipes, cigars and cigarettes, but not of pipes alone, was significantly associated with lip cancer, but the data do not include amount smoked or duration of smoking.

Spitzer *et al.* (1975) studied all male cases of squamous-cell carcinoma of the lip occurring in Newfoundland, Canada, over an 11-year period (1961-1971) (366 cases). Three control groups were used: 132 patients with oral cavity cancer, 81 patients with squamous-cell carcinoma of the skin of the head and neck, and 210 randomly selected population controls. In a comparison with the population controls, the relative risk for lip cancer associated with pipe smoking, adjusted for age, was 1.5 ($p < 0.05$), and that for lip cancer associated with all tobacco use was 1.1 (not significant). [The Working Group noted that the paper focused on risk of lip cancer related to the occupation of fishing and gave no other information on tobacco use.]

Lindqvist (1979) studied all cases (290) of lip cancer diagnosed in Finland in 1972-1973. Patients with squamous-cell cancer of the skin of the head and neck were used as controls. He concluded that, in men, tobacco smoking and outdoor work act together to cause lip cancer (relative risk, 15.4; $p < 0.001$) but that neither factor had a significant independent effect (relative risk for smoking only, 2.0; that for outdoor work only, 1.4). Cigarette smoking accounted for almost all of the tobacco use; only 8% of male cases (compared to 6% of male controls) smoked a pipe.

(ii) *Cancer of the oral cavity*

Among nondrinkers, the relative risk for oral cancer for cigarette smokers was found to be 3.0 (Wynder *et al.*, 1957b), 1.5 (Rothman & Keller, 1972) and 1.5 (Graham, S. *et al.*, 1977). The first two studies indicated a dose-response relationship. For three levels of increasing smoking, the values computed from the data of Wynder *et al.* (1957b) were 2.9, 1.8 and 8.4 (given by Rothman & Keller, 1972), and from those of Rothman and Keller (1972), 1.5, 1.4 and 2.4, respectively. The relative risk for oral cancer among pipe, cigar and mixed smokers in the study of Wynder *et al.* (1957b) was 4.9.

In an early hospital-based case-control study in India and Sri Lanka Hirayama (1966) found a significant association between current smoking and cancer of the buccal mucosa (relative risk, 3.3 in men who did not chew betel quid or tobacco). The relative risk for male *bidi* smokers in Sri Lanka was 2.6.

Jussawalla and Deshpande (1971) conducted a case-control study in Bombay of patients with cancers of the oral cavity, pharynx, larynx and oesophagus. Equal numbers of controls matched by age, sex and religion were selected from voters' lists. Risks relative to those for nonsmokers and nonchewers were determined for those who smoked, for chewers of betel quid with or without tobacco and for those with both habits. The relative risks for oral cancer were 2.8, 6.0 and 10.1, respectively. Examination of risks separately for cigarette smokers and for *bidi* smokers suggested that there was little or no effect of cigarette smoking on the incidence of oral cancer, but an important effect of *bidis* (relative risk, 2;

$p < 0.001$). Jayant *et al.* (1977), using data from the same study, calculated 'etiologic fractions' [attributable risks] of 65% for smoking and 90% for smoking plus chewing.

Reverse *chutta* smoking (in which the burning end is inserted in the mouth) has been associated with cancer of the hard palate (Ramalu & Reddy, 1972).

(iii) *Cancer of the larynx*

Wynder *et al.* (1976) in an analysis of laryngeal cancer in the USA found the following relative risks among male cigarette smokers who were non- and light drinkers: for smokers of 1-15 cigarette equivalents/day of tobacco, 3.0; for 16-34 cigarette equivalents/day, 6.0; and for smokers of >35 cigarette equivalents/day, 7.0. Similar risks were found for supraglottic and glottic tumours.

In a Canadian study (Burch *et al.*, 1981), the risks for laryngeal cancer among nondrinkers were estimated as follows: relative risk for smokers who had smoked <150 000 cigarettes (lifetime consumption), 2.0; for 150 000-299 000, 3.9; and for ⩾300 000, 7.6. In another study from Canada, Elwood *et al.* (1984) distinguished cancers of the extrinsic and intrinsic larynx; for smokers of 1-9, 10-19, 20-29 and ⩾30 cigarettes/day, the relative risks were 2.1, 6.8, 5.4 and 4.1 for extrinsic larynx and 1.7, 2.1, 4.0 and 3.9 for intrinsic larynx, respectively.

In a hospital-based case-control study of cancer of the larynx in the USA, Wynder and Stellman (1979) examined the risk from nonfilter cigarette use relative to long-term (at least 10 years) use of filter cigarettes. After adjustment for duration of smoking, number of cigarettes used per day and alcohol consumption, the relative risks were 1.5 (95% confidence limits, 1.1-2.1) for men and 4.0 (2.0-7.7) for women.

Jussawala and Deshpande (1971) found relative risks of 7.7, 4.6 and 20.1 for smokers, chewers and smokers + chewers, respectively, for laryngeal cancer. Using the same data, Jayant *et al.* (1977) calculated an 'etiologic fraction' [attributable risk] of 87% for smoking and 95% for smoking + chewing for cancer of the larynx.

(iv) *Cancer of the pharynx*

Cancers of the pharynx have usually been considered in conjunction with cancers at other sites in case-control studies. Elwood *et al.* (1984) reported some increase in risk for cancer of the pharynx (grouping oro-and hypopharynx) with increasing smoking, but the relationship was weak and nonsignificant.

In a case-control study in India and Sri Lanka, a relative risk of 21.0 was found for oropharyngeal cancer among nonchewing tobacco smokers of both sexes (Hirayama, 1966). Jussawalla and Deshpande (1971) found relative risks for oropharyngeal cancer of 11.8, 3.3 and 31.7, respectively, for smokers, for chewers of betel quid with or without tobacco and for people who both smoked and chewed. Cigarette smokers had a relative risk of 2, while *bidi* smokers had a risk of 14; smokers of both cigarettes and *bidis* had a risk of 6; all were statistically significant ($p < 0.001$). Using the same data, Jayant *et al.* (1977) calculated 'etiologic fractions' [attributable risks] of 92% for smoking and 97% for smoking and chewing in relation to oropharyngeal cancer.

With regard to hypopharyngeal cancer, Jussawalla and Deshpande (1971) reported relative risks of 3.6, 6.2 and 16.9 for smokers, chewers and those with both habits, respectively; and the 'etiologic fractions' [attributable risks] were 72% for smoking and 94% for smoking and chewing (Jayant *et al.*, 1977).

Three case-control studies have reported a positive association between nasopharyngeal tumours and cigarette smoking. Relative risks of about 3 in Taiwan (Lin, T.M. *et al.*, 1973) and of 1.8 in Kwantung province of China (Hu & Huang, 1972, cited by Henderson & Louie, 1978) were reported for smokers of >20 cigarettes/day, as compared to nonsmokers. Jussawalla and Deshpande (1971) found relative risks of 3.3, 1.8 and 4.8 for smokers, chewers and those with mixed habits, respectively, in relation to nasopharyngeal cancer. Two case-control studies conducted in California, USA (Henderson *et al.*, 1976) and Singapore (Shanmugaratnam *et al.*, 1978) demonstrated no such association. In a case-control study in Hong Kong (Geser *et al.*, 1978), the choice as controls of patients with cancers related to smoking precluded evaluation of the association.

(v) *Cancer of the oesophagus*

As for other sites in the upper digestive tract, the effect of smoking on the incidence of oesophageal cancer is often combined with that of other factors. In the western world, alcohol is the most common additional factor. In a study in New York, USA, Wynder and Bross (1961) reported an association between oesophageal cancer incidence and smoking among light drinkers, and mentioned that the risk was greater for cigar and/or pipe smokers than for cigarette smokers. In a region of France where the incidence of oesophageal cancer is high, the relative risks among light drinkers were 3.4 for males smoking 10-19 g tobacco/day and 5.1 for smokers of ⩾20 g (Tuyns *et al.*, 1977). An analysis of the data by type of smoking (Tuyns & Estève, 1983) also indicated that the risk might be greater among pipe smokers and smokers of hand-rolled cigarettes than among smokers of commercial cigarettes.

From the data of Jussawalla (1971), Day *et al.* (1982) calculated relative risks for oesophageal cancer among non-chewing male smokers of *bidis* and of western cigarettes to be 8.0 and 2.8, respectively, and that for smokers of both types, 37.5. Using the data of Jussawalla and Deshpande (1971), Jayant *et al.* (1977) calculated 'etiologic fractions' [attributable risks] of 54% for smokers and 84% for smokers and chewers in relation to cancer of the oeosophagus.

In Iran, another area where the incidence of oesophageal cancer is very high, Cook-Mozaffari *et al.* (1979) found a statistically significant relative risk of 1.5 among male cigarette smokers.

In South Africa, the relative risks for oesophageal cancer among male cigarette smokers, pipe smokers and combined smokers were reported by Day *et al.* (1982) to be 2.3, 3.7 and 5.0 in Johannesburg and 0.8, 2.3 and 8.5 in Durban. They noted a higher risk among users of pipe tobacco than among cigarette smokers.

(*b*) *Cancer of the stomach*

(i) *Cohort studies*

The major cohort studies on smoking have also addressed the risk of stomach cancer among smokers. Most studies have reported relative risks of the order of 1.4 to 1.5 for cigarette smoking, but no dose-response relationship (Hammond, 1966; Kahn, 1966; Doll & Peto, 1976). [The Working Group noted that if the association reported in the study by Hirayama (1982) is causal, the number of excess deaths from stomach cancer attributed to smoking in the Japanese cohort would be equivalent to those from lung cancer.]

(ii) *Case-control studies* (Table 83)

Wynder *et al.* (1963b) found no relationship between smoking and stomach cancer in their hospital-based, multicentre case-control study.

A negative association between smoking and stomach cancer was observed in a gastroscopy-clinic-based case-control study in Chile (Armijo *et al.*, 1981). [The Working Group noted that the smoking experience of the study subjects was presented as mean number of years smoked for cases and controls, and that control selection may not have been appropriate since they may have had diseases associated with smoking.]

A hospital-based case-control study carried out in Hiroshima and Miyagi, Japan, demonstrated a weak association between cigarette smoking and stomach cancer (Haenszel *et al.*, 1976).

A hospital-based case-control study carried out among Hawaiian Japanese (Haenszel *et al.*, 1972) and another in France (Hoey *et al.*, 1981) revealed increased risks for stomach cancer among cigarette smokers as compared to nonsmokers. In the study in Hawaiian Japanese, the risk was greater in Issei (first-generation migrants) than in all Hawaiian Japanese. [The Working Group considered that, in the study of Hoey *et al.* (1981), alcohol did not seem to confound the association with cigarette smoking; however, although the relative risks observed were high, the population studied was very small.]

One population-based case-control study carried out in three areas of Canada (Newfoundland, Manitoba and Toronto, Ontario) revealed only a slight elevation of relative risk for stomach cancer with cigarette smoking, after adjustment for various dietary factors (Risch *et al.*, 1985).

(*c*) *Cancer of the liver*

Cancer of the liver was positively associated with cigarette smoking in the Japanese Study (Hirayama, 1981a) and the American Cancer Society 25-State Study (Hammond, 1966). The latter reported relative risks of 2.8 for men aged 45-64 and of 1.3 for men aged 65-79. No information was available on alcohol consumption, but the finding of standardized mortality ratios for liver cirrhosis of 2.1 and 2.0 in the two age groups, respectively, is indicative of a major confounding effect. In the Japanese Study, the results were stratified by alcohol consumption (daily drinking *versus* less than daily): within each drinking category a significant increase in risk is seen with increasing level of smoking

Table 83. Case-control studies on stomach cancer and cigarete smoking

Reference (place and years of study	No. of cases	No. of controls	Factors adjusted for	Relative risk (95% confidence limits)	Comments
Haenszel *et al.* (1972) (Hawaii, 1963-1969)	220 men and women	440 men and women	-	1.5 (Hawaiian Japanese)[a]; 1.9[a] (Issei)	Smokers *versus* nonsmokers; no dose-response
Haenszel *et al.* (1976) (Japan, 1962-1964: Hiroshima; 1962-1965: Miyagi)	367 men and women (Hiroshima); 416 men and women (Miyagi)	734 men and women (Hiroshima); 832 men and women (Miyagi)	-	1.1 (Hiroshima) 1.3 (Miyagi)	Smokers *versus* nonsmokers
Hoey *et al.* (1981) (France, 1978-1980)	40	168	Eating lettuce, age	4.8 (1.6-14.8)	Smokers *versus* nonsmokers
				9.3 (4.9-19.0)	Smokers and drinkers *versus* nonsmokers
Risch *et al.* (1985) (Canada, 1979-1982)	246	246	Alcohol, diet	1.3 (1.0-1.6) ($p = 0.036$)	Smokers of > 20 cigarettes *versus* nonsmokers

[a]Significant at $p < 0.05$

(Table 84). [The Working Group noted that both studies are based on examination of death certificates, on which secondary liver cancers may have been included in the category 'liver cancer', and that many smoking-related cancers metastasize to the liver.]

