Tobacco Related Exposures

Introduction

Tobacco Smoking, Smokeless Tobacco and Environmental Tobacco Smoke were all listed in the Ninth Edition of the Report on Carcinogens (RoC) in 2000. The profiles for tobacco smoking, smokeless tobacco, and environmental tobacco smoke follow this introduction. The listings for tobacco smoking, smokeless tobacco, and environmental tobacco smoke in the Tenth Edition of the RoC are as follows:

Tobacco smoking is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between tobacco smoking and human cancer (IARC 1986).

The oral use of smokeless tobacco is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between exposure to smokeless tobacco and human cancer (IARC 1985, 1987, Gross *et al*. 1995).

Environmental tobacco smoke (ETS) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between passive exposure to tobacco smoke and human lung cancer (IARC 1986, EPA 1992, CEPA 1997). Studies also support an association of ETS with cancers of the nasal sinus (CEPA 1997).

ENVIRONMENTAL TOBACCO SMOKE*

First listed in the *Ninth Report on Carcinogens*

CARCINOGENECITY

Environmental tobacco smoke (ETS) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between passive exposure to tobacco smoke and human lung cancer (IARC 1986, EPA 1992, CEPA 1997). Studies also support an association of ETS with cancers of the nasal sinus (CEPA 1997).

Evidence for an increased cancer risk from ETS stems from studies examining nonsmoking spouses living with individuals who smoke cigarettes, exposures of nonsmokers to ETS in occupational settings, and exposure to parents' smoking during childhood. Many studies, including recent large population-based case control studies, have demonstrated increased risks of approximately 20% for developing lung cancer following prolonged exposure to ETS, with some studies suggesting higher risks with higher exposures. Exposure to ETS from spousal smoking or exposure in an occupational setting appears most strongly related to increased risk.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

ETS is a complex mixture of gases and particles comprising smoke from the burning cigarette, cigar, or pipe tip (sidestream smoke), smoke which is drawn through the tobacco column and exists through the mouthpiece during puffing (mainstream smoke), and exhaled smoke. Sidestream smoke and mainstream smoke contain many of the same chemical constituents, including at least 250 chemicals known to be toxic or carcinogenic. There is evidence from animal studies that the condensate of sidestream smoke is more carcinogenic to the skin of mice than equivalent weight amounts of mainstream smoke. Exposure to primarily mainstream smoke through active 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 to 90% of all human lung cancers are attributed to tobacco smoking.

Exposure of nonsmokers to ETS has been demonstrated by detecting nicotine, respirable smoke particulates, tobacco specific nitrosamines, and other smoke constituents in the breathing zone, and by measurements of a nicotine metabolite (cotinine) in the urine. However, there is no good biomarker of cumulative past exposure to tobacco smoke, and all of the information collected in epidemiology studies determining past exposure to ETS relies on estimates which may vary in their accuracy (recall bias). Other suggestions of systematic bias have been made concerning the epidemiological information published on the association of ETS with cancer. These include misclassification of smokers as nonsmokers, factors related to lifestyle, diet, and other exposures that may be common to couples living together and that may influence lung cancer incidence,

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* No separate CAS registry number is assigned to environmental tobacco smoke.

misdiagnosis of metastatic cancers from other organs in the lung, and the possibility that epidemiology studies examining small populations and showing no effects of ETS would not be published (publication bias).

Three population-based (Stockwell *et al*. 1992, Brownson *et al*. 1992, Fontham *et al*. 1994) and one hospital-based (Kabat *et al*. 1995) case control studies have addressed potential systematic biases. The three population-based studies each showed an increased risk from prolonged ETS exposure of a magnitude consistent with prior estimates. The hospital-based study gave similarly increased risk estimates, but the results were not statistically significant. The potential for publication bias has been examined and dismissed (CEPA 1997), and the reported absence of increased risk for lung cancer for nonsmokers exposed only in occupational settings has been found not to be the case when the analysis is restricted to higher quality studies (Wells 1998). Thus, factors related to chance, bias, and/or confounding have been adequately excluded, and exposure to ETS is established as causally related to human lung cancer.

