

SMOKING and HEALTH

a report of the Surgeon General

- ☐ The Health Consequences of Smoking
- ☐ The Behavioral Aspects of Smoking
- ☐ Education and Prevention



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1 INTRODUCTION AND SUMMARY.

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Introduction

In the 15 years which have elapsed since the Report of the Advisory Committee on Smoking and Health to the Surgeon General of the U.S. Public Health Service (15), there has been an increasing number of scientific studies on the relationship between tobacco consumption and health. Where the 1964 Committee had access to some 6,000 articles in the world literature on smoking and health, there are now more than 30,000 such articles. In fact, no sound epidemiologic study of chronic disease today would omit from its design a history of tobacco use as a significant factor. It is on this greatly expanded source of data that this current review and re-evaluation of the evidence on the hazard of smoking to human health is based.

For historical perspective, it should be remembered that concern over the effect of tobacco on health did not begin with the Report to the Surgeon General, although that evaluation was the first American review and judgmental analysis of the tobacco hazard for all aspects of human mortality, morbidity, and specific diseases other than lung cancer. Indeed, almost from the moment of its introduction into Europe in 1558, the *Nicotiana tabacum* prompted serious concern over the effects which uses of this leaf had on human health. In less than 60 years, tobacco had become a staple agricultural commodity in Virginia and its principal currency. The "tobacco culture" expanded rapidly both societally and agronomically in America; in Europe, in the 17th Century, Simonis Pauli published his treatise "On the Abuse of Tobacco" (6).

Although the growth of tobacco use has been extensively documented, reliable data on its use within the total U.S. population did not become available until 1880 (8). Since then, per capita tobacco consumption has increased almost three-fold, with dramatic changes in its forms of use. Prior to World War I, tobacco chewing was the principal use in the United States, but the 1920's saw cigarette consumption, particularly of prefabricated cigarettes, increase astronomically as use of chewing and other smoking tobacco declined. A cigarette consumption plateau in the 1930's was followed by a sharp increase during World War II, when widespread adoption of the cigarette habit by women was added to large-scale consumption by American troops. These changes in overall consumption and forms of tobacco use had marked influences on mortality and disease patterns.

Concern over the effects of tobacco use on health increased over the years, but it was not until the 20th century that systematic scientific studies of the problem were launched. Clinical impressions and suspicions had been recorded and some had persisted for decades and centuries before appropriate tools for scientific investigation were developed. For example, the relationship between cancer of the lip and tobacco use was noted by Holland early in the 18th century (5) and Soemmerring made the same observation in 1795 (13). Not until 1920,

however, was the first systematic approach to that association made (1). In 1900, statisticians began to note increases in lung cancer. In 1928, Lombard and Doering presented initial suspicions of a relationship between tobacco and disease when they noted that heavy smoking was more common among cancer patients than among control groups (7).

In the 1930's, trends in diseases such as lung cancer became evident, promoting the start of intensive inquiries and animal experiments into disease relationships and into the chemical composition and pathogenic effects of tobacco and tobacco smoke. In 1938, Pearl found that heavy smokers had a shorter life expectancy than nonsmokers (9), and in 1939 saw the beginnings of large-scale epidemiologic studies of the relationship between tobacco use and lung cancer. A large number of clinical and pathological observations on effects of tobacco smoke on man had accumulated by this time.

The end of the 1930's marked the beginning of almost 40 years of retrospective (case-control) studies on selected diseases suspected of association with tobacco use (primarily lung cancer, chronic bronchitis, emphysema, and coronary artery disease) and prospective studies of diseases and mortality among cohorts of smokers and nonsmokers. By the early 1950's, there had been reports of many significant epidemiologic studies, and four of the seven prospective (cohort) mortality studies had been launched. Tobacco was increasingly being identified as a health hazard. In 1954, a group of tobacco manufacturers, growers, and warehousemen established the Tobacco Industry Research Committee to launch a research program on tobacco use and health.

The accumulation of consistent results from a growing number of studies on lung cancer led the then Surgeon General, Dr. Leroy E. Burney, to instigate the establishment by the National Cancer Institute, the National Heart Institute, the American Cancer Society and the American Heart Association of a scientific study group to assess the problem. The group agreed that a causal relationship between cigarette smoking and lung cancer existed (11); and on July 12, 1957 the Surgeon General placed the Service on record as saying that the weight of evidence indicated a causative relationship between excessive smoking and lung cancer. A brilliant analysis and defense by Cornfield, et al. of the evidence supporting this causal relationship by appeared in 1959 (3). In that year, the U.S. Public Health Service reiterated its position and took one step further when Burney stated that the principal factor in the increased incidence of lung cancer was smoking, particularly smoking of cigarettes (2).

In the early 1960's, a trend toward policies of intervention was hastened and encouraged by a number of events. On June 1, 1961, the presidents of the American Cancer Society, the American Public Health Association, the American Heart Association, and the National

Tuberculosis Association urged President Kennedy to establish a commission to study the tobacco problem. On January 4, 1962, representatives of these organizations met with Surgeon General Luther L. Terry once more to urge action. A proposal from Terry to the Secretary of Health, Education, and Welfare called for an expert advisory committee to assess existing knowledge and make appropriate recommendations. In March, a resolution introduced by Senator Maurine Neuberger (SJRI74) called for the establishment of a Presidential commission on tobacco and health, but it was never brought to a vote.

On April 16, the Surgeon General presented a detailed proposal for an advisory group to re-evaluate the 1959 position of the Service. He cited new studies on major adverse health effects, evidence that medical opinion was now very strong against smoking, a request from the Federal Trade Commission for guidance on labeling and advertising of tobacco products, and a recent report of the Royal College of Physicians of London which concluded that "cigarette smoking is a cause of lung cancer and bronchitis and probably contributes to the development of coronary heart disease..." (10).

Consultations between the White House and Public Health Service officials led to Surgeon General Terry's announcement on June 7, 1962, of the planned formation of an expert committee to review all data on smoking and health. Representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, the Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology met with the Surgeon General on July 27 to establish the work of the expert committee and to agree on a list of some 150 scientists and physicians qualified to evaluate data on the relationship between tobacco use and health. Terry selected 10 from the list and, thus, the Surgeon General's Advisory Committee on Smoking and Health was launched at its first meeting on November 9, 1962.

The members of the Committee were: Stanhope Bayne-Jones, M.D., L.L.D., Former Dean, Yale School of Medicine; Walter J. Burdette, M.D., Ph.D., University of Utah; William G. Cochran, M.A., Harvard University; Emmanuel Farber, M.D., Ph.D., University of Pittsburgh; Louis F. Fieser, Ph.D., Harvard University; Jacob Furth, M.D., Columbia University; John B. Hickam, M.D., University of Indiana; Charles LeMaistre, M.D., University of Texas; Leonard M. Schuman, M.D., University of Minnesota; and Maurice H. Seevers, M.D., Ph.D., University of Michigan.

The judgments of the Advisory Committee led to a series of significant conclusions, released in 1964 in the now historic Report of

the Advisory Committee to the Surgeon General of the Public Health Service on Smoking and Health (15):

1. Cigarette-smoking males were found to have a 70 percent excess risk of mortality over nonsmokers. Female smokers were found to have an elevated risk of mortality, but less than that of males.