Table 84. Age-standardized[a] mortality ratios for liver cancer according to cigarette consumption and alcohol use[b]

Life-long no. of cigarettes smoked	Alcohol use	
	Occasional, rare or none	Daily
None	26.5	24.0
1-190 000	38.8	49.4
200 000-390 000	39.9	45.8
400 000	45.2	66.9

[a]Standardized to the age distribution of the entire study population

[b]From Hirayama (1981a)

Hardell *et al.* (1984) examined a variety of exposures for 83 cases of hepatocellular carcinoma (HCC), 15 cases of cholangiocellular carcinoma and 200 controls in Sweden. A small positive association between HCC and smoking disappeared after controlling for alcohol consumption. A strong association was found between cholangiocellular carcinoma and smoking.

A case-control study of incident HCC among 11 black and 81 white non-Asians in Los Angeles, USA, in 1975-1979 (Yu *et al.*, 1983) reported an excess risk associated with cigarette smoking. The risks relative to that for nonsmokers and ex-smokers combined were 2.6 (95% confidence limits, 1.0-6.7) for smokers of >1 pack/day, and 1.2 (0.6-2.5) for smokers of ≤1 pack/day. Results were stratified by alcohol consumption (≥80 g ethanol/day *versus* 0-79 g ethanol/day). [The Working Group considered that because only four controls drank ≥80 g/day ethanol, there were insufficient data to study the effect of smoking among heavy drinkers. Among lighter drinkers, the effect does not reach significance, is lower in magnitude than the unstratified effect, and may be influenced by residual confounding.]

In two studies (Trichopoulos *et al.*, 1980; Lam, K.C. *et al.*, 1982), increased risks for HCC were associated with smoking among individuals whose sera gave negative results for the presence of hepatitis B surface antigen (HBsAg).

The study from Athens (Trichopoulos *et al.*, 1980) was based on 79 patients with HCC, 23 patients suspected of having HCC but in whom the diagnosis had not been confirmed, and 204 matched controls. The controls were diagnosed as having diseases other than cancer or liver disease. The sera of 40 of the HCC cases were HBsAg-negative, and a strong relationship with smoking of >20 cigarettes/day was seen in this group (relative risk, 5.5); the effect persisted after adjusting for alcohol consumption.

The study in Hong Kong (Lam, K.C. *et al.*, 1982) was based on an incident series of cases of HCC diagnosed over a 32-month period, and sex- and age-matched controls chosen from the orthopaedic ward of the same hospital. The series consisted of 149 cases, of which 107 were included in the study; but only 19 were HBsAg-negative. The cigarette consumption of these 19 cases was compared with that of the 107 controls; the relative risk for smokers of >20 cigarettes/day was 3.3 (95% confidence limits, 1.0-13.4). Only one of the HCC patients who was a heavy smoker was also a heavy drinker, and, overall, there was no significant association between alcohol consumption and risk for HCC. In this study, peanuts were not considered to be an important source of aflatoxin.

[The Working Group noted that in three of the studies no data were given on possible exposure to aflatoxins.]

(*d*) *Cancer of the pancreas*

(i) *Correlation studies*

Pancreatic cancer incidence and mortality rates have been rising in western countries and in Japan for many decades, with a possible decrease or levelling off from around 1970 (Gordis, 1980). This may be due in part to improving ability to diagnose the disease. The high rates in blacks in the USA suggest, however, that this is not solely a diagnosis of those with access to advanced medical care (Levin, D.L. *et al.*, 1981).

Stocks (1970) compared the average cigarette consumption per adult for the years 1951-1954 in 20 industrialized countries with the sex-specific, age-standardized pancreatic cancer mortality rates from those same countries in 1964-1965. Comparing mortality rates in countries with average adult cigarette consumption above the median to those with below median consumption, he found nonsignificant excesses for both men and women in countries where there was higher use. Using a somewhat more sensitive analysis (Pearson product-moment correlation coefficient; Kendall & Stuart, 1958), but very similar data, Binstock *et al.* (1983) found small, nonsignificant, positive correlations between pancreatic cancer mortality in 1971-1974 in 17 countries and the corresponding annual number of cigarettes and total tobacco consumption in adults in 1957-1965.

Breslow and Enstrom (1974) found that cigarette consumption, as estimated from US tax revenue data, showed a nonsignificant positive correlation with mortality from pancreatic cancer in both men and women. Kono and Ikeda (1979), using Japanese tax and mortality figures, found a similar lack of association. [The Working Group noted that, in both studies, the pattern of purchase of cigarettes, as reflected in tax figures, may not reflect actual geographic patterns of consumption.]

Two studies employed specific survey data within countries, as opposed to national trade or tax data, to estimate exposure to tobacco. In Hawaii, Hinds, M.W. *et al.* (1980) used cigarette consumption data from personal interviews to estimate male and female intakes for each of five ethnic groups, from which they estimated that 20 pack-years of cigarette use resulted in approximately a 50% increase in pancreatic cancer rate. Using exposure data derived from survey and trade statistics compiled by the Tobacco Research Council, Moolgavkar and Stevens (1981) found that all gender effects and a substantial

portion of cohort effects in pancreatic cancer mortality in England and Wales from 1941 to 1975 could be explained by taking into account age-, sex-and calendar time-specific estimates of lifetime cumulative smoking histories, with a relative risk of 1.6 for 20 pack-years of smoking.

Three studies have indicated an association between lung and pancreatic cancer (Winkelstein *et al.*, 1977; Blot *et al.*, 1978; Howe *et al.*, 1984).

(ii) *Cohort studies* (Table 85)

In the cohort study of male British Doctors (Doll & Peto, 1976), 92 cases of pancreatic cancer had accumulated by 1971. The comparison of pancreatic cancer mortality between nonsmokers and all others (current and ex-smokers of different forms of tobacco) was nonsignificant, but the trend in risk among smokers was statistically significant. The experience of women who responded in the same survey has been reported through 1973 (Doll *et al.*, 1980). Only 14 deaths from pancreatic cancer had occurred, and no pattern relating to tobacco use is evident.

In the cohort of US Veterans (Kahn, 1966), 415 deaths from or associated with pancreatic cancer were identified from July 1954 to December 1962, with a monotonic increase in risk over categories of intensity of current smoking. Current smokers of pipes and cigars only had no excess risk (cigars only, 1.5; pipe only, 0.7; pipe and/or cigars, 1.1; pipe plus cigars, 0.9), and ex-smokers had a modest gradient according to intensity of former smoking. A follow-up of this cohort to the end of 1969 (Rogot & Murray, 1980) continued to indicate elevated risks for both current and ex-smokers. In a follow-up of Canadian veterans (Lossing *et al.*, 1966), results very similar to those of Kahn (1966) were obtained.

The American Cancer Society cohort studies (Hammond & Horn, 1958a,b; Hammond, 1966; Hammond & Seidman, 1980) indicated approximate doubling of risk for pancreatic cancer in male and female smokers of all ages. Male pipe and cigar smokers had risks only slightly lower than those of cigarette smokers. Risks for nonsmoking men and women were very similar.

Follow-up of the mortality experience of the Swedish cohort over 10 years also yielded a picture of a graded effect of smoking on risk for pancreatic cancer for both men and women (Cederlöf *et al.*, 1975).

In the Californian cohort study, Weir and Dunn (1970) found a ratio of directly age-standardized death rates in smokers to nonsmokers of 2.4, based on 71 observed deaths, with a striking gradient of *decreasing* relative risk for pancreatic cancer with increasing quantity typically smoked. Strong positive risk gradients were seen for both lung and bladder cancer; the paradoxical pattern for pancreatic cancer remains unexplained.

In the Japanese cohort (Hirayama, 1981a), the relative risk for pancreatic cancer in male smokers after 13 years of follow-up was of the order of 1.6, an effect which persisted after adjustment for social class and consumption of meat and of green, leafy vegetables.

Heuch *et al.* (1983) assembled three subgroups of Norwegians for whom smoking data were available from 1960. When analysis was confined to the 22 histologically verified cases, a marginally significant relative risk for pancreatic cancer of 2.0 was identified.

Table 85. Cohort studies on pancreatic cancer and tobacco smoking

Reference	Cases	Rate/Ratio estimates[a]									Comments
Doll & Peto (1976)	78 men	G/D	0	1-	15-	25+	Ex				Trend $p < 0.1$ among current smokers
		Rate	14	14	18	27	12				
Doll *et al.* (1980)	14 women	Rate	9	4	24	16	11				
Kahn (1966)	415 men	C/D	0	Oc	1-	10-	21-	40+	Ex	P+C	
		Ratio	1.0	1.1	1.4	1.8	2.2	2.7	1.3	0.9	
Lossing *et al.* (1966)	-[b]	Ratio	1.0		1.4	2.0	2.4				
			Never	regular							
Hammond & Horn (1958b)	117 men	Ratio	1.0	1.5							
Hammond (1966)		Rates	Age	Never	Ever						
	274 men		45-64	7	19						
			65-79	31	66						
	108 women		45-64	6	11						
Cederlöf *et al.* (1975)		C/D	0	1-	8-	16+	Ex	Pipe G/D	1-	6+	C + P
	46 men	Ratio	1.0	1.6	3.4	5.9	4.8[c]		2.2	6.2[c]	3.8[c]
		Rate	0.8								
	37 women	Ratio	1.0	2.4	2.5	3.0	5.5				
		Rate	1.6								
Weir & Dunn (1970)	71 men	C/D	0	10	20	30+					'Smokers', current and ex-smokers; 'non-smokers', also pipe and cigar
		Ratio	1.0	2.9	2.5	1.4					
Hirayama (1981a)	251 men	C/D	0	Oc	1-	10-	20+	Ex			Ratio ever *vs* never, 1.6[c]
		Rate	13.3	12.8	14.7	19.8	20.3	15.4			
Heuch *et al.* (1983)	22 men and women	C/D	0	10+							Histologically confirmed
		Ratio	1.0	2.0							

[a]Rates per 100 000 person-years at risk. Abbreviations: C/D, no. of cigarettes/day; ex, former cigarette use; oc, occasional cigarette use; P+C, pipe and cigar use; G/D, grams of tobacco/day; C+P, cigarette and pipe use

[b]No. of cases in nonsmoking men not given; 28 cases in male cigarette smokers

[c]$p < 0.05$

(iii) *Case-control studies* (Table 86)

The most common study design has included incident cases diagnosed in hospitals and compared to hospitalized controls, excluding patients admitted for tobacco-related diseases. The oldest data of this type stem from a study carried out by Stocks in 1952-1954 but reported only recently (Kinlen & McPherson, 1984). In both men and women, there was a modest, positive association between smoking and relative risk. Wynder *et al.* (1973) reported a smooth increase in relative risk with typical (current or former) cigarette consumption in men. A subsequent, larger study from a hospital-surveillance scheme (Wynder *et al.*, 1983) yielded similarly increased risks. In a study in which the control group further excluded patients with diabetes and any biliary or pancreatic disease, MacMahon *et al.* (1981) found modestly increased relative risks for male and female daily smokers.

Whittemore *et al.* (1983) reported an analysis of data on pancreatic cancer mortality drawn from a follow-up system covering 50 000 men who were students at Harvard University from 1916-1950 or at the University of Pennsylvania from 1931-1940. In a case-control analysis of 126 pancreatic cancer decedents and 504 men sampled from the cohort at risk, they examined data obtained during university health examinations and later surveys in relation to subsequent risk for pancreatic cancer. They found relative risks of approximately 2.5 for men who had smoked ⩾10 cigarettes/day at college as compared to nonsmokers at college. Similar risk elevations were identified on the basis of cumulative adult cigarette exposure.

In two case-control studies with controls taken from the general population, results of the same order of magnitude as those of the hospital-based studies were found. Durbec *et al.* (1983) obtained 199 controls for 69 cases in a door-to-door neighbourhood search. They estimated a nonsignificant relative risk of 1.3 for each 10 g/day increase in tobacco consumption after controlling for age, sex and alcohol consumption (which was a strong predictor of pancreatic cancer). Using more refined control sampling techniques as part of a regional case-control study of cancer and water-borne asbestos, Polissar *et al.* (1984) found a statistically significant overall relative risk of 1.7 for women who had ever smoked.

[The Working Group noted that the only case-control study in which a positive association between smoking and pancreatic cancer was not found (Lin, R.S. & Kessler, 1981) included persons with smoking-related diseases in the control group, an approach that can produce a negative bias in estimates of relative risk.]

(*e*) *Cancer of the cervix*

Data from 15 studies in which the association between cigarette smoking and risk of cervical cancer was explicitly considered are displayed in Table 87. The studies vary widely in size, in methods and in the type of case included. Some are confined to invasive cancers, or even to death from invasive cancers; others concentrate on precancerous conditions; some include both invasive and preinvasive lesions.