PROPERTIES

Environmental tobacco smoke (ETS) is a complex mixture of thousands of chemicals that are emitted from burning tobacco. Tobacco smoking produces both mainstream smoke, which is drawn through the tobacco column and exists through the mouthpiece during puffing, and sidestream smoke, which is emitted from the smoldering tobacco between puffs. Approximately 4,000 chemicals have been identified in mainstream tobacco smoke and some have estimated that the actual number of compounds may be more than 100,000; however, the current identified compounds make up more than 95% of the total mass. ETS is the sum of sidestream smoke, mainstream smoke, compounds that diffuse through the wrapper, and exhaled mainstream smoke. Sidestream smoke contributes at least half of the smoke generated. The composition of tobacco smoke is affected by many factors including the tobacco product, properties of the tobacco blend, chemical additives, smoking pattern, pH, type of paper and filter, and ventilation (IARC 1986, NRC 1986, EPA 1992, Vineis and Caporaso 1995, CEPA 1997).

Although many of the same compounds are present in both mainstream and sidestream smoke, important differences exist. The ratios of compounds in sidestream and mainstream smoke are highly variable; however, there is less variability in emissions from sidestream smoke compared to mainstream smoke because smoking patterns and cigarette design have more of an impact on mainstream smoke (CEPA 1997). Sidestream smoke is generated at lower temperatures than mainstream smoke (600°C versus 900°C), in an oxygen-deficient environment, and is rapidly diluted and cooled after leaving the burning tobacco. Mainstream smoke is generated at higher temperatures in the presence of oxygen and is drawn through the tobacco column. These conditions favor formation of smaller particulates in sidestream smoke (0.01 to 0.1 μm) compared to mainstream smoke (0.1 to 1 μm). Sidestream smoke also typically contains higher concentrations of ammonia (40 to 170 fold), nitrogen oxides (4 to 10 fold), and chemical carcinogens (e.g., benzene, 10 fold; N-nitrosoamines, 6 to 100 fold; and aniline, 30 fold) than mainsteam smoke (IARC 1986).

Tobacco pyrolysis products are formed both during smoke inhalation and during the interval between inhalations (NRC 1986). A number of chemicals present in ETS are known or suspected toxicants/irritants with various acute health effects. Prominent among them are the respiratory irritants, ammonia, formaldehyde, and sulfur dioxide. Acrolein, hydrogen cyanide, and formaldehyde affect mucociliary function and at higher concentrations can inhibit smoke clearance from lungs (Battista 1976). Nicotine is addictive and has several pharmacological and toxicological actions. Nitrogen oxides and phenol are additional toxicants present in ETS. Over 50 compounds in ETS have been identified as known or reasonably anticipated human carcinogens, including some naturally occurring radionuclides. Most of these compounds are present in the particulate phase (IARC 1986, CEPA 1997).

USE

ETS is a by-product of smoking and has no industrial or commercial uses. ETS is used in scientific research to study its composition and health effects. See the profile on "Tobacco Smoking" for a brief description of the history and uses of tobacco products.

PRODUCTION

Burning tobacco products generate ETS. Tobacco has been an important economic agricultural crop since the 1600s. The total tobacco harvest in the U.S. ranged from approximately 1.19 to 1.79 billion lb/yr between 1987 and 1997. The tobacco harvest in 1997 was the highest for this reporting period (USDA 1993, 1998). In 2000, the U.S. imported more than 11 billion cigarettes and exported more than 148 billion cigarettes (ITA 2001).

EXPOSURE

Smoking prevalence in the U.S. has declined by approximately 40% since reaching a peak in the mid 1960s. In recent years, public policies have restricted smoking in buildings and other indoor public places. Nevertheless, ETS remains as an important source of exposure to indoor air contaminants. Based on data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1991, approximately 43% of U.S. children aged 2 months to 11 years lived in a home with at least one smoker. In addition, 37% of non-smoking adults reported exposure to ETS at home or at work (Pirkle *et al*. 1996). It is estimated that more than half of U.S. youth are still exposed to ETS (CDC 2001) and approximately 9 to 12 million children, aged six and younger, are exposed to ETS in their homes (EPA 2002).