2. Cigarette smoking was judged to be causally related to lung cancer in men, the magnitude of the effect of cigarette smoking far outweighing all other factors. A similar trend was noted in females, but studies then available presented insufficient grounds for a firm judgment on causality (4). Included as evidence in the judgment of causality were the several findings of a dose-response relationship: The risk of death from lung cancer increased directly with duration of smoking, number of cigarettes smoked per day, inhalation, and, indirectly, with age when smoking began; discontinuance of smoking lowered the risk. For the combined group of pipe, cigar and pipe, and cigar smokers, the risk of lung cancer was greater than for nonsmokers, but was much less than for cigarette smokers.

3. Cigarette smoking was judged to be the most important of the causes of chronic bronchitis in both men and women in the United States and was found to increase the risk of dying from chronic bronchitis and emphysema.

4. Male cigarette smokers were found to have significantly higher death rates from coronary artery disease than nonsmoking males. The data then available were borderline for a judgment of causality by the rigid criteria employed for all disease entities.

5. A causal relationship was not established at the time for a number of other cardiovascular diseases.

6. Significant associations between several other cancer sites and tobacco use were judged to be causal, including pipe smoking and lip cancer, and cigarette smoking and laryngeal cancer.

7. Although the evidence revealed associations between cancer of the oral cavity and the several forms of tobacco use, between such tobacco use and esophageal cancer, and between cigarette smoking and urinary bladder cancer, the data subjected to the judgment criteria did not at that time support a judgment of causality.

A number of other diseases or conditions suggested to be associated with smoking by clinical impressions or by showing excess mortalities in the prospective studies were also scrutinized. They included: peptic ulcer, tobacco amblyopia, cirrhosis of the liver, accidents, influenza and pneumonia, and low infant birth weight.

In the instance of peptic ulcer, epidemiologic studies indicated a consistent excess risk of mortality from peptic ulcer, particularly gastric ulcer, among cigarette smokers, but in 1964 a judgment of causality could not be made.

Tobacco amblyopia had been clinically associated with pipe and cigar smoking, but the Committee could find no substantiation of this

clinical impression, since there had been no epidemiologic studies of this now rare entity and experimental studies had not been adequately controlled.

Cirrhosis of the liver had been found to contribute to excess mortality among cigarette smokers in the seven prospective studies. However, because of the relationship of alcohol consumption (and nutritional deficiencies) to cirrhosis, the correlation of heavy drinking with heavy smoking, and lack of definitive studies on the compartmentalization of these two factors at the time, there was inadequate support of a causal association.

As for accidents, an obvious relationship between smoking and fires in the home was noted in 1964.

A moderate excess risk of mortality from influenza and pneumonia was noted in six of the seven prospective studies but this association had not been evaluated by further studies. Other acute respiratory illnesses had been studied in families and in college graduates and no differences had been found between cigarette smokers and nonsmokers.

There had been some interest in the relationship between maternal smoking during pregnancy and pregnancy outcome. By 1964, five retrospective and two prospective studies revealed an association of cigarette smoking during pregnancy with lower birth weight and premature deliveries. A relationship with fetal and/or neonatal death was deemed equivocal at the time.

Finally, although smokers were found to differ from nonsmokers in a number of ways, none of the studies appraised by the Advisory Committee revealed any single variable discriminating significantly between the two groups. The report emphasized that "the overwhelming evidence points to the conclusion that, smoking—its beginning, habituation and occasional discontinuance—is to a large extent psychologically and socially determined."

The Committee concluded: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

The release of the Advisory Committee's Report to the Surgeon General stimulated many studies and reports, the data from which augmented the earlier studies, strengthened the conclusions of the Committee, provided information in areas for which data had not existed, and shed light on the pathogenetic mechanisms of the thousands of compounds in tobacco and tobacco smoke. These studies were epidemiologic, clinical, experimental, and, in the area of smoking control, psychologic and sociologic as well.

The Federal Cigarette Labeling and Advertising Act of 1965 (P.L. 89-92) required the Secretary of Health, Education, and Welfare to submit regular reports to Congress on the health consequences of smoking, together with legislative recommendations. The purpose was

to monitor the scientific literature on smoking and health. This surveillance of world literature was performed by the National Clearinghouse for Smoking and Health (now succeeded by the Office on Smoking and Health). The updated reports were issued in 1967, 1968, 1969, 1971, 1972, 1973, 1974, 1975, 1976, and 1978.

This current 15th anniversary volume on smoking and health is offered as a detailed review and reappraisal of smoking and health relationships. Its contents are the work of numerous scientists both within and outside the Department of Health, Education, and Welfare. All are acknowledged elsewhere.

On the following pages, this introductory chapter seeks to summarize the principal findings and extensions of knowledge contributed by the scientific community over these 15 years. An attempt has been made to highlight particularly the earlier gaps in knowledge that have been closed or shortened in the intervening period.

Summary

Health Consequences of Smoking

Mortality

This 1979 appraisal strengthens earlier conclusions as to the relationship between smoking and mortality. Materials reviewed include the seven original prospective studies and new data derived from long-term follow-up of three of these investigations: the British doctors' study (20 years), the Hammond study (12 years) and that initiated by Dorn (16 years). Also reviewed are data from Japanese and Swedish prospective studies. The overall findings yield quantitative results over time which are substantially identical with earlier conclusions. These findings include:

1. The overall mortality ratio for all male current cigarette smokers, irrespective of quantity, is about 1.7 (70 percent excess) compared to nonsmokers.
2. Mortality ratios increase with amount smoked. The two-pack-a-day male smoker has a mortality ratio of 2.0 compared to nonsmokers.
3. Overall mortality ratios are directly proportional to the duration of cigarette smoking. The longer one smokes, the greater the risk of dying.
4. Overall mortality ratios are higher for those who initiated their cigarette smoking at younger ages compared to those who began smoking later.
5. Overall mortality ratios are higher among cigarette smokers who inhale than among those who do not.
6. Although mortality ratios for smokers are highest at the younger ages and decline with increasing age, the actual number of excess deaths attributable to cigarette smoking increases with age.

7. Former cigarette smokers experience declining overall mortality ratios as the years of discontinuance increase. After 15 years of cessation, mortality ratios for former cigarette smokers are similar to those who never smoked. Although mortality ratios for any given age for former smokers are directly proportional to the amount smoked before cessation and inversely related to the age of smoking initiation, cessation of smoking does diminish such individuals' risk regardless of these former factors, provided they are not ill at time of cessation. (Actually, the mortality ratios among those who had discontinued smoking less than 1 year before enrollment in several of the prospective studies were higher than for current cigarette smokers. This was also manifest in the total mortality rates for former cigar and pipe smokers. Further analyses separating those who stopped smoking because of illness from those ex-smokers who stopped for other reasons revealed higher mortality rates among the former.)

8. Cigar smoking is not without risk of increased mortality. The overall mortality ratios for cigar smokers are somewhat higher than for nonsmokers and are directly proportional to the number of cigars smoked per day.

9. Pipe smoking seems to have a slight effect in increasing overall mortality, but individuals who combine their pipe smoking (or cigar smoking) with cigarette smoking experience a level of risk of mortality intermediate between those who smoke only pipes or cigars and those who smoke only cigarettes.