Table 86. Case-control studies of pancreatic cancer and tobacco smoking

Reference (place and years of study)	Numbers and sources of: Cases	Numbers and sources of: Controls	Covariates adjusted for	Rate ratio estimates[a]	Comments
Kinlen & McPherson (1984) (UK, 1952-1954)	109 men 107 women Not specified	218 men 214 women Cancers unrelated to smoking	Age, sex	C/W: 0; 10-49; 50-149; 150+; Pipe Men: 1.0; 1.3; 1.6; 1.1; 1.2 Women: 1.0; 1.1; 1.6	
Wynder *et al.* (1973) (USA, 1950-1964)	100 men 42 women 9 hospitals	200 men 107 women hospitalized, without tobacco-related disease	Controls matched for age, sex, race	C/D: 0; 1-10; 11-20; 21-40; ≥41 Men: 1.0; 2.0; 2.2; 3.6; 5.0 Women: 1.0; 0.7; 5.3; 1.6; 0	$p<0.25$, $p<0.5$ } Calculated by the Working Group
Wynder *et al.* (1983) (USA, 1981)	153 men 122 women 15 hospitals	7994 men and women hospitalized without tobacco-disease	Age	C/D: 0; 1-10; 11-20; 21-30; >31; ex; P/C Men: 1.0; 0.9; 2.1[b]; 2.3[b]; 3.0[b]; 1.7[b]; 2.0[b] Women: 1.0; 1.8; 1.5; 2.0[b]; 1.4	
MacMahon *et al.* (1981) (USA, 1974-1979)	218 men 149 women 11 hospitals	306 men 337 women hospitalized without tobacco- or alcohol-related disease	Age, sex	C/D: 0; 1-19; ≥20; ex Men: 1.0; 1.1; 1.4; 1.4 Women: 1.0; 1.5; 1.6; 1.3	Trend: $p>0.05$ $p<0.05$

Table 86 (contd)

Reference (place and years of study)	Numbers and sources of		Covariates adjusted for	Rate ratio estimates[a]						Comments
	Cases	Controls								
Whittemore *et al.* (1983) (USA, 1962-1966)	122 men University of Harvard and University of Pennsylvania	481 men Random classmates	Age, school year	Pack-years	0	1-9	10-19	20-29	≥30	Overall $p<0.05$ Data obtained by mail survey prior to diagnosis
					1.0	1.0	2.1	2.4	2.5	
Durbec *et al.* (1983) (France, 1979-1980)	37 men 32 women 3 hospitals	100 men 99 women Neighbourhood search	Age, sex, neighbourhood, alcohol	1.3 per 10 g/day current intake						
Polissar *et al.* (1984) (USA, 1977-1980)	13 men 10 women Population-based tumour registry	213 men 249 women Census tract	Age, alcohol, education, asbestos		Never	Ever				
				Men	1.0	0				
				Women	1.0	5.4[b]				

[a]Abbreviations: C/W, no. of cigarettes/week; C/D, no. of cigarettes/day; ex, former smokers; P/C, pipe and/or cigar smoker

[b]$p<0.05$ for the value given

Table 87. Summary of studies with data on the association between cervical cancer and smoking

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Tokuhata (1967) (Southern USA, 1950-1966)	283	Deaths from carcinoma of cervix (266), vagina and vulva (17)	1.2	Similar in white and black women		Use of snuff more strongly associated (overall relative risk, 1.5) not affected by adjustment for a number of social variables
Thomas, D.B. (1973) (USA, 1963-1969)	209	CIS and dysplasia	CIS, 1.7 Dysplasia, 1.2		Variety of social factors After adjustment, CIS, 1.5 Dysplasia, 1.1	'Cases and controls did not differ significantly by the proportion that had ever smoked regularly, the proportion that smoked when interviewed, amount smoked, or age at which smoking started' (statement by authors)
Cederlöf *et al.* (1975) (Sweden, 1963-1973)	178	Not explicitly stated but must contain many CIS cases Prospective study	Age-adjusted, 3.0	By amount smoked/day 1-7 2.8 8-15 3.0 ≥16 3.4 Ex-smoker 1.4	Place of residence and income Little confounding	

Table 87 (contd)

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Hirayama (1975b) (Japan, 1965-1973)	288	Deaths from cervical cancer Prospective study	SMR for smoking, 1.72	Cigs /day 0 1.0 <20 1.8 20-29 3.5		
Williams, R.R. & Horm (1977) (USA, 1969-1971)	266	Invasive		Packs-years ≤20 1.2 21-39 1.6 ≥40 1.8	After adjustment for race, no. of children and socioeconomic indicators, a 'mild' positive association remained	Relative risk higher for snuff taking (3.1, 2.3 for different consumption levels), which increases after adjustment for smoking (4.7, 3.6) and remains after adjustment for education level
Wright *et al.* (1978) (UK, 1968-1974)	65	6 invasive 33 CIS 26 dysplasia Prospective study		Cigs/ day 1-14 1.5 15+ 2.9	Significance unaltered by adjustment for contraceptive method	'In our view, it is unlikely that use of tobacco could have any direct effect on the cervix.' (statement by authors)

Table 87 (contd)

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Garfinkel (1980) (USA, 1960-1972)	308	Deaths from cervical cancer Prospective study	Non-smokers/ all of cohort, SMR, 0.87			
Harris, R.W.C. *et al.* (1980) (UK, 1974-1979)	237	Dysplasia and CIS	Cigs/ day: 0 — Mild dysplasia 1.0; Severe dysplasia 1.0; CIS 1.0 <15 — 3.1; 2.7; 1.9 15-19 — 1.7; 3.5; 3.3 20-24 — 5.0; 3.1; 4.3 ≥25 — 1.7; 5.1; 2.8		No. of sexual partners; pregnancy outside marriage; use of oral contraceptives: Cigs/ day: None 1.0; <15 2.2; 15-19 2.4; ≥20 2.1	Weak effect of alcohol consumption, made weaker by adjustment for number of sexual partners
Stellman *et al.* (1980) (USA, 1974-1977)	332	Invasive	Risk ratios for >10 cigarettes/day range from 1.4-1.6 before adjustment and from 1.2-1.3 after adjustment for age and socioeconomic status, the value depending on the amount smoked. Smokers of <10/day have a relative risk of <1			Socioeconomic status has little confounding effect; the reduction of the relative risks after adjustment is due mainly to age

Table 87 (contd)

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Wigle *et al.* (1980) (Canada, 1971-1973)	676	168 invasive 508 CIS	Invasive: current, 2.0 former, 1.0 CIS: current, 3.8 former, 1.3	Pack-years / Invasive / CIS <10 / 1.2 / 2.8 11-20 / 1.7 / 4.0 21-30 / 2.1 / 3.9 ≥31 / 2.7 / 3.7 No adjustment made for social or sexual variables		
Buckley *et al.* (1981) (UK, 1974-1979)	31 cases all reporting only 1 sexual partner	17 preinvasive 14 invasive	Matched Current smokers, 7.0 Ex-smokers, 2.8		No. of sexual partners of husband Current, 7.8 Ex-smokers, 3.7	Smoking of husbands of cases Before adjustment / After adjustment Current 3.2 / 2.2 Ex-smokers 2.7 / 2.0 Relative risk, 35, among a small series of multiple-partner women with husbands who smoke *versus* those with non- or ex-smoking husbands

Table 87 (contd)

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Clarke *et al.* (1982) (Canada, 1973-1976)	178	Invasive squamous-cell cancer	Current smokers, 2.3 Ex-smokers, 1.7	<10/day, 2.2 >20/day, 2.9	'Sexual stability'; age at first intercourse; grade of education. Current smoker, 2.2	'Sexual stability' and age at first intercourse equally related to smoking and cervical cancer risk, 2 and 2.1
Berggren & Sjöstedt (1983) (Sweden, 1974-1978)	609	Preinvasive	2.7 (crude)	None given in terms of relative risk	Urban/rural difference	Relative risk changes sharply with age: Relative risk / Age (years) 9.5 / 15-24 4.4 / 25-29 3.1 / 30-34 2.5 / 35-39 2.8 / 40-44 1.6 / 45-49 1.3 / 50-54 1.5 / 55-59 5.1 / 60+

Table 87 (contd)

Reference (place and years of study)	No. of cases	Type of case[a]	Relative risk	Dose-response	Variables adjusted for and effect of adjustment	Other comments or relevant findings
Marshall, J.R. *et al.* (1983) (USA, 1957-1965)	513	Cervical cancer (presumably invasive)	Current smokers, 1.6 Ex-smokers, 0.8	Cigs/day Never 1.0 Occa-sionally 1.3 <10 1.7 19-19 1.7 20-40 1.0 >40 0.4	No. of marriages; age at marriage; dietary factors Unmarried women smokers, [1.1][b] Married women smokers, [0.5][b]	'Smoking and number of marriages are interchangeable suggesting that both are surrogates of some third factor' (paraphrase of authors' comments)
Martin & Hill (1984) (South Africa, 1950-1969 [survey] 1970-1974 [follow-up])	257	Cervical cancer	Use of tobacco in any form, 1.5		Use of alcohol 1.3; χ^2=2.32	Relative risk associated with indigenous alcohol, 3.2, which is the strongest association in the study

[a]CIS, carcinoma *in situ*

[b]Calculated by the Working Group

SMR, standardized mortality ratio

The studies of Tokuhata (1967), Hirayama (1975b), Williams, R.R. and Horm (1977), Garfinkel (1980), Stellman *et al.* (1980), Wigle *et al.* (1980), Clarke *et al.* (1982), Marshall, J.R. *et al.* (1983) and Martin and Hill (1984) gave results separately for invasive disease. Leaving aside the study by Garfinkel (1980), since the comparison group used consisted entirely of women, not smokers, the values for the unadjusted (except for age) relative risks by amount smoked are well within the range explicable by moderate confounding effects, except for heavy smokers in the two Canadian studies (Wigle *et al.*, 1980; Clarke *et al.*, 1982) and the Japanese study (Hirayama, 1975b) (Table 88). In the studies by Tokuhata (1967), Hirayama (1975b) and Wigle *et al.* (1980), no adjustment for social or sexual variables was performed. In the study of Clarke *et al.* (1982), adjustment for 'sexual stability' and age at first intercourse had little effect, but neither variable is strongly associated with disease; they are both moderately related to smoking. [The Working Group considered that the effect of smoking is confounded by sexual variables, but that the data were not adequate to remove the confounding effect.] In the studies by Stellman *et al.* (1980), Marshall, J.R. *et al.* (1983) and Martin and Hill (1984), the crude odds ratios were reduced by adjusting for a range of variables. [The Working Group considered that a reasonable conclusion to draw from the studies of invasive disease is that the results, although all indicating a positive effect of smoking, are compatible with the residual confounding effects of variables that play a more basic role in the epidemiology of the disease.]

Table 88. Relative risks for invasive cancer of the cervix

Reference	Nonsmokers	No. of cigarettes/day				
		<10	10-19	20-29	30-39	≥40
Tokuhata (1967)	1.0	←		1.2		→
Hirayama (1975b)	1.0	←	1.8 →	3.5		
Williams, R.R. & Horm (1977)[a]	1.0	←	1.2 →	←	<1.6 —	1.8 →
Stellman *et al.* (1980)	1.0	0.7	1.4	1.5	←	1.4 →
Wigle *et al.* (1980)	1.0	1.2	1.7	2.1	←	2.7 →
Clarke *et al.* (1982)	1.0	2.2	-	←		2.9 →
Marshall, J.R. *et al.* (1983)	1.0	1.7	1.7	←	1.0 →	0.4
Martin & Hill (1984)	1.0	←		1.5		→

[a]Consumption expressed as pack-years

In the study by Buckley *et al.* (1981), husband's smoking was strongly related to his sexual activities and to his wife's cervical cancer risk, although the association was weakened by adjustment for the husband's sexual experience.

In a review by Winkelstein *et al.* (1984), data are presented showing a strong association between level of herpes simplex virus-2 antibodies and smoking. Low levels of antibodies gave relative risks of 3 and 8 in smokers and nonsmokers, respectively; and high antibody levels gave values of 12 and 8 for smokers and nonsmokers.

[The Working Group considered that the results of these two studies add weight to the contention that smoking is associated with determinants of a sexually-transmitted disease.]

The studies of preinvasive lesions, or in which a majority of cases were preinvasive (Thomas, D.B., 1973; Cederlöf *et al.*, 1975; Harris, R.W.C. *et al.*, 1980; Wigle *et al.*, 1980; Buckley *et al.*, 1981; Berggren & Sjöstedt, 1983) give, on average, higher relative risks for smoking than do the studies of invasive disease.

[A large number of studies have reported an increased risk for cervical cancer or its preinvasive precursors among women who smoke. The data refer almost entirely to cigarette smoking. In general, the increase in risk reported is about two fold, although higher values have been reported. Little information seems to be available on whether smokers are more or less frequent attenders at screening clinics, but it is conceivable that smoking and non-attendance are positively correlated: the incidence of invasive cancer is often five to ten times higher among non-attenders than among regular attenders; for preinvasive lesions, the prevalence at first attendance is typically five times greater or more than at the third or later attendance, so that both for invasive and preinvasive disease a woman's screening history is a strong potential confounder.

[For cervical cancer, it is reasonable to suppose that there is a specific causal agent — most probably an infective agent transmitted sexually. Since this agent has not been unequivocally identified, and, in particular, was not included in the studies under review, surrogate measures have been used to reflect degree of sexual activity. Smoking is positively related to sexual activity. Any observed crude association between smoking and risk of cervical cancer may be confounded. Since the specific factor by which the analysis should be adjusted is not known, the confounding effect can be removed only partially.]

(*f*) *Cancer of the endometrium*

In four studies, a decreased risk for the development of endometrial cancer among smokers compared to nonsmokers is reported. A population-based case-control study in Washington State, USA, in 1975-1976 (Weiss, N.S. *et al.*, 1980), in which 322 incident cases aged 50-74 years were compared with a random control sample of 289 women aged 50-74 years from the general population, showed a deficit of endometrial cancer among smokers, with a relative risk of 0.4 (95% confidence limits, 0.2-0.7) among nonusers of exogenous oestrogens. The results were obtained using logistic regression in a model which included parity, hypertension, smoking, weight, age (three strata), duration, mode and dose of

oestrogen use, and time since stopping use of oestrogens. This negative association did not vary with daily number of cigarettes smoked.