Because ETS is a complex mixture, measuring ETS exposure is difficult. Various monitoring methods typically focus on nicotine levels or respirable suspended particulates in indoor air, or conitine levels (the primary metabolite of nicotine) in blood, saliva, or urine.

Mean nicotine levels in a variety of indoor environments ranged from 0.3 to 30 $\mu g/m^3$. Typical average concentrations in homes with at least one smoker ranged from 2 to 14 $\mu g/m^3$. Nicotine concentrations measured at work from the mid 1970s to 1991 were similar to those measured in

homes; however, maximum values were much higher at work (CEPA 1997). Levels of ETS in restaurants were found to be approximately 1.6 to 2.0 times higher than other office workplaces and 1.5 times higher than residences of at least one smoker. Isolating smokers to a specific section of restaurants was found to afford some protection for nonsmokers, but the best protection resulted from seating arrangements that segregated smokers by a wall or partition. Nonsmokers are still exposed to nicotine and respirable particles. Food-servers, who spend more time in restaurants, are exposed even more to ETS, though they may work in nonsmoking sections (Lambert *et al*. 1993).

Levels of ETS in bars were found to be approximately 3.9 to 6.1 times higher than in office workplaces and 4.4 to 4.5 times higher than in residences (Siegel 1993). Nicotine levels as high as 50 to 75 $\mu g/m^3$ were measured in bars and on airplanes (before smoking was banned). The highest measured nicotine concentration (1,010 $\mu g/m^3$) was measured in a car with the ventilation system shut off (CEPA 1997).

ETS exposure levels have been estimated by measuring respirable suspended particles (RSP) (particles <2.5 μm in diameter) in many studies. The average RSP values reported in these studies generally ranged from 5 to 500 $\mu g/m^3$. RSP values in homes with one or more smokers had concentrations that were 20 to 100 $\mu g/m^3$ higher than in comparable homes with no smokers (CEPA 1997).

The NHANES III survey indicated that approximately 90% of the U.S. population aged 4 years and older had detectable levels of conitine (Pirkle *et al*. 1996). The median serum conitine level among nonsmokers was 0.20 nanograms per milliliter (ng/mL) in 1991, but decreased by more than 75% to 0.05 ng/mL by 1999 (CDC 2001). An independent, nonfederal Task Force on Community Preventive Services, in collaboration with the U.S. Department of Health and Human Services and various public and private partners, recommended various strategies for reducing cigarette smoking and exposure to ETS. The baseline levels for cigarette smoking (1997), nonsmokers exposed to ETS (1994), and children exposed to ETS (1994) were 24%, 65%, and 27%, respectively. The objective is to reduce cigarette smoking to 12% and ETS exposure to 45% and 10%, in nonsmoking adults and children, respectively, by 2010 (CDC 2000).

REGULATIONS

EPA regulates environmental tobacco smoke under the Clean Air Act (CAA).

NIOSH reccomends that the exposure to environmental smoke be the lowest feasible concentration. Regulations are summarized in Volume II, Table 176.

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SMOKELESS TOBACCO*

First listed in the *Ninth Report on Carcinogens*

CARCINOGENICITY

The oral use of smokeless tobacco is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between exposure to smokeless tobacco and human cancer (IARC 1985, 1987; Gross *et al.* 1995).