A number of new findings in the relationship between smoking and overall mortality were found over the 15-year interval:

1. Calculations from prospective study data have indicated that life expectancy at any given age is significantly shortened by cigarette smoking. For example, a 30- to 35-year-old, two-pack-a-day smoker has a life expectancy 8 to 9 years shorter than a nonsmoker of the same age.
2. Overall mortality ratios increase with the "tar" and nicotine content of the cigarette. For smokers of low "tar" and nicotine cigarettes (less than 1.2 mg nicotine and less than 17.6 mg "tar"), overall mortality ratios are 50 percent greater than for nonsmokers, and 15 to 20 percent less than for all smokers of cigarettes.
3. For the 1964 report, data were inadequate for firm judgments on the mortality status of female cigarette smokers. Adequate follow-up in the prospective studies during these past 15 years has revealed mortality ratios for female cigarette smokers somewhat less than those for male smokers. This difference is deemed to be due to differences in exposure (later age of initiation, fewer cigarettes per day, and use of cigarettes with lower "tar" and nicotine content). Female dose-responses (quantity, age at initiation, duration of smoking, inhalation, "tar" and nicotine content) are the same as for male cigarette smokers.

Subsets of females with smoking characteristics similar to those of men experience mortality rates similar to those of male smokers.

4. From the detailed data of two prospective studies (Hammond and Dorn) the excess in mortality is noted to be greatest for the 45- to 54-year age groups among men and women. Thus, smoking mortality is premature mortality.

Cause-Specific Mortality

1. Although mortality ratios are particularly high among cigarette smokers for such diseases as lung cancer, chronic obstructive lung disease, and cancer of the larynx, coronary heart disease is the chief contributor to the excess mortality among cigarette smokers.

2. Lung cancer and chronic obstructive lung disease, in that order, follow after coronary heart disease in accounting for the excess mortality.

3. Pipe and cigar smoking are associated with elevated mortality ratios for cancers of the upper respiratory tract, including cancer of the oral cavity, the larynx, and the esophagus.

Morbidity

Following the 1964 Report to the Surgeon General, the National Center for Health Statistics began collecting information on smoking as part of the National Health Interview Survey. On the basis of probability samples of the population, estimates can be made for the general population. These data have proven valuable in assessing the relationships between tobacco use and illnesses, disability, and other health indicators. The findings include:

1. In general, male and female current cigarette smokers tend to report more chronic conditions, such as chronic bronchitis and/or emphysema, chronic sinusitis, peptic ulcer disease, and arteriosclerotic heart disease, than persons who never smoked.

2. A dose-response gradient was noted with the amount of cigarettes smoked per day for most of the chronic conditions. Particularly impressive is the gradient for chronic bronchitis and/or emphysema, with an increase in prevalence among male smokers of two packs or more a day to four times that of those who have never smoked, and among female smokers of two packs or more, to 10 times that of those who never smoked.

3. The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes.

4. Indicators of morbidity which are not dependent upon physicians' diagnoses include measures of disability such as work-days lost, days in bed, and days of limitation of activity resulting from chronic diseases.

(a) Male current smokers of cigarettes reported a 33 percent excess, and female current smokers a 45 percent excess, of work days lost in comparison to persons who never smoked. Male former smokers had an excess of 41 percent, and female former smokers an excess of 43 percent, of work days lost. From the 1974 survey data, this calculates to more than 81 million excess days of work lost for the U.S. population in 1 year.

(b) Male current smokers had a 14 percent excess, and female current smokers a 17 percent excess, of days of bed disability over those who never smoked. Smokers in all age and sex groups, except for women over age 65, reported more days in bed due to illnesses than did persons who never smoked. From 1974 data, this calculates to more than 145 million excess days of bed disability for the U.S. population in 1 year.

(c) The excesses of disability measures are dose-related.

(d) For most age and sex groups, a higher proportion of current and former smokers report longer limitation of activity due to chronic diseases than do persons who never smoked.

5. A tendency was noted for higher proportions of former smokers and those who never smoked, as compared to present smokers, to assess their own health status as excellent.

6. Current smokers and former smokers reported more hospitalizations than nonsmokers in the year prior to interview. Data on the reasons for these hospitalizations have not been analyzed.

While most studies show a reduction in the risk of mortality among former smokers, data on disability and illness often show continued high risk among former smokers. This finding should be interpreted more as an indication of the need for both additional data and further analysis of existing data, rather than as an indication of the lack of a beneficial impact on health status from smoking cessation.

These findings on morbidity are consistent with the vast amount of evidence on the relationship between cigarette smoking and mortality.

Cardiovascular Diseases

The tremendous amount of research on the relationship between cardiovascular disease and smoking, undoubtedly stimulated by a lack of adequate information in the areas of the nature of atherosclerosis, the mechanisms of atherogenesis, and the pathogenetic pathways for smoking components, has provided a basis for firmer judgments on the relationship than could be made in 1964. The present report on cardiovascular disease and smoking draws heavily on the 1976 reference report on smoking and health (14) and adds more recent data.

Systematic observations on the association between smoking and cardiovascular diseases have been made on considerably more than a

million individuals in the United States (the majority on men) and have involved many millions of person-years of experience.

Sample sizes are now extensive in both retrospective and prospective studies. Variables observed in retrospective studies have been relatively limited; in some prospective studies, they have been more numerous and have allowed for complex analyses in which the independence of smoking as a risk factor among other risk factors has been defined. Autopsy and experimental studies in animals have also been extended and serve to clarify earlier issues.

The 1979 Report includes the following conclusions:

1. The data collected from Western countries, particularly the United States, but also the United Kingdom, Canada, and others, show that smoking is one of three major independent risk factors for heart attack manifested as fatal and nonfatal myocardial infarction and sudden cardiac death in adult men and women. Moreover, the effect is dose-related, synergistic with other risk factors for heart attack, and of stronger association at younger ages.

2. Smoking cigarettes is a major risk factor for arteriosclerotic peripheral vascular disease and is strongly associated with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta.

3. The data establish adequately that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries than is found among nonsmokers. The effect is dose-related.

4. Epidemiologic data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive.

5. Smoking increases the possibility of a heart attack recurrence among survivors of a myocardial infarction.

6. In acute experiments on arteriosclerotic patients with angina pectoris or with intermittent claudication of peripheral vascular disease, smoking or exposure to carbon monoxide reduces the patient's established threshold for the precipitation of angina or claudication. Both nicotine and carbon monoxide (CO) aggravate exercise-induced angina.

7. Women who smoke and use oral contraceptives are at a significantly elevated risk for fatal and nonfatal myocardial infarction. A synergistic role of cigarette smoking and oral contraceptive use is suggested for subarachnoid hemorrhage.

8. Smokers of low "tar" and nicotine cigarettes experience less risk for coronary heart disease than smokers of high "tar" and nicotine cigarettes, but their risk is considerably greater than that of nonsmokers.

9. Cigarette smoking does not induce chronic hypertension. However, in the presence of hypertension as a risk factor for coronary heart

disease, smoking acts synergistically to increase the effective risk by joining the risks attributable to hypertension and to smoking alone.

10. Cigarette smoking is a major risk factor for ischemic peripheral vascular disease of arteriosclerotic type; cigarette smoking increases appreciably the risk of peripheral vascular disease in diabetes mellitus.

11. Cessation of cigarette smoking improves the prognosis of arteriosclerotic peripheral vascular disease and is advantageous to its surgical treatment.

12. Cessation of smoking reduces the risk of mortality from coronary heart disease, and after 10 years off cigarettes this risk approaches that of the nonsmoker.

13. The relationship of smoking to the incidence of stroke is not established; however, an association with subarachnoid hemorrhage has been reported in women.