In a second case-control study, with 167 incident cases and 903 hospital controls (Kelsey *et al.*, 1982; Baron, 1984), a risk of 0.8 was reported for women who had ever smoked regularly relative to nonsmokers. The analysis was adjusted for age, parity, weight, menopausal status, education and use of oral contraceptives and oestrogens.

The US Third National Cancer Survey (Williams, R.R. & Horm, 1977), which comprised 358 cases and 3188 hospital controls, resulted in a risk of 0.7 for women with 20-40 pack-years of cigarette smoking relative to nonsmokers. The analysis controlled for age and race.

The Swedish cohort study (data derived by Baron, 1984, from Cederlöf *et al.*, 1975), with 80 incident cases (33 deaths), reported a risk of 0.7 for current smokers relative to nonsmokers, after adjusting for age. This study and an American Cancer Society cohort study (Garfinkel, 1980) reported standardized mortality ratios for cigarette-associated risk of death from endometrial cancer of 1.9 (based on 33 deaths) and approximately 1, respectively.

[The Working Group noted that there are a number of methodological problems in the interpretation of mortality studies of endometrial cancer, relating in particular to the accuracy of death certification. For these reasons, results based on mortality should be given less weight than those based on incidence.]

There is consistent evidence that age at menopause is reduced by one to two years among cigarette smokers (Baron, 1984). [This effect indicates that smoking affects hormonal status, which is known to be related to endometrial cancer.]

(*g*) *Cancer of the breast*

A large number of studies have addressed the association between breast cancer and cigarette smoking, including 18 case-control and cohort studies (summarized in Tables 89 and 90) investigating the health effects of oral contraceptives and the major prospective studies of smoking. There is some suggestion of a decreased risk, but the reported relative risks are distributed on both sides of unity, ranging from 0.7 (Doll *et al.*, 1980) to 1.4 (Hirayama, 1975a).

[The Working Group considered that the effect of smoking on age at menopause could be expected to reduce breast cancer risk, but by an amount scarcely detectable by epidemiological studies, i.e., about 5%. The epidemiological results are consistent with such a decrease, but cannot be said to demonstrate it.]

(*h*) *Summary*

For cancers of the upper respiratory and upper digestive tracts, all the studies that examined the role of smoking in the absence of alcohol drinking showed an effect of tobacco smoking and a dose-response relationship (see following section for combined effects). The relative risks observed for cancer of the oesophagus, however, were lower than those for oral

Table 89. Case-control studies on breast cancer and smoking

Reference (place and years of study)	Subjects	Confounding variables considered	Contrast	Relative risk
MacMahon & Feinleib (1959) (USA, 1957-1959)	340 cases; 340 hospital controls	Age, race, religion, nativity, marital status, parity, hospital, hospital service	Current smoker *vs* nonsmoker	1.0[a]
Valaoras *et al.* (1969) (Greece, 1965-1967)	799 cases; 2470 hospital controls	Age, hospital	Ever smoker *vs* never smoker	1.0[a]
Lin, T.M. *et al.* (1971) (Taiwan, 1954-1963)	213 cases; 648 hospital controls	Age, hospital	Ever smoker *vs* never smoker	0.9[a]
Mirra *et al.* (1969) (Brazil, 1966-1968)	536 cases; 1550 hospital controls	Age, hospital	Smoker *vs* nonsmoker	Approximately 1
Williams, R.R. & Horm (1977); Cutler *et al.* 1974 (USA, 1969-1971)	1167 cases, 3188 hospital controls	Age, race	20-40 pack-years *vs* nonsmoker	0.9
Paffenbarger *et al.* (1979) (USA, 1973-1977)	1432 cases, 2560 hospital controls	Age, race	Ever smoker *vs* never smoker	0.8[a,b]

Table 89 (contd)

Reference (place and years of study)	Subjects	Confounding variables considered	Contrast	Relative risk
Kelsey *et al.* (1981) (USA, 1977-1979)	332 cases; 1353 hospital controls	Age, age at first birth, age at menarche, age at menopause, history of benign breast disease, family history of breast cancer, menopausal status, oral contraceptive/oestrogen use, and others	Ever regular smoker *vs* never smoker	0.8[c]
Vessey *et al.* (1982, 1983) (UK, 1968-1980)	1176 cases, 1176 hospital controls	Age, marital status, parity, age at first term birth, social class, menopausal status, family history of breast cancer, history of benign breast disease, oral contraceptive/oestrogen use	1-14 cigarettes daily *vs* never smoker	0.8[c,d]
Centers for Disease Control (1983) (USA, 1980-1981)	1473 cases; 1839 community controls	Age, region of residence	Ever smoker *vs* never smoker	1.0[c]
Janerich *et al.* (1983) (USA, 1974-1976)	278 cases; 520 community controls	Age, county of residence, age of first term birth	Ever smoker *vs* never smoker	1.2[a]

[a]Derived by Baron (1984) from data given in the reference

[b]Observed number of smoking cases significantly less than expected, at $p<0.05$

[c]Reported by Baron (1984)

[d]Statistically different from 1, at $p<0.05$

Table 90. Cohort studies on breast cancer and tobacco smoking[a]

Reference (place and years of study)	No. of incident cases or deaths	Source of subjects	Confounding variables considered	Contrast	Event followed	Rate ratio
Royal College of General Practitioners (1974)[b] (UK, 1968-1976)	133 cases[c]	Patient volunteers	Age, parity, social class	Current smoker *vs* nonsmoker	Incidence	0.81[c]
Cederlöf *et al.* (1975) (Sweden, 1963-1973)	214 cases[a] 136 deaths[a]	Population sample	Age	Current smoker *vs* nonsmoker	Incidence Death	0.92[c] 0.69[c]
Hirayama (1975a) (Japan, 1965-1973)	108 deaths	Population sample	Age, social class	Daily smoker *vs* nonsmoker	Death	1.39
Vessey *et al.* (1976) (UK, 1968-1974)	92 cases[c]	Family planning clinic volunteers	Age, social class, age at first term birth	Current smoker *vs* nonsmoker	Incidence	0.71[c]
Doll *et al.* (1980) (UK, 1951-1973)	84 deaths	British physicians	Age	1-14 cigarettes daily *vs* never smokers	Death	0.65[a]

Table 90 (contd)

Reference (place and years of study)	No. of incident cases or deaths	Source of subjects	Confounding variables considered	Contrast	Event followed	Rate ratio
Garfinkel (1980) (USA, 1959-1972)	3096 deaths[d]	Volunteers	Age	Ever smoker *vs* entire cohort	Death	Approximately 1[e]
Ramcharan *et al.* (1981) (USA, 1969-1977)	94 cases	Health screenees	Age, parity, education, oestrogen use	≥1 pack/day *vs* never smoker	Incidence	0.85[a,f] 1.13[a,g]
Hiatt *et al.* (1982) (USA, 1960-1977)	714 cases	Health screenees	Age, parity, race, Quetelet's index, menopausal status, age at menarche, alcohol consumption, education, serum cholesterol	Ever smoker *vs* never smoker	Incidence	1.10

[a]Derived by Baron (1984) from data given in the reference

[b]Interim report

[c]Reported by Baron (1984)

[d]Among never regular smokers only

[e]Rate ratio of 1.0 for never regular smokers *versus* the entire study cohort

[f]Never users of oral contraceptives

[g]Ever users of oral contraceptives

and laryngeal cancer. The available data did not allow a firm conclusion to be reached about the relation of pharyngeal cancer to smoking.

Pipe and/or cigar smokers have excess risks for oral and oesophageal cancer that are about as high as those for cigarette smokers.

For stomach cancer, in general, the relative risks due to tobacco smoking are of the order of 1.5. There is, however, no consistent dose-response relationship. In some of the reported studies, the possible confounding effect of other variables, such as some dietary factors, were considered. However, at present it is not possible to conclude that the observed association is causal.

Moderate excesses of hepatocellular carcinoma have been observed in some of the major cohort studies, but mention of liver cancer on death certificates may be unreliable, and the possible role of confounding factors make interpretation of these findings difficult. Two studies of populations with relatively high rates of liver cancer found associations with cigarette smoking among hepatitis B surface antigen-negative individuals, but, in the absence of information on other risk factors, e.g., aflatoxin, generalization of these results to other populations is at present unjustified.

For pancreatic cancer, correlation, case-control and cohort studies are consistent in pointing to a role of tobacco smoking as an important cause. No factor that could explain this relationship by confounding has been identified.

A large number of studies have reported an increased incidence of invasive cervical cancer or its precursors (carcinoma *in situ* or dysplasia) among women who smoke. However, in none of the studies has there been adequate control for the possible major cause — associated with sexual activity. Accordingly, the causal nature of the association of carcinoma of the cervix with smoking remains uncertain.

For cancer of the endometrium, with the exception of one prospective study, studies have consistently shown lower relative risks for women who smoke cigarettes. Since smoking has been shown to reduce the age at which menopause occurs, a protective effect of smoking against endometrial cancer through an endocrine mechanism is plausible, but the possibility of confounding has not been excluded.

In contrast, a number of studies have shown no consistent effect of smoking on the risk for breast cancer.

5. Interactions with other causative factors

Many factors could potentially modify the effects of smoking in causing lung or other cancers. The Working Group has, however, restricted its attention to the possible modifying effects of alcohol, asbestos exposure and some exposures to ionizing radiation, as these are well-documented environmental factors that give rise to greatly increased risks of tobacco-related cancers.

(*a*) *Alcohol*

(i) *Cohort studies*

Only the Japanese prospective study (Hirayama, 1978) covered risks in male cigarette smokers who do not drink and in those who do. Their respective standardized mortality ratios with respect to nondrinking nonsmokers were 2.5 and 5.3 for cancer of the buccal cavity, 0.8 and 3.0 for pharyngeal cancer, and 1.2 and 2.3 for oesophageal cancer. No such difference was seen either for laryngeal (4.9 and 4.5) or lung cancer (4.8 and 4.6).

(ii) *Case-control studies*

Early quantitative assessments of the relation between use of alcohol and tobacco and the risk of cancers of the oral cavity, oropharynx and hypopharynx suggested that the risk associated with smoking was multiplied in the presence of alcohol. In a hospital-based case-control study, Schwartz *et al.* (1957) observed that the risk relative to low consumers of alcohol for all three cancers combined increased with increasing levels of alcohol consumption in every category of smoking. The multiplicative effect of smoking on cancer risk observed in the lowest category of alcohol consumption applied essentially unchanged to the higher risk, high consumption categories.

With regard to *oral* cancers alone, Rothman and Keller (1972) reviewed the effect of joint exposure to tobacco and alcohol, using data published earlier by Keller and Terris (1965). The relative risks observed are shown in Table 91. The authors concluded that a simple multiplicative function of the relative risks associated with alcohol and tobacco separately provided an adequate summary of their joint effect.

Table 91. Relative risks of oral cancer according to level of exposure to smoking and alcohol[a]

Alcohol (g/day)	Smoking (cigarette equivalents/day)			
	0	<20	20-39	≥40
0	1.0	1.5	1.4	2.4
<11.3	1.4	1.7	3.2	3.3
11.3-42.5	1.6	4.4	4.5	8.2
≥45.4	2.3	4.1	9.6	15.5

[a]From Keller and Terris (1965), adapted by Rothman and Keller (1972)

In an extensive study of etiological factors in cancer of the *oesophagus*, Wynder and Bross (1961) considered the effects of tobacco and alcohol separately and together. Consumption of three, compared to less than three, alcoholic drinks per day increased the risk by about five fold; consumption of less than one or one or more packs of cigarettes increased the risks by about two and three fold, respectively, over that for nonsmokers, and the combined effect again appeared to be multiplicative. The risk for heavier drinkers

among pipe and cigar smokers was increased by about 50% above that that would have been anticipated from a simple multiplication of the individual effects. [The Working Group noted that precise quantitative estimates are not available from this publication, since key results are presented only in graphical form.]

In a study of oesophageal cancer in Britanny, France, Tuyns *et al.* (1977) found a similar pattern of joint effect (Table 92). Further analyses of the same material, adjusting for alcohol consumption, showed that the effect of heavy smoking predominates in causation of cancer in the upper third of the oesophagus as compared with the middle third (Keil *et al.*, 1980). A more detailed statistical analysis indicated that the relative risks of joint exposure could be expressed as a multiplicative function of the individual exposures (Breslow & Day, 1980).

Table 92. Relative risks for oesphageal cancer according to daily amounts of tobacco and alcohol consumed[a]

Alcohol consumption (g/day)	Tobacco consumption (g/day)			
	0 - 9	10 - 19	20 - 29	⩾ 30
0-40	1.0	3.4	3.2	7.8
41-80	7.3	8.4	8.8	35.0
81-120	11.8	13.6	12.6	83.0
⩾121	49.6	65.9	137.6	155.6

[a]From Tuyns *et al.* (1977), adapted by Day and Muñoz (1982)

In their study on environmental factors in cancer of the *larynx*, Wynder *et al.* (1976) showed a combined effect of tobacco and alcohol (Table 93). Cigarette smoke appears to act on laryngeal epithelium even in the absence of alcohol. In the presence of smoking, however, heavy drinking increases the risk, especially for cancer of the supraglottic portion of the larynx. Similar findings were obtained by Burch *et al.* (1981).