Smokeless tobacco has been determined to cause cancers of the oral cavity. Cancers of the oral cavity have been associated with the use of chewing tobacco as well as snuff which are the two main forms of smokeless tobacco used in the United States. Tumors often arise at the site of placement of the tobacco.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

The IARC (1985) determined that there was inadequate evidence for the carcinogenicity of smokeless tobacco in experimental animals. Most reported studies had deficiencies in design. Subsequent studies provided some evidence that snuff or extracts of snuff produced tumors of the oral cavity in rats. Smokeless tobacco products contain a variety of nitrosamines that are carcinogenic to animals. The oral use of smokeless tobacco is estimated to be the greatest exogenous source of human exposure to these compounds. Nitrosamines are metabolically hydroxylated to form unstable compounds that bind to DNA. Extracts of smokeless tobacco have been shown to induce mutations in bacteria and mutations and chromosomal aberrations in mammalian cells. Furthermore, oral cavity tissue cells from smokeless tobacco users have been shown to contain more chromosomal damage than those from nonusers (IARC 1985).

PROPERTIES

Chewing tobacco and snuff are the two main forms of smokeless tobacco used in the United States. Chewing tobacco consists of the tobacco leaf with the stem removed and various sweeteners and flavorings such as honey, licorice, and rum. Snuff consists of the entire tobacco leaf (dried and powdered or finely cut), menthol, peppermint oil, camphor, and/or aromatic additives such as attar of roses and oil of cloves (IARC 1985).

Tobacco contains more than 2,500 chemical constituents. Some of these chemicals are applied to tobacco during cultivation, harvesting, and processing. The major chemical groups include

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* No separate CAS registry number is assigned to smokeless tobacco.

aliphatic and aromatic hydrocarbons, aldehydes, ketones, alcohols, phenols, ethers, alkaloids, carboxylic acids, esters, anhydrides, lactones, carbohydrates, amines, amides, imides, nitrites, *N*- and *O*-heterocyclic compounds, chlorinated organic compounds, and at least 35 metal compounds. Smokeless tobacco products contain known carcinogens such as volatile and nonvolatile nitrosamines, tobacco-specific *N*-nitrosamines (TSNAs), polynuclear aromatic hydrocarbons, and polonium-210 (^{210}Po). The carcinogenic TSNAs are present at concentrations that are at least two-fold higher than the concentration found in other consumer products (Brunnemann *et al.* 1986).

TSNAs, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN), present in tobacco are formed from nicotine and other tobacco alkaloids. The concentrations of NNK and NNN, the most carcinogenic of the TSNAs, are high enough in tobacco that their total estimated doses to long-term snuff users are similar in magnitude to the total doses required to produce cancer in laboratory animals (Hecht and Hoffman 1989).

USE

Tobacco was widely used by native populations throughout both North and South America by the time the first European explorers arrived in the late 1400s and early 1500s. Over the next few centuries, tobacco use spread to Europe, Africa, China, and Japan. Snuff use was introduced to North American colonists at Jamestown, Virginia in 1611. Tobacco chewing among American colonists began in the early 1700s, but was not widely accepted until the 1850s (IARC 1985).

Snuff was the most popular form of tobacco in both Europe and the U.S. prior to the 1800s. At that time, the finely ground tobacco was primarily sniffed through the nose. The current practice in the U.S. is to place a small pinch between the lip and gum or cheek and gum (IARC 1985). Moist snuff is the only smokeless tobacco product that has shown increased sales in the United States in recent years. This product is considered the most dangerous form of smokeless tobacco (NCI 1991, USDA 2001). In the three leading brands of snuff that account for 92% of the U.S. market, concentrations of nicotine and TSNAs were significantly higher than in the fourth and fifth most popular brands (Hoffman *et al*. 1995). The highest per capita consumption of snuff in the U.S. occurred from 1910 to 1920 at 0.5 lb, but had decreased to 0.15 lb by 1979. After the USDA reclassified several chewing tobacco products as snuff in 1982, the male per-capita consumption of snuff increased to 0.26 lb and remained at 0.2 to 0.3 lb through 2000 (IARC 1985, USDA 2001).

Peak consumption of chewing tobacco in the U.S. for persons aged 15 years and over occurred in 1900 at 4.1 lb and gradually declined to 0.5 lb by 1962. However, per-capita consumption for males aged 18 and over ranged from 1.05 to 1.34 lb between 1966 and 1983 (IARC 1985). Per-capita consumption for males declined to 0.8 lb in 1991, increased to 1.04 lb in 1992, and then declined gradually to 0.9 lb by 2000 (USDA 2001).