In summary, for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States.

Cancer

The strongest evidence of a causal relationship between tobacco use and disease was delineated for lung cancer in the 1950's and 1960's and subjected to the rigid criteria of appraisal in the 1964 Report. In the intervening years, additional epidemiological, clinical, autopsy, and experimental studies have augmented and strengthened the earlier conclusions, particularly with regard to women smokers, for whom only preliminary data were then available.

New evidence has also accumulated since 1964 with respect to the relationships between tobacco use and cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas.

In the case of laryngeal cancer, the accumulated evidence since 1964 has strengthened, but not materially changed, the conclusions of the 1964 Report.

In the case of cancer of the oral cavity, the 1964 Report had to base its conclusions primarily on retrospective studies because of the diversity of sites, their varying incidence of tobacco exposure, and the relatively small numbers derivable in the early years of the prospective studies. These studies, unfortunately, varied in approach and either did not separate the several sites of the oral cavity or found the classes of smoking too numerous for testing their significance. Thus, the only firm judgment which could then be made was that a causal relationship exists between pipe smoking and cancer of the lip.

The 1964 Report found that an association existed between tobacco use and esophageal and urinary bladder cancer, but the Committee could not determine from the available data whether there was a causal relationship.

The 1964 Report did not address kidney or pancreatic cancer. While retrospective studies were not examined, the seven prospective studies indicated that the average mortality ratio for kidney cancer was 1.5. Present knowledge about the relationship between smoking and the various cancers is summarized below, excerpted from the conclusions to be found in Chapter 5. As will be seen, the evidence is now overwhelming.

Lung Cancer

1. Cigarette smoking is causally related to lung cancer in both men and women.
2. The risk of developing lung cancer is increased with increasing dosages of smoking as measured by: number of cigarettes smoked per day, duration of smoking, age of initiation of smoking, degree of inhalation, "tar" and nicotine content of cigarettes smoked, and several other measurements.
3. Lung cancer mortality rates in women are increasing more rapidly than in men and, if present trends continue, will be the leading cause of cancer death in women in the next decade.
4. Use of filter cigarettes and smoking of cigarettes with lower amounts of "tar" and nicotine decrease lung cancer mortality rates among smokers; however, these rates are significantly elevated compared to rates for nonsmokers.
5. Ex-smokers experience decreasing lung cancer mortality rates which approach the rates of nonsmokers after 10 to 15 years of cessation. The residual risk of developing lung cancer in ex-smokers is proportional to the overall dosage of lifetime cigarette-smoking exposure, and inversely related to the interval since cessation.
6. Pipe and cigar smokers have lung cancer mortality rates above nonsmokers, but these rates are lower than those for cigarette smokers.
7. Certain occupational exposures can act synergistically with smoking to significantly increase lung cancer mortality rates far above those resulting from either exposure alone.

Cancer of the Larynx

8. Cigarette smoking is a significant causative factor in the development of cancer of the larynx in men and women and is directly related to several measures of dosage.
9. Pipe and cigar smokers experience approximately the same risk as cigarette smokers for cancer of the larynx.
10. There appears to be a synergistic effect between smoking and alcohol intake, as well as between asbestos exposure and smoking, for laryngeal cancer.

11. There is a substantial decrease in the risk of developing cancer of the larynx with long-term use of filter cigarettes compared to the use of nonfilter cigarettes; ex-smokers, after 10 years of cessation, have mortality rates which approximate those of nonsmokers.

Oral Cancer

12. Epidemiological studies indicate that smoking is a significant causal factor in the development of oral cancer. The risk increases with the number of cigarettes smoked per day.
13. Pipe and cigar smokers experience almost the same high risk for oral cancer as experienced by cigarette smokers.
14. A synergism exists between smoking and alcohol consumption for oral cancer.

Cancer of the Esophagus

15. Cigarette smoking is a causal factor in the development of cancer of the esophagus, and the risk increases with the amount smoked.
16. The risk of esophageal cancer for pipe and cigar smokers is about the same as that for cigarette smokers.
17. A synergism also exists for esophageal cancer and the marked use of alcohol and cigarette smoking.

Cancer of the Urinary Bladder

18. Epidemiological studies have demonstrated a significant association between cigarette smoking and bladder cancer in both men and women.
19. Cigarette smoking acts independently and synergistically with other factors, such as occupational exposures, to increase the risk of developing cancer of the urinary bladder.

Cancer of the Kidney

20. Cigarette smoking is associated with cancer of the kidney for men. No data exist to substantiate a relationship for women.

Cancer of the Pancreas

21. Cigarette smoking is related to cancer of pancreas, and several epidemiological studies have demonstrated a dose-response relationship.

Experimental Studies

22. Experimental studies on a variety of animal models have confirmed the carcinogenic effects of tobacco smoke and its constituents on several sites including lung, larynx, esophagus, and oral cavity.

Non-Neoplastic Bronchopulmonary Diseases

Of the non-neoplastic bronchopulmonary diseases, only chronic bronchitis was judged to be causally related to cigarette smoking in the 1964 Report. In fact, cigarette smoking was then deemed the most important cause of chronic bronchitis in the U.S. and a cause of increased risk of mortality from chronic bronchitis. A relationship to pulmonary emphysema was deemed to exist, but a causal interpretation of this relationship could not then be ascribed. Cigarette smoking was then judged to exceed atmospheric pollution and environmental exposures as a cause of chronic obstructive lung disease (COLD). These diseases rank second only to coronary artery disease as a cause of Social Security-compensated disability.

In the 15 intervening years, the updating of several of the larger prospective studies and numerous retrospective and cross-sectional studies have strengthened the conclusions of the 1964 Report.

1. Cigarette smokers have a higher prevalence of chronic bronchitis and emphysema than nonsmokers and have an increased chance of dying from these diseases compared to nonsmokers. These risks are significant for both men and women who smoke, although higher rates generally exist for men than women.

2. Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related.

3. Pulmonary function abnormalities, as measured by various tests, are greater among cigarette smokers than nonsmokers.

4. Impairment of pulmonary function can be detected among smokers even in young age groups, and respiratory symptoms can be demonstrated in teenagers and adolescents who smoke.

5. Cigar and pipe smokers show higher mortality rates for chronic bronchitis and emphysema than nonsmokers, but these rates are not as great as those for cigarette smokers.

6. Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms. Cessation reduces the chance of premature death from chronic bronchitis and emphysema.

7. Although the majority of studies demonstrate a higher prevalence of pulmonary function abnormalities in smokers when compared to nonsmokers, conflicting data make it difficult to substantiate racial differences among smokers and nonsmokers.

8. Autopsy data have demonstrated more frequent abnormalities in macroscopic and microscopic lung sections among smokers compared to nonsmokers, and these effects were dose-related.

9. Several mechanisms have been suggested by which smoking might induce lung damage, including an imbalance of protease-antiprotease.

10. A wide variety of alterations in the immune system have been observed due to cigarette smoking. These alterations include macro-

phages from smokers responding abnormally to migration inhibitory factor (MIF) or antigen challenges, and T lymphocytes in smokers showing a diminished response to phytohemagglutinin (PHA), compared to those of nonsmokers. However, the role of these alterations in lung damage is unclear at this time.

11. Individuals with severe alpha-1-antitrypsin deficiency have an excess risk for developing emphysema, and the onset of symptoms is probably abbreviated in these persons by smoking. It is unclear if individuals with mild deficiency represent a group at special risk.