When cancers of the oral cavity, pharynx and larynx in British Columbia, Canada, were considered together (Elwood *et al.*, 1984), additive and multiplicative effects of alcohol and tobacco consumption could not be distinguished clearly. [The Working Group noted that the risk ratios observed by Elwood *et al.* were lower than those reported in Tables 91-93, making specification of the mathematical model difficult.]

(*b*) *Asbestos*

A large cohort, consisting of 17 800 insulation workers in the USA and Canada, exposed to chrysotile and amosite (Selikoff *et al.*, 1973) was followed for a 10-year period, and the mortality rates for lung cancer in smoking and nonsmoking insulation workers were compared to those in 73 763 unexposed male subjects in the American Cancer Society

Table 93. Relative risks for laryngeal cancer in males according to daily amounts of tobacco and alcohol consumed[a]

No. of alcoholic drinks/day	Cigarette equivalents/day							
	0		1-15		16-34		≥35	
	No. of cases	Relative risk	No. of cases	Relative risk	No. of cases	Relative risk	No. of cases	Relative risk
None/ occasional	5	1.0	12	3.0	38	6.0	31	7.0
1-6	0	-	5	4.0	18	6.7	25	10.3
≥7	0	-	5	3.3	39	13.8	46	22.1

[a]From Wynder *et al.* (1976)

(ACS) 25-State Study (Hammond, 1966), with adjustment for age (Hammond *et al.*) (Table 94). The relative risk for lung cancer associated with smoking in the asbestos insulation workers was 10.3 and in the ACS volunteers, 10.9. [These results indicate that the joint effects of asbestos exposure and smoking are multiplicative.]

Table 94. Age-standardized death rates[a] from lung cancer in cigarette smokers and nonsmokers with or without occupational exposure to asbestos dust[b]

Smoking status	Asbestos exposure	Death rate	Mortality ratio
Nonsmoker	No	11.3	1.00
	Yes	58.4	5.17
Smoker	No	122.6	10.85
	Yes	601.6	53.24

[a]Rate per 100 000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on information from death certificates

[b]From Hammond *et al.* (1979)

Several investigations have been reported on other classes of workers, often with mixed exposure (chrysotile and amphiboles; Lindell, 1973) to asbestos. For example, in men and women at one factory in the UK followed from 1971-1980 (Berry *et al.*, 1985), the relative risks for lung cancer associated with factory employment were, for both sexes combined, 2.4 (calculated by the Working Group: observed deaths, 75; expected deaths, 31.2) in smokers and 7.3 (standardized for sex and category, and duration of exposure; observed deaths, 4; expected deaths, 0.4) in nonsmokers. Factory workers exposed to amosite at one US plant

and followed from 1961 to 1977 (Selikoff *et al.*, 1980) had a relative risk of 4.7 (observed deaths, 45; expected deaths, 9.6) in smokers and 25.0 (observed deaths, 5; expected deaths, 0.2) in nonsmokers. In a case-control study including 223 cases and 715 controls who had died from lung cancer between 1951 and 1975 in a defined population of chrysotile-asbestos miners and millers in Quebec, Canada, relative risks associated with asbestos exposure of 1.7 in smokers (714 subjects) and 3.0 in nonsmokers (224 subjects) were observed (Berry *et al.*, 1985). [The Working Group noted that, although accurate dust exposures for relevant job categories are difficult to obtain, those that are available suggest lower exposures for asbestos miners and millers and some factory workers than for insulation workers.]

[The pattern that emerges from these studies is of an interaction between occupational exposure to the different varieties of asbestos and tobacco smoking. In insulators, the joint effect is multiplicative. The pattern of a higher relative risk for lung cancer from asbestos exposure in nonsmokers than in smokers, which has been found regularly in other groups (in particular miners and millers) suggests a weaker joint effect, perhaps related to lower levels of dust exposure.]

(*c*) *Radiation*

The relationship between cancer mortality and cigarette smoking and exposure to ionizing radiation among atomic-bomb survivors in Hiroshima and Nagasaki has been studied with regard to all nonhaematological cancer, stomach cancer and other digestive-tract cancers and to lung cancer. For lung cancer, the patterns of relative risk were consistent equally with a multiplicative or an additive relationship. For the other cancers studied, the joint effect was less than multiplicative and possibly even additive, especially for those cases who were young at the time of exposure to radiation (Prentice *et al.*, 1983).

Uranium miners exposed to radioactive alpha emissions in underground mines in Colorado, Arizona, New Mexico and Utah, USA, have formed the object of several studies. Using the data base of the US Public Health Service, Whittemore and McMillan (1983) selected 194 lung cancer deaths and four times as many controls and, through a proportional hazard model analysis, derived an estimate of relative risk of 19.2 for workers exposed to more than 1800 working-level months as compared to those exposed to 1-21 working-level months in smokers of more than 30 pack-years and an estimate of 18.2 in smokers of 0-10 pack-years, i.e., indicating a multiplicative effect.

Studies have been reported from other underground mining operations involving exposure to radon daughters at levels considerably lower than those analysed by Whittemore and McMillan (1983). All of the studies indicated that the joint effect of smoking and lower level of radon daughter exposures was less than the multiplicative relationship observed by Whittemore and McMillan in uranium miners (Axelson & Sundell, 1978; Dahlgren, 1979; Damber & Larsson, 1982; Edling, 1982; Edling & Axelson, 1983; Radford & St Clair Renard, 1984).

(*d*) *Summary*

Studies of tobacco smokers who were exposed jointly to certain other agents show that there are segments of the population for whom tobacco smoking poses risks of cancer

substantially greater than that for the general population. Most prominent among these groups are heavy alcohol drinkers, heavily-exposed asbestos-insulation workers and persons heavily exposed to ionizing radiation in uranium mines. For each of these agents, exposures have been shown to interact approximately multiplicatively with smoking to increase the risk of cancer.

The available studies show that the enhancement of risk by alcohol is dose-dependent. The risk relative to nonsmoking nondrinkers for each level of smoking increases approximately multiplicatively with increasing level of alcohol consumption. The evidence that occupational exposures to asbestos and radiation other than in insulation work and uranium mining enhance multiplicatively the risk of lung cancer induced by smoking is equivocal.

6. Cancers related to passive exposure to tobacco smoke

(*a*) *Cancer of the lung*

(i) *Cohort studies*

The mortality of 91 540 nonsmoking women was examined in relation to their husbands' smoking habit in a cohort study in Japan (Hirayama, 1981b, 1983, 1984a,b). A total of 429 deaths from lung cancer was recorded in women during the 16 years of follow-up from 1966 to 1981. Of these, 303 were nonsmokers and 200 were married women whose husbands' smoking habits were known. The exposure index in this study was based on smoking habits of husbands. The standardized mortality ratios of lung cancer in nonsmoking women were 1.0, 1.4, 1.4, 1.6 and 1.9 when the husbands were nonsmokers, ex-smokers, daily smokers of 1-14, 15-19 and ⩾20 cigarettes/day, respectively (p for trend = 0.002). A similar dose-response relationship was observed in each subcategory, defined by age and by occupation of husband, by age of wife, and in each time period of observation. No other characteristic of husbands or wives themselves was found to elevate the risk of lung cancer in their nonsmoking partners. Nonsmoking husbands of women smokers also showed an elevated risk of lung cancer, with standardized mortality ratios of 1.0, 2.1 and 2.3 for nonsmoking husbands with nonsmoking wives, for wives smoking 1-19, and for wives smoking ⩾20 cigarettes daily, respectively ($p = 0.02$). [The Working Group noted that some nonsmoking women could have been ex- or current smokers, but such a possibility is likely to be quite small.]

In an American Cancer Society cohort study of 375 000 nonsmoking women (Garfinkel, 1981), the husband's smoking habits were known for 176 739 (47%). The follow-up rate was 92.8%. Of the 153 nonsmoking women with lung cancer, 88 were married to smokers. The lung cancer mortality ratios were 1.0, 1.3 and 1.1 for women married to men who never smoked, to men who currently smoked <20 cigarettes/day, and to men who currently smoked ⩾20 cigarettes/day, respectively. When matched on the basis of the wife's five-year age group, husband's occupational exposure, highest educational level of husband or wife, race, urban-rural residence and absence of serious disease at the start of the study, the mortality ratios became 1.0, 1.4 and 1.0, respectively. Neither analysis showed a statistically significant increase in risk.

CONCLUSIONS AND EVALUATIONS

1. Conclusions

(*a*) *Usage and trends*

Smoking of tobacco is practised worldwide by hundreds of millions of people. In 1982, 6.7 million tonnes of tobacco were produced; annual per-caput consumption in the USA ranged up to more than 3500 cigarettes. In developing countries, cigarette smoking is increasing, and many cigarettes and other products, including *bidis*, have very high tar (up to 55 mg per cigarette) and nicotine yields. In many developed countries, sizeable decreases in total consumption, sales and smoking rates have occurred. Generally, between one-third and one-half of men smoke, with some countries having notably higher rates. In most developed and some developing countries, about one-third of women smoke, although in some countries fewer do.

Sales-weighted average tar and nicotine contents (as measured by standard laboratory methods) have declined significantly since the 1950s in some parts of the world. The chemical composition of smoke depends on (a) the type of tobacco; (b) cigarette design, including filtration, blend selection (e.g., reconstituted sheet, expanded tobacco), ventilation, paper and additives; and (c) the smoking pattern.

Tobacco is smoked principally in cigarettes, with pipes, cigars, *bidis* and other forms being used either to a minor extent or only in certain regions. Combustion of tobacco products delivers mainstream and sidestream smoke which differ in physicochemical nature. In addition, sidestream smoke contains greater amounts of identified carcinogens than mainstream smoke. Passive smoking is a universal phenomenon where smoking is common. The uptake of smoke constituents by smokers and by passive smokers has been studied in only a few countries, although extensive analysis of smoke shows cigarette smoking to be a major source of exposure to tobacco-specific nitroso compounds, polynuclear aromatic compounds, aromatic amines and some other carcinogens.

(*b*) *Carcinogenicity in animals*

Cigarette smoke has been tested for carcinogenicity in experimental animals by inhalation and by topical application of condensate and in other ways. Exposure of hamsters and rats to whole smoke results in the induction of malignant respiratory-tract tumours. Cigarette smoke condensate induces skin cancers in mice and rabbits after application to the skin, and lung cancers in rats after intrapulmonary injection. Cigarette smoke contains many chemicals known to produce cancer in animals and/or humans.

More tumours occur in animals exposed to both cigarette smoke and 7,12-dimethylbenz[*a*]anthracene than to either one alone; the same is true for concomitant exposure to benzo[*a*]pyrene or radon daughters.

No study was available that was designed specifically to investigate the carcinogenicity of passive smoking to experimental animals.

(*c*) *Genetic activity and short-term test results*

Tobacco smoke and smoke condensate are mutagenic and cause chromosomal damage in various test systems with multiple genetic endpoints. Exposure to these complex mixtures results in mutagenic urine in smokers and in increased chromosomal damage in the somatic cells of smokers compared to nonsmokers. Cigarette-smoke condensate induces neoplastic transformation in mammalian cells *in vitro*.

Overall assessment of data from short-term tests[a] on cigarette smoke

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/ Green plants		+	+[b]	
Insects		+		
Mammalian cells (*in vitro*)			+[b]	
Mammals (*in vivo*)			+	
Humans (*in vivo*)			+	
Degree of evidence in short-term tests for genetic activity: *Sufficient*				Cell transformation: No data

[a]The groups into which the table is divided and the symbols are defined on pp. 21-22 of the Preamble; the degrees of evidence are defined on pp. 22-23.

[b]Gas phase of smoke only

Overall assessment of data from short-term tests[a] on cigarette smoke condensate (CSC)

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/ Green plants		+	+	
Insects		+		
Mammalian cells (*in vitro*)		+	+	+
Mammals (*in vivo*)			+	
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity: *Sufficient*				Cell transformation: Positive

[a]The groups into which the table is divided and the symbols are defined on pp. 21-22 of the Preamble; the degrees of evidence are defined on pp. 22-23.

(*d*) *Human exposure*

Smokers of cigarettes with low 'tar' yields tend to inhale to a greater extent than do smokers of cigarettes with high 'tar' yields, but, in general, their intake of smoke components is reduced.

Certain biochemical markers of smoke intake, e.g., cotinine in plasma, urine or saliva, are sufficiently sensitive and specific to identify passive smokers. Passive smokers who have been examined in western Europe and North America generally have levels between about 0.1% to 1% of these markers as compared to active smokers. The precise quantitative relationship between the measured levels of these markers and the intake of carcinogenic compounds in tobacco smoke is not known.

Approximately 80% of inhaled particles from cigarette mainstream smoke is deposited in the respiratory tract, the majority in the tracheobronchial region. Wide variation is found, however, among individuals. The distribution of particulate matter in the lung is similar in smokers of 'high-' and 'low-tar' cigarettes. The pattern of deposition of sidestream smoke is very different: the proportion deposited is smaller and is likely to occur mainly in the periphery of the lung.

(*e*) *Genetic host factors*

Genetic polymorphism in microsomal monooxygenases exists in humans. Lung cancer patients with a history of smoking are more often extensive metabolizers of the drug debrisoquine or have high induced levels of aryl hydrocarbon hydroxylase than smokers without lung cancer. It remains to be established whether this association implies that individuals with such genotypes are at increased risk of tobacco smoke-associated cancer.