PRODUCTION

There are five major manufacturers of smokeless tobacco products in the U.S. These five companies control approximately 99% of the market. The largest of these companies controls more than 40% of the total smokeless tobacco market and approximately 75% of the moist snuff market (FTC 2001).

U.S. production of snuff increased from approximately 4 million lb in 1880 to more than 40 million lb in 1930. Production remained steady through 1950 at approximately 36 to 44 million lb/yr and then declined to approximately 24 million lb by 1980 (IARC 1985). Since 1986, U.S. sales of moist snuff have steadily increased from approximately 36 million lb to more than 58 million lb in 1999. Sales of Scotch snuff or dry snuff products declined from approximately 8.1 million lb in 1986 to 3.6 million lb in 1999 (FTC 2001). The U.S. imported approximately 17,400 lb of snuff and snuff flours and exported approximately 1.4 million lb in 2000 (ITA 2001).

Chewing tobacco products include plug, moist plug, twist/roll, and loose leaf. Total U.S. production declined from approximately 148.3 million lb in 1931 to 64.7 million lb in 1962. Production then rose to 105.8 million lb by 1980, but has shown steady declines over the past couple of decades. Plug tobacco accounted for approximately 51% of production in 1931, but only approximately 16% by 1980. During this time, loose-leaf tobacco increased its share of the market from approximately 41% to 68% (IARC 1985). Sales of loose-leaf chewing tobacco were approximately 65.7 million lb in 1986, but declined to approximately 44.5 million in 1999. Sales of plug and twist chewing tobacco combined were 8.8 million lb in 1986 and 2.8 million lb in 1999 (FTC 2001). Imports and exports of chewing tobacco in 2000 were approximately 84,000 and 256,000 lb, respectively (ITA 2001).

EXPOSURE

Individuals that use smokeless tobacco are primarily exposed by absorption through the oral or nasal mucosa and ingestion. Occupational exposure to tobacco may occur from skin contact, inhalation of dust, and ingestion of dust during processing and manufacturing. Many smokeless tobacco users are exposed during most of their working hours, and some use these products 24 h/day (IARC 1985).

Consumption of smokeless tobacco products showed a resurgence in the late 1970s after decades of decline. Increased use of these products was particularly dramatic among adolescent boys, increasing by 250% or more between 1970 and 1985 (NCI 1991). The percentage of current users, aged 18 and up, in the U.S. population ranges from approximately 1.4% to 8.8% across the states. Use is much higher among men (2.6% to 18.4%) than women (0 to 1.7%) in 17 states surveyed in 1997 (CDC 1998). The estimated number of smokeless tobacco users in the early 1980s ranged from 7 to 22 million (IARC 1985). In 1991, 2.9% of adults aged 18 and over were current users of smokeless tobacco. This value included an estimated 4.8 million men and 0.53 million women. Approximately 67% of snuff users and 45% of chewing tobacco users reported

daily use. The prevalence of use was highest (8.2%) in men aged 18 to 24 (CDC 1993). More recent data indicate that there are approximately 10 million users of smokeless tobacco in the U.S. and approximately 3 million of these are under 21 years of age (University of Minnesota 2001).

REGULATIONS

Federal regulations related to tobacco products that concern taxation, customs duties, and the potential for hand-to-mouth transfer of toxic substances when using tobacco in the workplace 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 and enforces the Comprehensive Smokeless Tobacco Health Education Act of 1986, Public Law 99-252 (FTC 1998). Regulations published in 16 CFR Part 307 include the requirement that one of three warning messages appear in regular rotation and distribution throughout the United States on packages of smokeless tobacco products and in their advertisements. One of the messages is "WARNING: THIS PRODUCT MAY CAUSE MOUTH CANCER." The requirements are given in detail in the Regulations table.

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). 15 U.S.C. Sec. 4402(f), banned, effective August 1986, advertising for smokeless tobacco products on any electronic communication medium subject to FCC jurisdiction.