12. Other genetic factors may play a role in determining the risk for COLD, but these are far outweighed by the effect of cigarette smoking.

13. Certain occupations, primarily those exposing workers to dusty occupational environments, are related to COLD, and this relationship is increased further by cigarette smoking. In none of these studies are occupational effects as strong as smoking.

14. Although an increased risk of COLD due to air pollution probably exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed.

15. Childhood respiratory disease appears to be a risk factor for respiratory symptoms as an adult. However, cigarette smoking appears to be a more important factor in increasing the risk for developing the symptoms.

Interaction Between Smoking and Occupational Exposures

An extensive review of the literature on lung cancer in chromium and nickel workers and in uranium miners was prepared (12) for the 1964 Advisory Committee. Other studies had examined the relationships among coal gas and asbestos workers as well as in exposures to arsenic, hematite, isopropyl oil, beryllium, and copper. Significant excess lung cancer mortality was noted for chromate, nickel, coal gas and asbestos workers and for uranium miners; exposure to arsenic, hematite, beryllium, and copper remained suspect.

At the time of the 1964 report it was noted that "it must be emphasized quite strongly that the population exposed to industrial carcinogens is relatively small" (compared to the size of the smoking population), "and that these agents cannot account for the increasing lung cancer risk in the general population." It was further noted: "Of greater importance is the regrettable fact that in none of these occupational hazard studies were smoking histories obtained. Thus the contribution which smoking, as a contributory or etiologic factor, may have made to the lung cancer picture in these risk situations is unknown" (15).

Despite increasing recognition that smoking and occupational exposures may each contribute to the development of certain disease

states, few investigators have addressed the ways in which these two factors act together to produce disease.

This chapter has identified and illustrated six ways in which smoking may act in combination with physical and chemical agents found in the workplace to produce or increase a broad spectrum of adverse health effects. The six modes of action listed below are not mutually exclusive and several may prevail for any given agent. They may be compounded by occupational exposure to multiple chemical and physical agents.

1. Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent into the body by inhalation, ingestion, and/or skin absorption.
2. Workplace chemicals may be transformed into more harmful agents by smoking. Illustrative of this effect is the association between polymer fume fever and smokers as a result of cigarette contamination in the workplace.
3. Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent. Carbon monoxide levels in the occupational environment, for example, add to already high blood carbon monoxide levels found in smokers.
4. Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect. For example, exposure to coal dust may increase a smoker's risk of developing disease.
5. Smoking may act synergistically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influence of the agent and smoking added together. For example, cigarette smoking and exposure to asbestos may interact synergistically to greatly increase the risk of lung cancer.
6. Smoking may contribute to accidents in the workplace.

Those who have the highest risk for occupational exposures to toxic agents in general also have the highest smoking rates. Surveys have shown male blue-collar workers are much more likely to smoke than male white-collar workers. From 1920 to 1966, tobacco consumption increased as did the introduction into the workplace of chemicals with unstudied biological effects. During this same time period, the mortality rates for certain disease states associated with smoking and occupational exposures continued to increase. Some of the effects historically attributed to smoking may actually reflect interactions between smoking and occupational exposures.

Curtailment of smoking in the workplace should be accompanied by simultaneous control of occupational exposures to toxic physical and chemical agents.

Pregnancy and Infant Health

The 1964 report devoted approximately one printed page, including bibliography, to a discussion of the findings of five retrospective and two prospective studies on birth weight of infants born to mothers who smoked during pregnancy. Such infants tended to have a lower birth weight. The mechanism and its biologic significance were then not known and the findings were in some instances controversial. Since then, this area of scientific investigation has resulted in the amassing of significant data which provide many insights into the mechanisms of pathogenesis. The following conclusions are based on the work during this period:

Birth Weight and Fetal Growth

1. Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable women who do not smoke. Distribution of birth weights of smokers' babies is shifted downward, and twice as many of these babies weigh less than 2,500 grams, compared with babies of nonsmokers. There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight.
2. Birth weight is affected by maternal smoking independently of other determinants of birth weight. The more the mother smokes, the greater the baby's birth-weight reduction.
3. The ratio of placental weight to birth weight increases with increasing levels of maternal smoking. This increase may signify a response to reduced oxygen availability due to carbon monoxide and may have some survival value for the fetus.
4. There is no overall reduction in the duration of gestation with maternal smoking, indicating that the lower birth weight of smokers' infants is due to retardation of fetal growth.
5. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions; body length, chest circumference, and head circumference are smaller if the mother smokes.
6. According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11.
7. Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate directly and that fetal growth rate is not due to characteristics of the smoker rather than to the smoking, nor is it mediated by reduced maternal appetite, eating, and weight gain.

Perinatal Mortality

1. When adjustments are made for age-parity differences in mothers, their socio-economic status, and previous pregnancy histories, the risk of perinatal mortality attributable to smoking is highly significant, independent of these factors, and is dose-related.
2. Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes.
3. Although maternal smoking does not produce a lowering of mean gestational age, preterm births are increased in frequency among smokers, and a large proportion of the neonatal deaths occur among these preterm births.
4. Smoking by pregnant women contributes to the risk of their infants being victims of the "sudden infant death syndrome."
5. Maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes. Considerable literature has appeared in the area of clinical and animal experimental studies on the role of tobacco smoke, nicotine, and carbon monoxide, providing evidence for pathogenetic pathways accounting for both lower birth weight and fetal death.
6. The accumulated evidence does not support a conclusion that maternal smoking increases the incidence of congenital malformations.

Lactation and Breast Feeding

1. The epidemiologic studies on adequacy of lactation do not provide data for a conclusion on the effect of maternal smoking.
2. Although some animal studies reveal diminished milk production (but no reduction in release) following nicotine administration, human experimental studies have not thus far produced evidence for a reduction in lactation with forced smoking of large numbers of cigarettes over short periods of time.
3. There does exist a direct dose-response relationship between the number of cigarettes smoked and nicotine in breast milk.
4. Further detailed research in this area is imperative.

Peptic Ulcer Disease

The 1964 Report appraised the evidence for a relationship between tobacco use and peptic ulcer disease in five retrospective and the seven prospective studies (mortality) and concluded that only an association existed, particularly for gastric ulcers. The biological meaning of this association was not clear, particularly since studies of the effects of cigarette smoking on secretory activity and gastric motility were not consistent.

For the current report, two of the prospective mortality studies have been updated. Peptic ulcer disease mortality has continued to show excesses among smokers of cigarettes.

A number of additional studies of peptic ulcer disease and smoking were also addressed. Five of these studies showed a higher proportion of smokers among ulcer patients than among controls. Six studies showed a greater prevalence among male cigarette smokers than nonsmokers, the median ratio being 1.7. The findings in women are comparable. The majority of studies provided evidence of increased frequency of peptic ulcer disease with increases in the amount smoked. Experimental and clinical studies of gastric and pancreatic secretion and pyloric reflux were extended in this period to resolve the mechanism of action of smoking on occurrence of peptic ulcer disease.

On the basis of the research data surveyed, it is concluded:

1. Epidemiological studies have found that cigarette smoking is significantly associated with the incidence of peptic ulcer disease and increases the risk of dying from peptic ulcer disease. This risk is, on the average, twice as high for smokers compared to nonsmokers, and appears to be greater for gastric than for duodenal ulcer disease.
2. The risk of peptic ulcer disease is dose-responsive and exists for both men and women.
3. While the pathogenetic mechanisms have not been clearly elucidated, the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship.
4. Evidence that smoking retards healing of peptic ulcers is highly suggestive.
5. Pipe smoking appears unrelated to peptic ulcer disease.
6. Experimental and clinical studies on the effect of smoking on pancreatic secretion and pyloric reflux suggest mechanisms by which peptic ulcer disease may develop.