(*f*) *Cancer in humans*

Lung cancer is believed to be the most important cause of death from cancer in the world, with estimated total deaths in excess of one million annually. The major cause of the disease is tobacco smoking, primarily of cigarettes. Risk of lung cancer is particularly dependent on duration of smoking; therefore, the earlier the age at initiation of smoking, the greater the individual risk. Further, the longer the time period during which a major proportion of adults in a population have smoked, the greater the incidence and mortality from the disease in that population. Risk of lung cancer is also proportional to the numbers of cigarettes smoked, increasing with increasing cigarette usage. In populations with a long duration and heavy intensity of cigarette usage, the proportion of lung cancer attributable to smoking is of the order of 90%. This attributable proportion applies to men in most western populations; in populations in which women are increasingly using cigarettes, the attributable proportion in women is also approaching this level.

In smokers who have smoked for any length of time, the annual lung cancer risk incurred persists at approximately the same level after cessation of smoking, so that the increasing risk that would have been incurred by continuation of smoking is prevented.

Although cigarettes are the predominant cause of lung cancer, some increased risk also results from pipe and/or cigar smoking.

Smokers of other types of tobacco, particularly in Asia (e.g., of *bidis* in India), also appear to be at an increased risk of lung cancer. At present it is not possible to determine whether prolonged *bidi* smoking increases the risk of lung cancer to the same extent as does prolonged smoking of cigarettes.

Cigarettes appear to increase the risk of squamous-cell (epidermoid) and small-cell carcinomas of the lung to a greater extent than that of adenocarcinomas. However, each of these three main histological types of lung cancer is caused by tobacco smoking.

The risk of lung cancer associated with cigarette smoking is substantially increased in conjunction with high-dose exposures to radon daughters or asbestos.

Tobacco smoking (particularly of cigarettes) is an important cause of bladder cancer and cancer of the renal pelvis. The proportion of these diseases attributable to smoking in most countries with a history of prolonged cigarette usage is of the order of 50% in men and 25% in women. The relationships of risk with duration and intensity of smoking are similar to those for lung cancer, although the risks are lower. Pipe and/or cigar smoking probably also increases the risk of bladder cancer, but at lower levels than the risk caused by cigarette-smoking.

Tobacco smoking is an important cause of oral, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers. Pipe and/or cigar smoking appears to increase the risk of these cancers to approximately the same extent as cigarette smoking. The risks of these cancers associated with cigarette smoking are substantially increased in conjunction with high-dose exposure to alcohol. Tobacco smokers also appear to have increased risks for cancer of the lip.

Cigarette smoking is an important cause of pancreatic cancer and perhaps of renal adenocarcinoma. The proportion of these diseases that is attributable to smoking is not possible to quantify with the same accuracy as for lung cancer. The data now available on tobacco smoking and stomach and liver cancers do not permit a conclusion that the associations noted in some studies are causal.

Although the risk of cancer of the cervix is increased in tobacco smokers, it is not possible to conclude that the association is causal. Further, although in some studies a reduction in risk of endometrial cancer has been found in smokers as compared to non-smokers it cannot be concluded that smoking protects against cancer at this site.

The cigarettes that are currently sold differ, in many countries, from those that were sold prior to the general recognition of the hazards associated with their use. When the newer cigarettes are smoked under standard laboratory conditions, the yield of some components — particularly of tar and nicotine — is, in consequence, reduced. It is difficult, however, to deduce from this how hazardous such cigarettes are likely to be as they tend to be smoked differently, and the differences observed with laboratory testing may not be reproduced when they are smoked by people. It is difficult, too, to detect their effect on a national scale, as the harmful effects of smoking accumulate over many years and the risk of developing cancer attributable to smoking depends on both recent and past exposure.

Nevertheless, the Group noted that:

(1) Although smokers of 'low tar'-level cigarettes tend to compensate for lower yields of nicotine and perhaps other smoke components, chiefly by changing the manner of smoking, they do not in general compensate fully for lower tar yields.

(2) Case-control and cohort studies suggest that prolonged use of nonfilter and 'high-tar' cigarettes is associated with greater lung cancer risks than prolonged use of filter and 'low-tar' cigarettes.

(3) In a few countries, in which smoking had been established for many years, a substantial reduction in mortality from lung cancer has been observed in young and middle-aged men, which is greatest in the youngest age groups. This has occurred at a time when the number of cigarettes smoked by young men in these countries has remained approximately constant. No substantial cause (or cofactor) has so far been identified that offers a plausible explanation for the observed magnitude of the reduction of risk for lung cancer, other than changes in cigarette design which include reduction in tar content.

It was concluded that the risk of lung cancer associated with the types of cigarettes commonly smoked before the middle 1950s is greater than that for modified cigarettes with 'low tar' levels now generally available in some countries.[1]

The health benefits from the cessation of smoking, however, greatly exceed those to be expected from changes in cigarette composition.

Tobacco smoke affects not only people who smoke but also people who are exposed to the combustion products of other people's tobacco. The effects produced are not necessarily the same, as the constituents of smoke vary according to its source. Three main sources exist: (i) mainstream smoke, (ii) sidestream smoke, and (iii) smoke exhaled to the general atmosphere by smokers. Smokers are exposed to all three to a greater extent than are nonsmokers. It follows that it is unlikely that any effects will be produced in passive smokers that are not produced to a greater extent in smokers and that types of effects that are not seen in smokers will not be seen in passive smokers. Examination of smoke from the different sources shows that all three types contain chemicals that are both carcinogenic and mutagenic. The amounts absorbed by passive smokers are, however, small, and effects are unlikely to be detectable unless exposure is substantial and very large numbers of people are observed. The observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer.

2. Evaluations

There is *sufficient evidence* that inhalation of tobacco smoke as well as topical application of tobacco smoke condensate cause cancer in experimental animals.

There is *sufficient evidence* that tobacco smoke is carcinogenic to humans.

The occurrence of malignant tumours of the respiratory tract and of the upper digestive tract is causally related to the smoking of different forms of tobacco (cigarettes, cigars, pipes, *bidis*). The occurrence of malignant tumours of the bladder, renal pelvis and pancreas is causally related to the smoking of cigarettes.

[1]See General Introduction: Smoking and the Public Health', pp. 37-45, for a discussion of effects on other tobacco-related diseases.

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APPENDIX B

Excerpts from the NCI Monograph on Smoking and Tobacco Control (Changes in Cigarette-Related Disease and their Implication for Prevention and Control) Monograph 8, 1997, pp. 1-11

Introduction, Summary, and Conclusions

David M. Burns, Lawrence Garfinkel, and Jonathan M. Samet

Cigarette smoking is the largest preventable cause of death and disability in developed countries and is a rapidly growing health problem in developing countries. The magnitude and nature of the risks associated with smoking can be estimated using data from prospective epidemiological studies of smokers and nonsmokers and information on smoking in the population. In 1966 the National Cancer Institute (NCI) published the monograph *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases* (Haenszel, 1966), which included detailed presentations of the information available up to that time from several large prospective mortality studies examining relationships between smoking behavior and disease. Since then, several new large prospective mortality studies have been initiated, and additional years of followup are available for analysis for some of the studies whose results were presented in 1966. This new information can be used to more sharply characterize the risks of smoking.

The goal of this monograph is to provide detailed presentations of disease risks caused by smoking using data from these more recent studies and the more extensive followup data available from the American Cancer Society (ACS) Cancer Prevention Study I (CPS-I). This volume also contains descriptions of the quantitative relationships between various aspects of smoking behavior and disease occurrence as well as detailed tabular data contained in various chapter appendixes. Appendix data are presented in greater detail than would be required by most readers to facilitate use of this volume as a resource by investigators attempting to model or control for the effects of smoking in other epidemiological studies.

Five major prospective epidemiological studies are featured in this volume. CPS-I and CPS-II each followed more than 1 million individuals, with findings on followup of 6 years for CPS-II and 12 years for CPS-I reported in this volume. Because these two studies were initiated more than 20 years apart, they afford the opportunity to examine changes in mortality risks for smokers and nonsmokers in comparable populations over time; the mortality experiences during the first 6 years of followup for both studies are compared in Chapter 4 of this volume.

The Dorn study of U.S. veterans (Kahn, 1966) has the longest duration of followup of the prospective mortality studies, but it lacks repeat measures of smoking status during the followup period. It groups smokers who continued to smoke during followup and those who quit during the followup interval. Because of this limitation, analyses of this study are most informative for disease risks after prolonged periods of abstinence from smoking (Chapter 7). The mortality experience after 26 years of followup of veterans who were former smokers at the start of the study is used to describe the magnitude of disease risks in former smokers compared to lifelong never-smokers.

The Kaiser Permanente Prospective Mortality study (Chapter 6) followed 60,000 individuals enrolled in the Kaiser Permanente Health Plan and included a large proportion of Asian and African-American participants. The Nurses' Health Study (Chapter 8) enrolled 121,700 female registered nurses in 1976 and provides detailed risk estimates for these females, particularly those of younger and middle age.

Detailed estimates of the changes in smoking status with age and calendar year for white and black males and females by 5-year birth cohorts also are presented (Chapter 2).

Considerable effort was made to standardize the presentation of data among the studies, but significant differences exist in ascertainment of smoking status and in reporting of duration of smoking in the analyses. All the analyses accrued deaths and person-years of observation (PYO's) into age groups defined by age of the subject at death or in the year of followup (age was advanced during followup) and assumed that smoking status remained unchanged from the last followup measure of smoking status (CPS-I [Chapter 3] and the Nurses' Health Study) or from entry into the study (CPS-II [Chapter 5], Kaiser Permanente, and veterans studies). Analyses of the American Cancer Society CPS-I and the Kaiser Permanente study accrued deaths and PYO's into duration-of-smoking groups defined by duration of smoking at death or at the year of followup (duration was advanced during followup), but only CPS-I had questionnaire validation of smoking status during followup. Analyses of CPS-II accrued deaths and PYO's into duration-of-smoking groups defined by duration of smoking at entry into the study (duration was not advanced during followup). The study of U.S. veterans (Chapter 7) and the Nurses' Health Study do not present analyses by duration of smoking.

Understanding the impact of cigarette smoking on disease occurrence requires estimates of both the risks and prevalence rates of smoking. This volume provides descriptions of smoking behavior over time during the past century as well as disease-specific mortality estimates from several large prospective mortality studies. The goal is to provide, in one volume, as much information as possible on smoking and mortality to facilitate understanding of smoking-induced disease.

TRENDS IN SMOKING PREVALENCE

Cigarette smoking as a form of tobacco use has largely been a 20th century phenomenon. Before 1910 almost all tobacco was consumed in pipes and cigars or as chewing tobacco and snuff. Beginning in 1913 mass marketing efforts of Camel and other cigarette brands were followed by a rapid rise in the number of cigarettes sold. Cigarette smoking was predominantly a male behavior at that time, and among males, it increased dramatically during and subsequent to World War I. Smoking was a relatively uncommon behavior among females until the 1930's. The increase in smoking among females also coincided with a major national advertising campaign. Lucky Strike's "Reach for a Lucky Instead of a Sweet" campaign was one of the first tobacco advertising campaigns to directly target females.

The prevalence of current smoking among sequential 5-year birth cohorts of white males and white females is presented in Figures 1 and 2, respectively. A birth cohort consists of all individuals born during specific calendar years, and birth cohort analyses present the experience of those individuals as they age. Birth cohort analyses are presented in Figures 1 and 2 for 5-year birth cohorts of white males and females born between 1885 and 1969.

Differences in smoking behavior over time explain many of the differences in U.S. lung cancer death rates among white and black males and females. Lung cancer had been a rare disease at the turn of the century, but lung cancer death rates rose rapidly among males beginning in the 1930's, about 20 to 25 years after the upsurge of cigarette smoking among males. Figure 3 presents race- and gender-specific, age-adjusted U.S. lung cancer death rates for the calendar years 1950 to 1993. Male lung cancer rates continued to rise into the 1980's, whereas female lung cancer death rates began to increase sharply only in the late 1960's. A major reason for the temporal differences between male and female lung cancer rates relates to the differences in smoking behavior presented in Figures 1 and 2. Females did not initiate smoking in large numbers until the 1930's, 20 to 25 years after the upswing in prevalence among males. As expected, female lung cancer death rates did not begin to increase steeply until the late 1960's, about 20 to 30 years after the beginning of rapid increases in male lung cancer death rates.

Peak rates of smoking prevalence were much higher among males earlier in this century, consistent with the higher lung cancer rates among males across the century. Prevalence rates of smoking in all birth cohorts among white males have been declining since the late 1950's (Figure 1), which is probably the major reason for the leveling off and subsequent decline in male lung cancer death rates evident during the late 1980's (Figure 3) (20 to 25 years after cessation).

Black males born before 1915 and black females born before 1920 had lower rates of smoking initiation than white males and females. Blacks born later in the century had rates of smoking that equaled or exceeded those of whites. Current smoking prevalence among black males is substantially higher than among white males, reflecting both higher rates of initiation and lower rates of cessation.

Comparison of smoking prevalence rates for birth cohorts of white and black males shows a similar relationship between differences in smoking behavior and differences in white and black lung cancer death rates. Before 1950 most cohorts of white males had higher lung cancer rates than the comparable cohorts of black males. By 1965 the pattern had inverted, with most cohorts of white males having lower lung cancer rates than the comparable cohorts of black males. The expected differences between white and black male lung cancer death rates are evident in Figure 3. Before 1960 white male lung cancer death rates exceeded those for black males, but by the mid-1960's lung cancer death rates among black males began to exceed those for white males, and they are currently dramatically higher among black males.