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 DHHS's overall goal of reducing death and disability from use of tobacco products. Manufacturers, packagers, and importers of smokeless tobacco products are required by the Comprehensive Smokeless Tobacco Health Education Act of 1986 (Public Law 99-252) to report to the Secretary of HHS the ingredients, including nicotine, in smokeless tobacco products. HHS is authorized to undertake research on the health effects of ingredients. CDC has published requests for comments in the *Federal Register* on its proposed data collection in 61 FR 49145-49147, September 18, 1996, and 62 CFR 24115-24116, May 2, 1997. CDC has also requested comments on an analytical protocol proposed for measuring the quantity of nicotine in smokeless tobacco products (62 FR 24116-24119, May 2, 1997, and 62 FR 29729, June 2, 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. Some agencies have not restricted their corresponding regulations to cigarettes. For example, the General Services Administration (41 CFR) and the Treasury Department (31 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 are summarized in Volume II, Table 176.

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TOBACCO SMOKING

First listed in the *Ninth Report on Carcinogens*

CARCINOGENICITY

Tobacco smoking is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between tobacco smoking and human cancer (IARC 1986).

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; these patterns increase with increasing consumption of tobacco products and decrease in certain groups as the amount of tobacco 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.

ADDITIONAL INFORMATION RELEVANT 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 (IARC 1986).

PROPERTIES

Tobacco smoking produces both mainstream smoke, which is drawn through the tobacco column and exists through the mouthpiece during puffing, and sidestream smoke, which is emitted from the smoldering tobacco between puffs. The composition of tobacco smoke is affected by many factors including the tobacco product, properties of the tobacco blend, chemical additives, smoking pattern, pH, type of paper, filter, and ventilation. There are at least 3,800 chemicals present in tobacco smoke. These include carbon oxides, nitrogen oxides, ammonia, hydrogen cyanide, volatile aldehydes and ketones, nonvolatile alkanes and alkenes, benzene, hydrazine, vinyl chloride, isoprenoids, phytosterols, polynuclear aromatic compounds, alcohols, nonvolatile aldehydes and ketones, phenols, quinones, carboxylic acids, esters, lactones, amines and amides, alkaloids, pyridines, pyrroles, pyrazines, *N*-nitrosamines, metals, radioactive elements,

agricultural chemicals, and chemical additives. Mainstream smoke includes more than 400 individual gaseous components with nitrogen (58%), carbon dioxide (13%), oxygen (12%), carbon monoxide (3.5%) and hydrogen (0.5%) dominating. Particulate phase and other vapor phase components account for approximately 8% and 5% of mainstream smoke, respectively (IARC 1986, Vineis and Caporaso 1995).

Although many of the same compounds are present in both mainstream and sidestream smoke, there are important differences. Sidestream smoke is generated at lower temperatures than mainstream smoke (600°C versus 900°C), in an oxygen-deficient environment, and is rapidly diluted and cooled after leaving the burning tobacco. Mainstream smoke is generated at higher temperatures in the presence of oxygen and is drawn through the tobacco column. These conditions favor formation of smaller particulates in sidestream smoke (0.01 to 0.1 μm) compared to mainstream smoke (0.1 to 1 μm). Sidestream smoke also typically contains higher concentrations of ammonia (40 to 170 fold), nitrogen oxides (4 to 10 fold), and chemical carcinogens (e.g., benzene, 10 fold; *N*-nitrosoamines, 6 to 100 fold; and aniline, 30 fold) than mainstream smoke (IARC 1986).

USE

Smoking was introduced to Europe from the Americas in the middle of the sixteenth century and then spread throughout the world. Currently, the primary source for tobacco smoke is cigarettes. Pipes, cigars, *bidis*, and other forms are used less frequently (IARC 1986). 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. Per capita consumption of cigarettes in the United States rose from 54 in 1900, peaked at 4,354 in 1963, and declined to 2,054 by 2000. By comparison, per capita consumption of cigars, calculated for males 18 and over, was 39.3 in 1999 and 38.1 in 2000. This reduction was the first decline in cigar smoking prevalence in six years after showing marked increases during the 1990s (American Lung Association 2001).