Allergy and Immunity

Allergic manifestations to tobacco, its smoke, or its extracts were not reviewed in the 1964 report. Various studies in the late 1960's and 1970's probed the relationship of smoking to immunologic mechanisms and immune responses, not only in the acute infectious diseases, but also in several of the chronic diseases such as pulmonary disease.

The following is a summary of this research and our current understanding of this facet of human illness in relation to tobacco use.

1. Tobacco and tobacco smoke extracts have been found to act as antigens, including both precipitating and reaginic antibodies, in animals and man. These tobacco products can also sensitize lymphocytes participating in cell-mediated immune functions.

2. Tobacco and its combustion products present such an array of natural and derived components, additives, and contaminants that the precisely defined role for tobacco in immune and allergic processes cannot be delineated.

3. Several tobacco antigens have been isolated. However, epidemiologic studies on the frequency of true allergy to tobacco are inconclusive.

4. Tobacco smoke exerts a variety of effects on respiratory tract structures, and chronic smoking leads to consistent histologic changes in the respiratory tract.

- (a) Evidence indicates an adverse long-term effect on the mucociliary transport mechanisms and mucus composition.

- (b) The number of macrophages isolated from smokers' lung fluid is increased compared to nonsmokers.

- (c) Changes in the ultrastructure of macrophages are observed in smokers.

- (d) Alveolar macrophages from smokers have altered metabolism and measurable degrees of physiologic impairment.

5. Alterations in assays of cell-mediated immunity are noted locally and systemically in smokers.

6. Leukocytosis and reversible hyper eosinophilia have been seen in smokers.

7. Allergic individuals, particularly those with rhinitis or asthma, may be more sensitive to the nonspecific effects of cigarette smoke than healthy individuals.

8. Because the ability to make a definitive diagnosis of tobacco allergy is complicated by the difficulty in demonstrating a cause and effect relationship between immunologic events and disease manifestations, additional evidence is required to establish a definitive role for tobacco sensitization in causing allergic disease.

Involuntary Smoking

The effects of involuntary smoking (passive or second-hand smoking) on the nonsmoker were not examined or appraised in the 1964 report but were initially discussed in the 1972 report, *The Health Consequences of Smoking*, and updated in the 1975 edition. The current report's findings in this area are summarized below. It should be understood that the literature is of recent vintage and only a limited amount of systematic information regarding the health effects of involuntary smoking on the nonsmoker is available.

1. Sidestream smoke, which comes from the lighted tip of the cigarette between puffs, has higher concentrations of some of the irritating and hazardous substances than does mainstream smoke (that smoke inhaled by the smoker).

2. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life; this effect is independent of social class, birth-weight, and parental cough and phlegm production.

3. Simple extrapolation of dose-response relationships, which are traditionally used in assessing the hazards of smoking to the smoker, cannot be employed in assessing hazards in nonsmokers.

4. Cigarette smoking in enclosed spaces can produce carbon monoxide (CO) levels well above the Ambient Air Quality Standard (9 ppm) even where ventilation is adequate.

5. Substantial proportions of the population experience irritation and annoyance when exposed to cigarette smoke. The eyes and nose are most sensitive to irritation, and such irritation increases with increasing levels of smoke contamination. Unrestricted smoking on buses and planes annoys the majority of nonsmoking passengers even under conditions of adequate ventilation.

6. Little or no physiological response to smoke was detected in healthy nonsmokers exposed to cigarette smoke. Higher heart rates detected may be due to psychological factors.

7. A slight reduction in maximum exercise capacity was noted in older nonsmokers exposed to levels of CO occasionally found in involuntary smoking situations.

8. Changes in psychomotor function, especially attentiveness and cognitive function, at levels of CO found in involuntary smoking conditions have been noted, but these effects are measurable only at the threshold of stimuli perception.

9. Levels of COHb produced by involuntary smoking situations are functionally insignificant in healthy individuals.

10. Levels of carbon monoxide which can be reached in cigarette smoke-filled environments have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. These levels of CO also have been shown to reduce the exercise time until onset of dyspnea in patients with hypoxic chronic lung disease.

Interactions of Smoking with Drugs, Food Constituents, and Responses to Diagnostic Tests

The pervasiveness of tobacco use in our society and the frequency of altered disposition and pharmacological effects of many common drugs on smokers make it apparent that cigarette smoking is one of the primary causes of drug interactions in humans. An assessment of the literature in this area provides the following conclusions:

1. Most of the experimental work in humans, animals, and tissues involving enzyme systems indicates that the dominant effect of smoking is enhanced drug disposition caused by induction of hepatic microsomal enzymes.

2. Tobacco smoke, a complex mixture of noxious materials, contains, among other compounds, enzyme inducers such as polycyclic aromatic hydrocarbons, nicotine, cadmium and some pesticides, acrolein and hydrogen cyanide.

3. The primary inducers are probably polynuclear aromatic hydrocarbons which are potent and persistent in tissues. While several of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, this enhancement is unpredictable, and the effects of cigarette smoke on other potential rate-limiting disposition processes for drugs are largely unexplored.

4. Cigarette smoking alters the pharmacologic effects of drugs or their pharmacokinetics.

5. Tobacco smoke can induce the metabolism in humans of therapeutic agents, such as phenacetin, antipyrine, theophylline, caffeine, imipramine, pentazocine, and vitamin C; examples of drugs not affected by smoking include: diazepam, meperidine, phenytoin, nortriptyline, warfarin, and ethanol.

6. Tobacco smoke can modify the clinical effects of drugs.

7. Marijuana smoking may produce reactions similar to tobacco smoking since enzyme induction is also stimulated by the polycyclic aromatic hydrocarbons in marijuana smoke.

8. A woman who both smokes and uses oral contraceptives has a greater risk for myocardial infarction.

9. There is a suggestion that smoking produces a more rapid decline in influenza antibody titers after natural infection or vaccination with influenza virus.

10. Cigarette smoking appears to increase the serum carcinoembryonic antigen level in otherwise healthy individuals.

11. No information is available to indicate that the increase in body burden of trace elements by smoking has toxic effects.

12. Since tobacco smoking does affect the values of a number of clinical laboratory tests in humans, the knowledge of an individual's smoking status is important for the interpretation of such tests. Cigarette smoking increases the number of leukocytes, the red cell mass, the levels of hemoglobin and carboxyhemoglobin, the hematocrit, the mean corpuscular volume, platelet aggregation, plasma viscosity, and tensile strength of the clot; cigarette smoking decreases the serum levels of creatinine, albumin, globulin (female smokers) and uric acid (male smokers). These revert to normal levels after cessation of smoking.

Other Forms of Tobacco Use

References have already been made to the relationships between other forms of tobacco use and a number of specific diseases and cancer sites. Special attention was given in the 1973 issue of *The Health Consequences of Smoking* to the role of pipes and cigars. This attention was particularly relevant inasmuch as the 1964 Report appeared to have influenced a transient increase in consumption of cigars and pipe tobacco due to the prevailing belief that pipes and cigars were "safe."

