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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.
<table>
<thead>
<tr>
<th>Known To Be A Human Carcinogen:</th>
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<tr>
<td>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.</td>
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<tr>
<th>Reasonably Anticipated To Be A Human Carcinogen:</th>
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<td>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</td>
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<td>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</td>
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<th>Reasoning</th>
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<td>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.</td>
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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

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.

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<th>Regulatory Action</th>
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<td>21 CFR 801.126—Sec. 801.126 Exemptions for cigarettes and smokeless tobacco. Promulgated: 61 FR 44615, Aug. 28, 1996.</td>
<td>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. Part 897 regulates nicotine-containing cigarettes and smokeless tobacco as medical devices.</td>
</tr>
<tr>
<td>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.</td>
<td>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&amp;C Act. Restrictions on the sale, distribution, and use of cigarettes and smokeless tobacco are established &quot;to reduce the number of children and adolescents who use these products and to reduce the life-threatening consequences associated with tobacco use.</td>
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<tr>
<td>21 CFR 897.1—Sec. 897.1 Scope.</td>
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<td>21 CFR 897.2—Sec. 897.2 Purpose.</td>
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<td>21 CFR 897.3—Sec. 897.3 Definitions.</td>
<td>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).</td>
</tr>
<tr>
<td>21 CFR 897—Subpart B—Prohibition of Sale and Distribution to Persons Younger Than 18 Years of Age.</td>
<td>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.</td>
</tr>
<tr>
<td>21 CFR 897.10—Sec. 897.10 General responsibilities of manufacturers, distributors, and retailers.</td>
<td>Manufacturers shall remove self-service displays, advertising, labeling, and other items that do not comply.</td>
</tr>
<tr>
<td>21 CFR 897.12—Sec. 897.12 Additional responsibilities of manufacturers.</td>
<td>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.</td>
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## REGULATIONS

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<td>FDA 21 CFR 897.16—Sec. 897.16 Conditions of manufacture, sale, and distribution.</td>
<td>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.</td>
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<tr>
<td>21 CFR 897—Subpart C—Labels.</td>
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<tr>
<td>21 CFR 897.24—Sec. 897.24 Established names for cigarettes and smokeless tobacco.</td>
<td>Appropriate names for cigarette products as provided in Section 502 of the act are cigarette and cigarette tobacco.</td>
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<tr>
<td>21 CFR 897.25—Sec. 897.25 Statement of intended use and age restriction.</td>
<td>Each package shall bear the statement &quot;Nicotine-Delivery Device for Persons 18 or Older.&quot;</td>
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<tr>
<td>21 CFR 897—Subpart D—Labeling and Advertising.</td>
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<tr>
<td>21 CFR 897.30—Sec. 897.30 Scope of permissible forms of labeling and advertising.</td>
<td>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.</td>
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<td>F 21 CFR 897.32—Sec. 897.32 Format and content requirements for labeling and advertising.</td>
<td>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 &quot;Nicotine-Delivery Device for Persons 18 or Older&quot; after the appropriate product name as specified in 21 CFR 897.24.</td>
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<tr>
<td>D 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.</td>
<td>&quot;No manufacturer and no distributor of imported cigarettes and smokeless tobacco may market, license, distribute, or sell items or services&quot; (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.</td>
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<td>16 CFR CHAPTER I—FEDERAL TRADE COMMISSION.</td>
<td>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.</td>
</tr>
<tr>
<td>16 CFR 408—PART 408—UNFAIR OR DECEPTIVE ADVERTISING AND LABELING OF CIGARETTES IN RELATION TO HEALTH HAZARDS OF SMOKING.</td>
<td>Labels on cigarette packages and advertisements other than billboards must bear in rotation one of four warning statements, including: &quot;SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy&quot; and &quot;SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.&quot; 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.</td>
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<td><strong>F</strong> 15 U.S.C. Sec. 1335 Unlawful advertisements on medium of electronic communication [subject to the jurisdiction of the FCC].</td>
<td>See FCC in this table. Cigarette manufacturers were banned from cigarette advertising on television and radio in 1969 (FTC, 1998).</td>
</tr>
<tr>
<td>** FTC** 15 U.S.C. Sec. 1337 Reports to Congress by the Secretary [of Health and Human Services] and Federal Trade Commission.</td>
<td>FTC shall transmit annually to Congress a report on current practices and methods of cigarette advertising and promotion and recommendations for appropriate legislation.</td>
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<tr>
<td><strong>H S</strong> 45 CFR 96.122—Sec. 96.122 Application content and procedures.</td>
<td>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.</td>
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<tr>
<td><strong>H S</strong> 45 CFR 96.123—Sec. 96.123 Assurances.</td>
<td>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.</td>
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### REGULATIONS*

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<td>H 45 CFR 96.130—Sec. 96.130 State law regarding the sale of tobacco products to</td>
<td>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.</td>
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<td>S individuals under age of 18.</td>
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<td>15 U.S.C. Sec. 1335a List of cigarette ingredients; annual submission to</td>
<td>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.</td>
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<tr>
<td>Secretary; transmittal to Congress; confidentiality.</td>
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<tr>
<td>15 U.S.C. Sec. 1337 Reports to Congress by the Secretary [of Health and Human</td>
<td>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.</td>
</tr>
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<td>Services] and Federal Trade Commission.</td>
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<tr>
<td>15 U.S.C. Sec. 1341 Smoking, research, education, and information.</td>
<td>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.]</td>
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<td>41 CFR—TITLE 41—PUBLIC CONTRACTS AND PROPERTY MANAGEMENT. SUBTITLE E—FEDERAL PROPERTY MANAGEMENT REGULATIONS.</td>
<td>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.</td>
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<td>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.</td>
<td>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.</td>
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### 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


### 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 males, 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.


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.

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.


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.


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.
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.


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.


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.


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.


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


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 p53 gene as detected by immunostaining of sections of cancers of the head and neck. Smokers were much more likely to exhibit overexpression of the p53 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 p53 gene (Vineis, 1995). Overexpression of the p53 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 \textit{ras} or \textit{p53} 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 \textit{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-\textit{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).

8.0 REFERENCES


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
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
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
**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:

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<td>NTP EC Working Group (GR2)</td>
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<td>list as known human carcinogen</td>
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**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.