Figure 1
Prevalence of current cigarette smoking by 5-year birth cohorts of white males

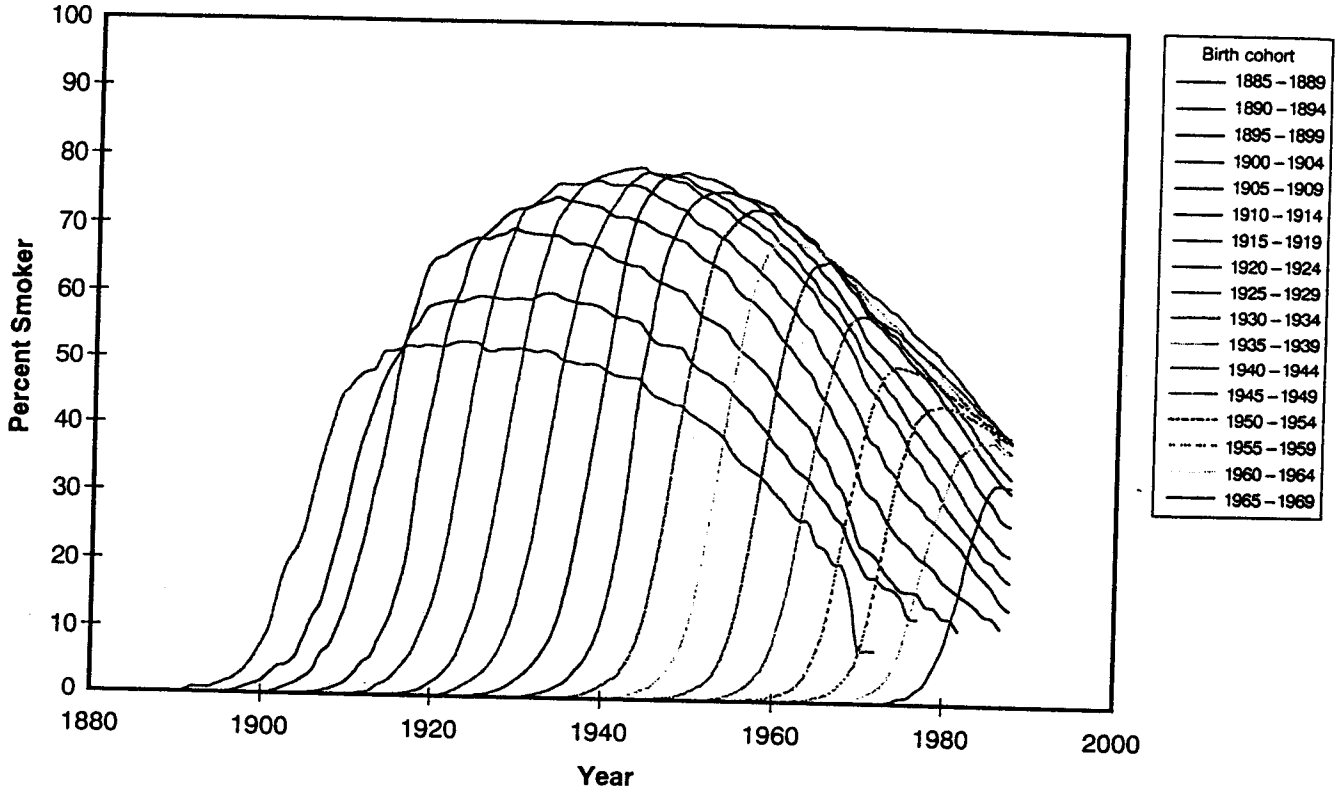


Figure 2
Prevalence of current cigarette smoking by 5-year birth cohorts of white females

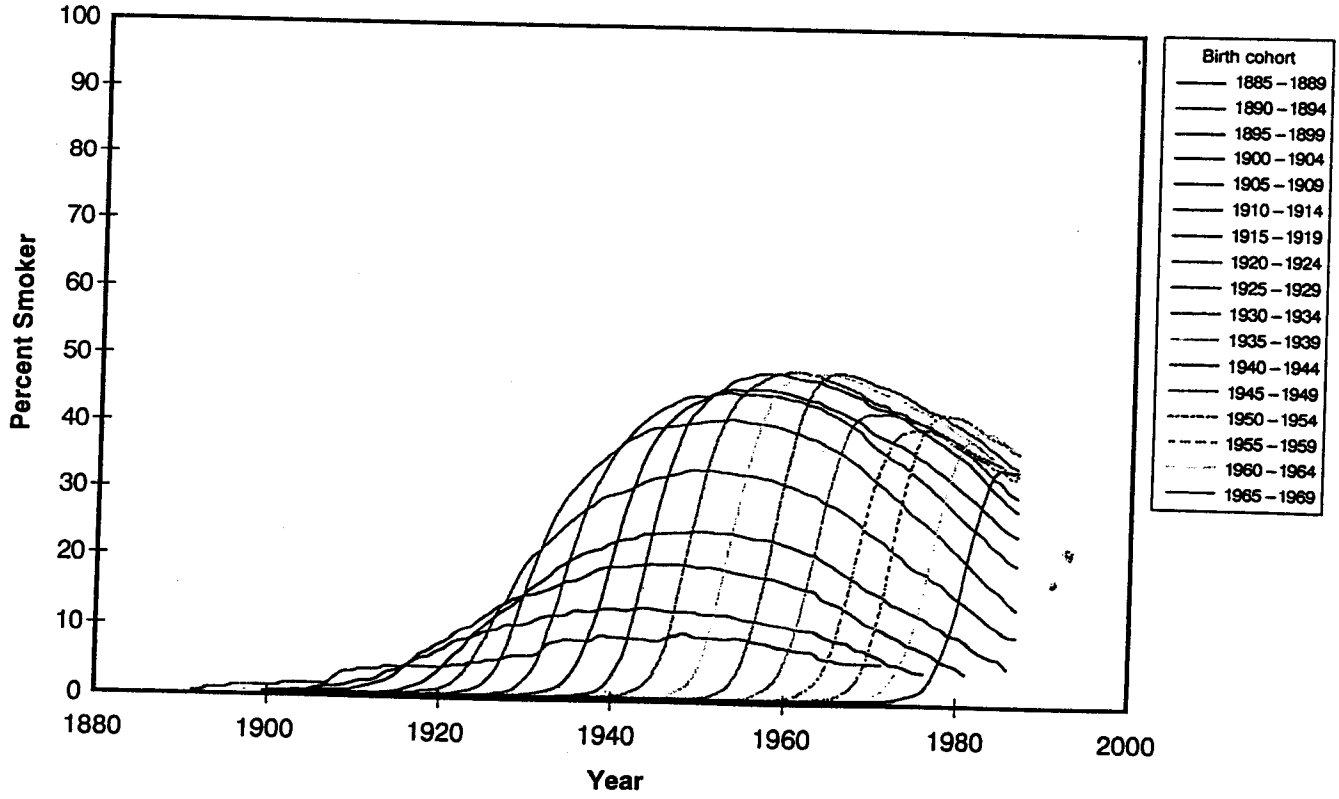
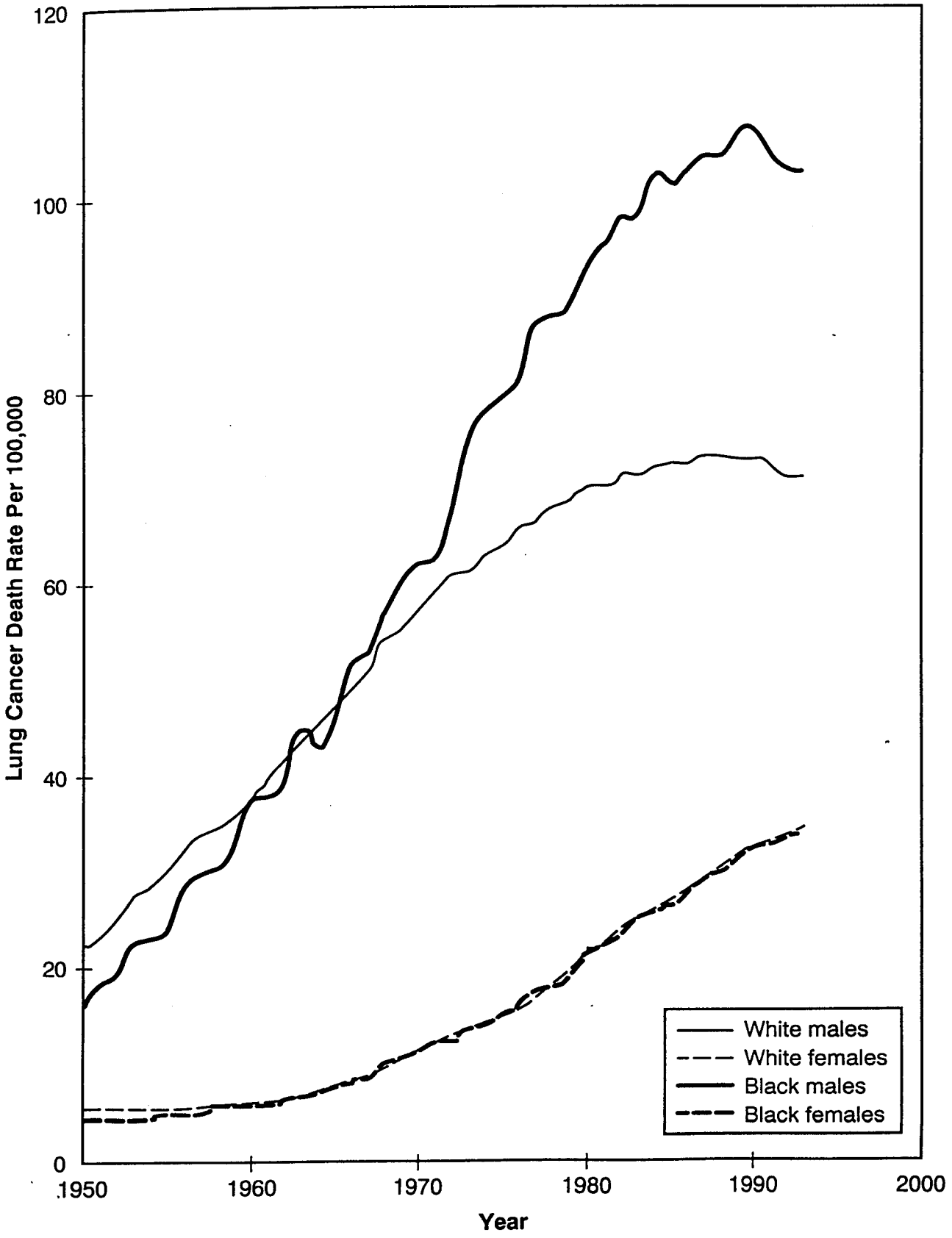


Figure 3
U.S. lung cancer death rates, 1950 to 1993



TRENDS IN SMOKING CESSATION

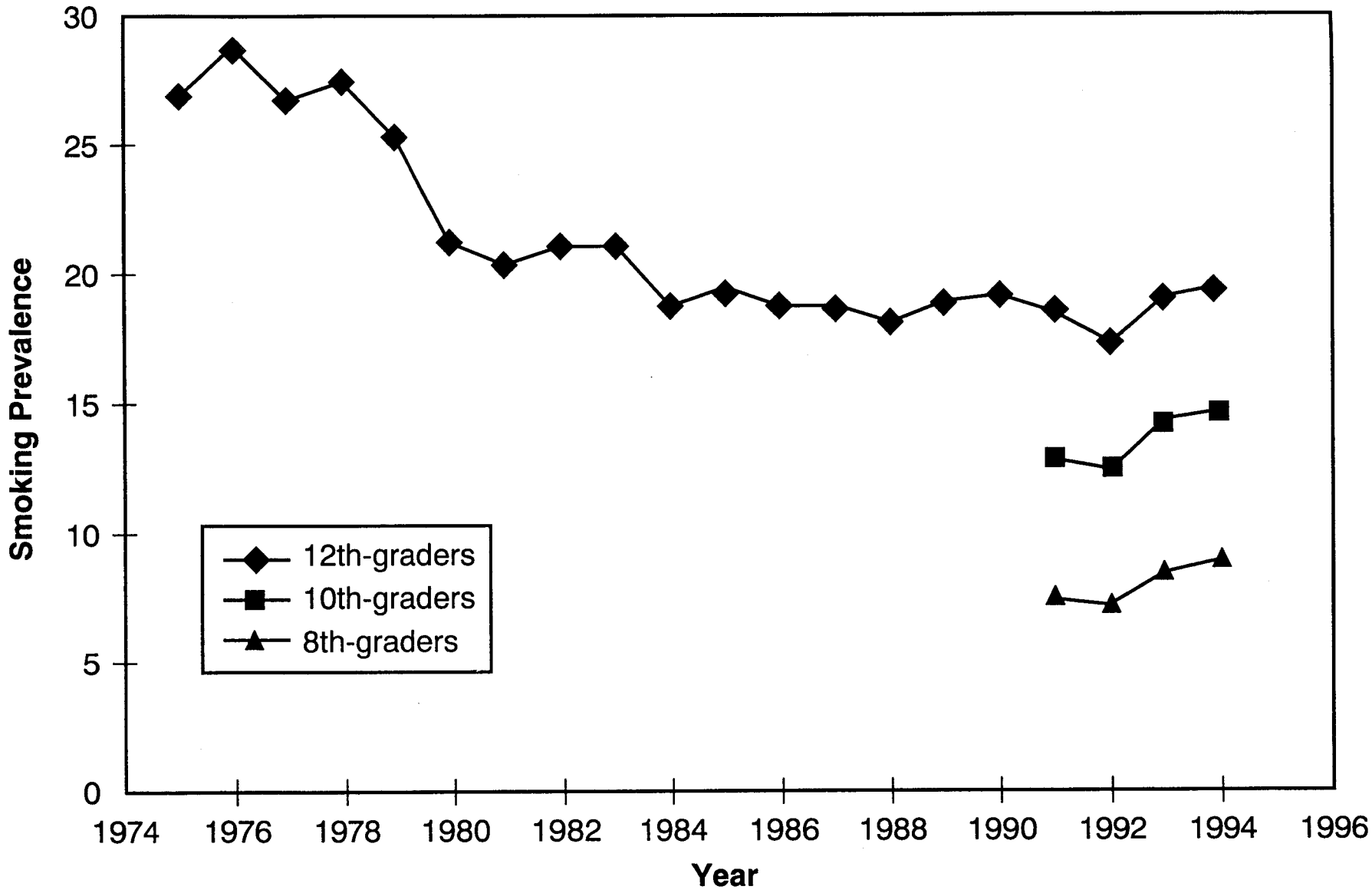
Successful cessation of cigarette smoking was uncommon prior to 1950, probably due to the addictive nature of cigarette smoking and the lack of a widespread understanding that smoking caused disease. White males began to quit smoking during the mid 1950's, when the substantial disease risks associated with smoking were first widely publicized. A large increase in cessation occurred among males and females of both races during the years 1967 to 1970, which coincided with a substantial tobacco control effort by governmental and nongovernmental agencies concerned about public health as well as with a large counter-advertising campaign on television. Cessation rates declined slightly following 1970 and then increased in the late 1970's and early 1980's.