The use of tobacco products varies with gender, age, education, and culture. The percentage of adults who smoke cigarettes has declined steadily from 42.4% in 1965 to 24.1% in 1998. By comparison, 21.9% and 6.8% smoked cigars and pipes, respectively, in 1998. Prevalence of smoking has always been higher in men than women. More than half (51.9%) of adult men smoked in 1965 compared to 33.9% for women. Smoking prevalence among men peaked at 67% in the 1940s and 1950s. By 1998, the percentages declined to 26.4% for men and 22.0% for women. Smoking prevalence was highest in the 25 to 44 age group between 1965 and 1996. However, smoking increased in the 18 to 24 age group during the 1990s, while prevalence continued to decrease in the 25 to 44 age group. For 1997 and 1998, smoking prevalence was highest in the 18 to 24 age group. Smoking prevalence by ethnic groups are as follows: Native Americans (40%), non-Hispanic whites (25%), non-Hispanic blacks (24.7%), Hispanics (19.1%) and Asians/Pacific Islanders (13.7%). Overall, smoking declined by approximately 40% in the U.S. from 1965 to 1990, but has remained virtually unchanged since (American Lung Association 2001).

PRODUCTION

Tobacco has been an important economic agricultural crop since the 1600s. North and Central America produce the highest quantity. *Nicotiana tabacum* is the most common species of tobacco used in cigarettes, but *N. rustica* is also used in some areas. 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). The total tobacco harvest in the U.S. ranged from approximately 1.19 to 1.79 billion lb/yr between 1987 and 1997 (USDA 1993, 1998). In 2000, the U.S. imported more than 11 billion cigarettes and exported more than 148 billion cigarettes (ITA 2001).

EXPOSURE

Smokers are primarily exposed by inhalation; however, some exposure may occur by absorption of chemicals present in the tobacco or tobacco smoke directly through the lining of the mouth and gums. In addition, nonsmokers may be exposed by inhalation of tobacco smoke any time they are near smokers (see the profile for Environmental Tobacco Smoke). For the first time in more than 25 years of observation, the percentage of the adult U.S. population who had not smoked or smoked less than 100 cigarettes was less than 50% in 1991. Nevertheless, there were an estimated 47.2 million adult smokers in the U.S. in 1998 compared with a high of 53.5 million smokers in 1983 (American Lung Association 2001).

As discussed above (see Use Section), the prevalence of smoking in the U.S. declined by approximately 40% between 1965 and 1990, but has plateaued since the early 1990s. In recent years, smoking among high school students has declined after increasing during the first half of the 1990s. Per capita consumption of cigarettes also declined. The percentage of adult smokers who smoke <15 cigarettes per day increased by 33% between 1974 and 1998, while the percentage of heavy smokers (>24 cigarettes/day) declined by 26.5%. The prevalence of smoking cessation increased by more than 72% between 1965 and 1998, with approximately 44.8 million former smokers identified in 1998 (American Lung Association 2001).

Current strategies in the U.S. for reducing exposure to tobacco smoke include goals for increasing tobacco-use cessation and reducing the number of new smokers. The objectives include reducing smoking prevalence among U.S. adults to 12%, and increasing smoking cessation attempts to 75% for adult smokers and 84% for adolescent smokers by 2010 (CDC 2000).

REGULATIONS

Federal regulations related to tobacco products that concern taxation, customs duties, and the potential for hand-to-mouth transfer of toxic substances when using tobacco in the workplace 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 which are available free on the Internet and by mail.

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). 15 U.S.C. Sec. 4402(f), banned, effective August 1986, advertising for cigarettes on any electronic communication medium subject to FCC jurisdiction.

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 DHHS'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. Some agencies have not restricted their corresponding regulations to cigarettes. For example, the General Services Administration (41 CFR) and the Treasury Department (31 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 and how to get help to quit. Regulations are summarized in Volume II, Table 176.

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