For the present report, the summary conclusions presented here refer to men only, since the use of pipes and cigars in the United States is limited almost exclusively to them.

It can be concluded that some risk exists from smoking cigars and pipes as they are currently used in the United States, but for most diseases this is small compared to the risk of smoking cigarettes as they are commonly used.

Overall Mortality

1. Overall mortality rates among pipe or cigar smokers are slightly higher than for nonsmokers.

2. Mortality rates among smokers of pipes, cigars, or both in combination with cigarettes are intermediate between the high rates of cigarette smokers and the lower rates of those who smoke only pipes or cigars.

3. Mortality associated with combinations of pipe and/or cigar and cigarette smoking is dependent upon the level of consumption and inhalation of each.

4. A dose-response relationship exists for the several forms of tobacco use and overall mortality in terms of amount smoked, degree of inhalation, duration of smoking, and age at initiation of smoking.

Cancer

1. Prospective studies have shown that mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus are approximately equal in users of cigars, pipes, and cigarettes.

2. Although several factors appear to be involved in cancer of the lip, pipe smoking alone or in combination with other forms of smoking is causally related to lip cancer.

3. Heavy alcohol consumption in combination with heavy smoking of pipes and cigars is associated with higher rates of oral cancer than for either alcohol consumption or heavy smoking of pipes or cigars alone. There is evidence that excessive alcohol consumption may increase the pipe and cigar smoker's risk for extrinsic laryngeal cancer. A distinct synergism with heavy alcohol intake exists in esophageal cancer.

4. Cigar and pipe smokers showed the same histological changes in the larynx and esophagus at autopsy as did cigarette smokers.

Snuff and Chewing Tobacco and Oral Lesions

Snuff and chewing tobacco have not been found to increase mortality (either overall or cause-specific) in the United States. Asian studies have found an association between tobacco chewing and leukoplakia as well as oral cancer. These differences between the American and Asian studies can partially be explained by nutritional factors but are confounded by other factors such as the use of other tobacco products along with the use of snuff and chewing tobacco in the United States.

Constituents of Tobacco Smoke

Extensive research has advanced the cultivation of tobacco varieties with commercially desirable characteristics. This research has also been directed toward precursor-product relationships among specific leaf tobacco components, agronomic characteristics, cigarette and smoke constituents, and biological responses involving 151 variables. Multivariate analysis has revealed that leaf characteristics serve as markers to predict individual smoke components. Thus, there is promise of modification for more desirable qualities and use of tobacco.

Smoke Formation

1. The lighted cigarette generates about 2,000 compounds by a variety of processes including hydrogenation pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation.
2. Tobacco smoke has been separated into gas and particulate phases.
3. The gas phase components shown to produce undesirable effects include carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile N-nitrosamines, hydrogen cyanide, volatile sulfur compounds, nitriles and other nitrogen-containing compounds, volatile hydrocarbons, alcohols, aldehydes, and ketones.
4. The particulate phase consists generally of nicotine, water, and "tar," which is the total particulate matter after subtracting moisture and nicotine, consists primarily of a wide variety of species of polycyclic aromatic hydrocarbons (PAH) to which carcinogenicity is attributed.

(a) These PAH include non-volatile N-nitrosamines, aromatic amines (regarded as being the etiologic agents in bladder cancer), isoprenoids, pyrenes, benzopyrenes, chrysenes, anthracenes, fluoranthenes, carcinogenic aza-arenes such as the acridines and carbazoles, and the mutagenic aza-arenes such as the quinolines and phenanthridines.

(b) In addition, the "tar" contains simple and complex phenols, cresols and naphthols, alkanes and alkenes, benzenes and naphthalenes, carboxylic acids, and metallic ions, as well as

5. Pipe and cigar smokers have histological abnormalities of the lung at autopsy that are intermediate in degree between nonsmokers and cigarette smokers. Some categories of pathologic changes in cigar smokers are similar to those seen in cigarette smokers.

6. The risk of pipe and cigar smokers developing lung cancer is higher than for nonsmokers, but is lower than for cigarette smokers. In the updated prospective studies, the relative risks of lung cancer for cigar and pipe smoking ranged from 1.6 to 3.4 for cigars only and from 1.8 to 8.5 for pipe only.

7. A dose-response gradient has been shown to be present in some studies.

Tumorigenic Activity of Pipe and Cigar Smoke Condensates

1. Pipe and cigar tobacco condensates have a carcinogenic potential comparable to that of cigarette condensates.

2. The alkaline smoke from pipe and cigar tobacco is usually not inhaled, and there appears to be a lower level of exposure of the harmful components of smoke than is noted with the inhalation of cigarette smoke.

Cardiovascular Diseases

1. Pipe and cigar smokers experience a small increase in coronary heart disease mortality compared to nonsmokers.

2. Similarly, pipe and cigar smokers show slight excesses of cerebrovascular death rates over nonsmokers.

Non-Neoplastic Bronchopulmonary Disease

1. Pipe and cigar smokers experience mortality rates from chronic bronchitis and emphysema that are intermediate between cigarette smokers and nonsmokers.

2. Pipe and cigar smokers have significantly more respiratory symptoms such as cough, sputum production, breathlessness, and wheezing than nonsmokers. A dose-response gradient is noted.

3. Little difference in pulmonary function was noted for pipe and cigar smokers as compared to nonsmokers.

4. Pipe and cigar smokers had far less pulmonary pathology at autopsy than did cigarette smokers.

Peptic Ulcer Disease

1. Cigar and pipe smokers experience higher death rates from peptic ulcer than nonsmokers; these rates, based on prospective mortality studies, indicated higher rates for gastric ulcer than for duodenal ulcer.

2. Retrospective and cross-sectional studies failed to find an association between pipe smoking and peptic ulcer.

radioactive compounds such as potassium-40, lead-210, polonium-210 and radium-226.

- ⑥ The particulate phase also contains agricultural chemicals and additives as flavoring agents and humectants.

Toxic and Carcinogenic Agents

Compounds in cigarette smoke have been classified by an expert panel into:

1. Those judged most likely to contribute to the health hazards of smoking.

(a) Carbon monoxide (gas phase).

(b) Nicotine and "tar" (particulate phase).

2. Those judged as probable contributors to the health hazards of smoking.

(a) Gas phase: acrolein, hydrocyanic acid, nitric oxide and nitrogen dioxide.

(b) Particulate phase: cresols and phenol.

3. Those judged as suspected contributors to the health hazards of smoking.

(a) Gas phase: acetaldehyde, acetone, acetonitrile, acrylonitrile, ammonia, benzene, 2,3 butadiene, carbon dioxide, crotononitrile, ethylamine, formaldehyde, hydrogen sulfide, methacrolein, methyl alcohol, and methylamine.

(b) Particulate phase: butylamine, dimethylamine, DDT, endrin, furfural, hydroquinone, nickel compounds, pyridine.

These compounds have been so designated not only because of their harmful actions but also because of their concentrations in tobacco smoke. Although other constituents are considered toxic, they are not present in concentrations deemed a health hazard.

A number of tumor initiators, co-carcinogens, and organ-specific carcinogens have been isolated and identified. The majority of co-carcinogens remain to be identified. The increased risk cigarette smokers have for cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic and N-nitrosamines.

Physiological Response to Cigarette Smoke

1. The smoking of a cigarette seems to satisfy a smoker's physiological and psychological needs, and it is generally accepted that nicotine is the principal constituent responsible for cigarette smokers' pharmacologic responses.