The 20th century has seen dramatic changes in both smoking initiation and smoking cessation, and these changes are responsible for the epidemic of disease among smokers documented in this volume. Changes in smoking behavior, and in male lung cancer incidence, suggest that we have reached the peak of the disease epidemic among males and may expect declining rates of smoking-induced disease in the future. There is some preliminary evidence that the lung cancer rate decreased between 1990 and 1995 (Cole and Rodu, 1996). The pattern of smoking behavior and the increasing rates of lung cancer among females suggest that the peak rates of disease among females are yet to be reached; ultimately, however, mortality rates among females also should decline, as they have among females younger than age 45 (Ries et. al., 1994). The projected future decline in disease is not inevitable; it is dependent on continued success in achieving cessation and preventing initiation. Recent data on the prevalence of smoking among high school seniors, as well as among 8th- and 10th-graders, are presented in Figure 4; they suggest that rates of smoking initiation may once again be rising. Recent national adult prevalence data (Centers for Disease Control and Prevention, 1996) also suggest that the decline in adult smoking prevalence may have stopped and that smoking may be increasing even among adults. These trends are of enormous public health concern, and they could eliminate any future decreases in disease-specific death rates.

DISEASE CONSEQUENCES OF SMOKING

The disease consequences of smoking are well documented in reports of the Surgeon General (U.S. Department of Health and Human Services, 1989 and 1990) and in a previous NCI monograph (Haenszel, 1966). This volume updates many of these findings and provides a more comprehensive understanding of the relationships among age, number of cigarettes smoked per day, duration of smoking, and duration of cessation in causation of disease. Estimates based on data from CPS-II demonstrate that 52 percent of deaths from all causes among male current smokers are attributable to cigarette smoking. Among female current smokers, 43 percent of deaths from all causes are attributable to smoking. If overall relative risks for all causes of death for current smokers, former smokers, and never-smokers from CPS-II are used to estimate the smoking-attributable fraction for the entire U.S. population older than age 35, the smoking prevalence rates in 1993 would generate smoking-attributable percentages of

Figure 4
Prevalence of daily cigarette smoking among 8th-, 10th-, and 12th-grade students, 1975 to 1994



35.25 percent for all male deaths and 21.00 percent for all female deaths. This translates into approximately 569,000 excess deaths in 1993, 354,000 among males and 216,000 among females.

These estimates are higher than those calculated using disease-specific relative risks and number of deaths for each cause of death. For example, the American Cancer Society estimates a total of 419,000 each year. They may overestimate the number of deaths because they include both causes of death for which smoking is synergistic with other factors in causing disease and diseases for which the association of smoking and disease is not causal (e.g., cirrhosis of the liver) and because they are based on the age distribution of the living population rather than the deaths. On the other hand, estimates derived from counts of specific causes of death ignore the contribution of smoking to overall poor health status. Poor general health may compromise survival for a broad range of diseases, including those not caused by cigarette smoking, and may limit the treatment options available for the patient. The excess deaths that result from poor health status would be excluded from estimates based only on those diseases caused by smoking. It is also possible that smoking makes small causal contributions to a variety of diseases other than those usually listed as caused by smoking. These small contributions might be difficult to identify in disease-specific epidemiologic analyses but would contribute to the all-cause mortality.

It is likely that the true contribution of smoking to overall mortality lies somewhere between the numbers generated by these two estimation techniques. Clearly, tobacco is a dominant causal factor for a wide variety of diseases and needs to be a principal focus for disease prevention efforts among cigarette smokers.

Excess rates of disease caused by cigarette smoking vary with a smoker's age, the number of cigarettes smoked per day, and the duration of smoking. Early age of initiation results in a longer duration of smoking at any given age. However, there is little evidence from the 12-year followup of CPS-I that early initiation results in an increase in lung cancer risk, independent of its contribution to duration of smoking. The excess risk of specific diseases among smokers also varies with age of the smoker. Among younger smokers, the largest excess disease risk results from coronary heart disease (CHD), with a rapid rise in excess lung cancer death rates developing after the smoker reaches age 55. Excess death rates from chronic obstructive pulmonary disease (COPD) rise even later, increasing dramatically after age 65.

CHANGES IN DISEASE RISK OVER TIME

U.S. death rates for CHD, COPD, and lung cancer have have changed dramatically over the past 40 years and vary substantially between males and females. As was discussed earlier, much of the difference between male and female lung cancer death rates can be explained by differences in smoking behaviors; a similar pattern of male and female death is also observed for COPD. Women began to smoke in large numbers later in the century than men; therefore, they have shorter average durations of smoking at any given age than men. In addition, they tend to smoke fewer cigarettes per day and are more likely to use filtered or

low-tar and -nicotine cigarettes. However, lung cancer rates among white females in CPS-I are lower than those of white males, even when stratified by number of cigarettes smoked per day and duration of smoking. This suggests that factors other than number of cigarettes per day and duration of smoking play a role in the differences between male and female lung cancer death rates. These factors may include differences in pattern of inhalation or type of cigarette smoked as well as other factors.

One of the major changes in cause of death over the past 40 years is the decline in deaths from CHD. Substantial changes in cigarette smoking, diet, and treatment of high blood pressure have occurred during this period, which are likely to be directly related to the decline in CHD deaths. Comparison of the CHD death rates in CPS-I and CPS-II (studies begun more than 20 years apart) reveals that CHD death rates declined between CPS-I and CPS-II among both current smokers and never-smokers. The temporal trend was so large that smokers in CPS-II had lower CHD death rates than lifelong never-smokers in CPS-I. However, the fall in CHD death rates between the two studies was slightly larger in proportionate terms among never-smokers than among current smokers.

Age-adjusted death rates for lung cancer increased dramatically between CPS-I and CPS-II among both male and female smokers. Rates for never-smokers changed little between the two studies. The dramatic changes in birth-cohort-specific smoking behavior among white females over time would be expected to result in these differences between the two studies among females. Careful examination of differences between the smoking behaviors of males in the two studies also suggests that much of the difference between male lung cancer death rates can be explained by differences between the smoking behaviors of males in the two studies. However, when age-, duration-of-smoking-, and cigarettes-per-day-specific strata are compared, lung cancer death rates for male smokers of 20 cigarettes per day who have smoked for more than 40 years are higher in CPS-II than in CPS-I.

These changes over time in the relative risks of death for smokers compared to never-smokers also have been reported for another large prospective mortality study, the British Doctors study. The results of 40 years of followup of these physicians (Doll et al., 1994) reveal that relative risks for all-cause mortality among smokers ages 45 to 64 years compared to never-smokers of the same ages increased threefold when the last 20 years of followup were compared with the first 20 years. A similar twofold increase was found for those ages 65 to 84.

CESSATION One of the principal goals of tobacco control efforts is mitigation of the disease consequences of cigarette smoking through promoting smoking cessation. New data on disease risks following cessation of smoking are presented in this volume, and those data reinforce our existing knowledge (U.S. Department of Health and Human Services, 1990) that smoking cessation dramatically reduces the risk of smoking-related illness in comparison with the risks for the continuing smoker.

Timing of this alteration in risk differs with different disease processes. The relative risk of death from CHD among former smokers in the CPS-I, Kaiser Permanente study, U.S. veterans study, and Nurses' Health Study populations approximates that of never-smokers once the smoker has been tobacco-free for 15 or more years. For shorter periods following cessation, the relative risk of CHD death is elevated but declines as the duration following cessation grows longer. In the U.S. veterans study, a small but statistically significant elevated relative risk (RR = 1.1) persisted among former smokers, even using the longest followup period (26 to 36 years).

The relative risk of death from lung cancer is essentially unchanged for the first 5 years following cessation, probably reflecting the long period between carcinogenic transformation of an individual cell and the death that results due to growth or metastatic spread of the lung cancer. Relative risk declines steadily over the period from 5 to 20 years following cessation. However, in contrast to CHD, the risk of death from lung cancer among former smokers remains elevated above that of never-smokers among the U.S. veterans, Kaiser Permanente, and CPS-I study populations, even 20 or more years following cessation.

Changes in relative risk of death from COPD following cessation mimic those for lung cancer. There is a slow decline in risk among former smokers compared to continuing smokers, but an increased risk persists among form smokers in comparison to never-smokers even 20 or more years following cessation.

PUBLIC HEALTH IMPLICATIONS

Data in this monograph describe the enormous disease burden produced by cigarette smoking. The best way to entirely avoid the disease consequences of smoking is to never start smoking. Prevention of smoking initiation has been a major focus of tobacco control efforts, and these efforts have resulted in a substantial reduction in the proportion of adolescents and young adults who become cigarette smokers. As these younger individuals age, the disease burden produced by tobacco among their cohorts also will fall.

However, the vast majority of tobacco-related diseases occur among older individuals, and large numbers of these older individuals are either current or former smokers. Reduction in disease rates among current smokers is best achieved through cessation, and since the mid-1960's substantial increases in cessation rates among smokers have resulted in more than half of the ever-smokers in the United States becoming former smokers. Translation of this achievement in cessation into reductions in disease-specific death rates is slow but will accelerate as larger numbers of the older population become former smokers of long duration. Early evidence of this effect is reflected in the decline in CHD deaths over the past few decades and the more recent suggestion that white male lung cancer incidence and death rates have leveled off and begun to decline.

However, even if everyone who is currently smoking were to quit and no new smokers were to begin, the data presented in this volume suggest

that a substantial burden of smoking-caused disease would persist for the next several decades because of the residual lung cancer and COPD risks that exist for long-term former smokers. The difference between the current enormous number of deaths caused by smoking and this residual disease burden is a disease prevention goal potentially achievable through comprehensive tobacco control programs.

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APPENDIX C

Description of Online Searches for Tobacco Smoking

DESCRIPTION OF ONLINE SEARCHES FOR TOBACCO SMOKING

Searches were limited to 1984 [the year before the IARC Monograph (1985), which has an extensive literature review] through July 1997. Searches were not extensive because of the availability of the recent NCI review (Burns et al., 1997a).

Online searches for tobacco smoking were performed in databases on the systems of NLM, DIALOG, STN International, and the Chemical Information System from 1984 to date. Toxicology information was sought in EMIC, EMICBACK, RTECS, and TOXLINE. The TOXLINE search focused on reviews from 1994 to 1997. Older government publications such as Surgeon General reports were sought in NTIS.

Regulatory information was sought in the Federal Register full text and the in-house FESA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FDA), 29 (OSHA), and 40 (EPA).

Also, the review of 1200 life sciences journals was accomplished using Current Contents on Diskette® (and 1995-1997 annual and quarterly cumulative issues on CD-ROM).

APPENDIX D

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Tobacco Smoking

NOMINATION
Review based on letter from Dr. Hiroshi Yamasaki (IARC) recommending listing in the RoC based on IARC classification of Tobacco Smoking as a known human carcinogen (IARC Vol. 38, 1986).

DISCUSSION
Tobacco smoking has been determined to cause cancer of the lung, urinary bladder and renal pelvis, oral cavity, pharynx, larynx, esophagus, lip, and pancreas in humans. Between 80 and 90% of all human lung cancers and approximately 30% of human cancers of all types are attributed to tobacco smoking. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known human carcinogen	11 yes/0 no
NTP EC Working Group (GR2)	list as known human carcinogen	8 yes/0 no
NTP Board RoC Subcommittee	list as known human carcinogen	6 yes/0 no

Public Comments Received
A total of 2 public comments was received, both providing additional published information and comments on the content of the background document prepared for the review of this nomination.