2. Nicotine causes the release of catecholamines, epinephrine and norepinephrine. Several physiologic responses are attributed to nicotine and/or catecholamines such as increased heart rate and blood

pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, oxygen consumption, coronary blood flow and arrhythmias, increased mobilization and utilization of free fatty acids, hyperglycemic effects, and a decreased patellar reflex response.

3. Considerable evidence exists, although it is not uniformly accepted, that smoking patterns of chronic smokers are to a large degree dependent on the nicotine content of the cigarette and dependent on what the nicotine delivery would be when measured by the standard methodology. Smoking patterns are dependent, to varying degrees, on the type of cigarette smoked, the number of cigarettes smoked, the length of the cigarette burned, the number of puffs, and the depth and length of inhalation.

Reduction in Toxic Activity of Cigarette Smoke

1. At the present time, selective filtration of carbon monoxide has not proven feasible.

2. Charcoal filtration has proven successful in the removal of certain ciliotoxic substances from the gas phase of cigarette smoke.

3. Selected types of cellulose acetate filter tips selectively remove volatile phenols.

4. Cigarette fillers low in wax-layer components deliver smoke reduced in catechols, but there is a question as to whether selective reduction in catechols leads to a significant reduction of the tumorigenic potential of cigarette smoke.

5. Lowering nitrate content of tobacco reduces volatile N-nitrosamines in tobacco smoke, but it has not been shown that a reduction of this compound will lead to a significant reduction in the tumorigenic potential of the smoke.

6. Experimentally, a dose-response gradient is demonstrable for "tar" application or smoke inhalation and tumor yield. A number of technical approaches, including modification of the filler, has reduced the "tar" content of smoke.

7. Similar technical approaches have reduced the nicotine content of tobacco smoke.

8. There is a possibility that nonvolatile N-nitrosamines can be reduced by addition of specific bacteria during the processing of tobacco. Selective filtration is not feasible for their removal.

9. A number of methods have led to reduction of "tar" and of toxic and tumorigenic agents in the smoke of cigarettes. Several approaches have led to the reduction of the ciliotoxicity and to selective reduction of the carcinogenicity and tumor-promoting activity of the smoke of experimental cigarettes. Many of these methods have already been incorporated in today's modified, blended U.S. cigarette.

Behavioral Aspects of Smoking

Because of the research over the past 4 years, much is now known about the health dangers of smoking. But research into reasons why the habit is so widespread and difficult to break is still in its infancy; little is known for certain, and questions far outnumber answers.

This part of the report summarizes current understanding of the biological, behavioral, and psychosocial aspects of the cigarette smoking habit and the dependence process associated with smoking. It is no exaggeration to say that smoking is the prototypical substance-abuse dependency and that improved knowledge of this process holds great promise for prevention of risk. Establishment and maintenance of the smoking habit are, obviously, prerequisite to the risk, and cessation of smoking can eliminate or greatly reduce the health threat.

Among the findings, tentative conclusions, and areas for research presented in this section are the following:

1. Nicotine, the most powerful pharmacological agent in cigarette smoke, has been proposed as the primary incentive in smoking and may be instrumental in the establishment of the smoking habit. The proposition that heavy smokers adjust their plasma nicotine levels is compatible with the observation that regular smokers commonly consume about 20 to 30 cigarettes during the smoking day (approximately one every 30 to 40 minutes) and that the biological half-life of nicotine in humans is approximately 20 to 30 minutes.

2. Recent research suggests that specific central nervous system receptor sites for nicotine can be blocked in a fashion analogous to the opiate antagonists. This phenomenon has implications for understanding the effect of nicotine on the body as well as in helping former smokers to maintain abstinence.

3. By far the most common, and clinically the most important, symptom to appear following withdrawal from tobacco is craving for tobacco. The importance of the tobacco-withdrawal syndrome is its provocative role in relapse among abstinent smokers. Abrupt and total withdrawal from tobacco is associated with a withdrawal syndrome that subsides more quickly and is no worse than that seen in partial abstinence. A partially-abstinent smoker is in a chronic state of withdrawal that typically leads to relapse and a return to baseline rates of smoking.

4. There is fragmentary evidence suggesting that the abstinence syndrome is more severe in women than in men, and it seems likely that this is at least partly responsible for lower rates of successful cessation among women.

5. Little is known about the millions of smokers who have quit on their own. It has been estimated that 95 percent of the 29 million smokers who have quit since 1964 have done so on their own.

6. Survey data show that only one-third or less of smokers motivated to quit are interested in formal programs, and only a small minority of

those who do express an interest actually attend programs when offered. It thus appears that available objective outcome data may be based on a small minority sample of smokers at large.

7. Objective data are lacking on most of the smokers who have been willing to attend formal programs. Public service clinics continue, but lack of objective outcome data precludes the evaluation of their efficacy. Similarly, proprietary programs remain virtually unmonitored and unevaluated in an objective fashion. Controlled research has yet to produce a clearly superior intervention strategy. However, rapidly accumulating and improving data now suggest that multi-component interventions offered by intervention teams with practical knowledge regarding the smoking problem are the most encouraging.

8. Too few carefully designed and implemented longitudinal studies exist in the area of smoking in children and adolescents to allow for true evaluation of the effectiveness of many past programs developed for them.

9. Inferences about the evolution of smoking suggest that by the end of the ninth grade very few adolescents are addictive smokers; the critical level of the onset of addictive smoking appears to be in high school. Therefore, the true impact of any deterrence-of-smoking program with adolescents may not even be measurable until after the adolescent has entered high school. This problem is not unlike the recidivism encountered in virtually all smoking cessation programs.

10. Too many programs for youth have focused on information about smoking or fear of serious disease due to smoking. Adolescents are present-oriented and appear to be less influenced by messages concerning smoking that focus exclusively on long-term dangers.

11. A focus on research into prevention of the onset of addictive smoking appears to be a reasonable parallel course to follow along with efforts at control and cessation.

12. A promising new approach may be in the "inoculation" of adolescents against various pressures to smoke which apparently override their knowledge about the dangers of smoking. The approach involves strategies to resist peer pressure, emphasis on understanding of how advertising and mass media work to influence smoking, and provision of information on ways to resist the models of parents, siblings, and older students who smoke. Also included is a focus on the immediate physiological effects of smoking rather than on long-term effects.

Education and Prevention

Research strongly indicates that educators and health care providers teach youth about smoking and health as much by example as through formal instruction. But, despite a proliferation of a wide variety of educational programs aimed at youth and adults, it is not known which methods are most effective in preventing the start of smoking or in

promoting cessation. Summarized below are some of the research findings, program and experimental approaches, and needs in the areas of smoking education and prevention discussed in this part of the report.

1. Most educational programs are based on what seems reasonable rather than on sound theoretical models. It is logical to assume, for example, that young people who know about the harmful effects of cigarette smoking on health will resist smoking. Thus, many programs are based on knowledge dissemination and a health threat. However, we know that 94 percent of teenagers say that smoking is harmful to health and 90 percent of teenage smokers are aware of the health threat.
2. The trend in adult education programs is toward emphasis on personal responsibility for individual health and adoption of a health-promoting lifestyle.
3. Researchers find that "significant adults"—physicians, nurses, dentists, other health professionals, coaches, and parents—are powerful influences on teenage smoking. A nationwide survey of teenagers, for example, indicated that 72 percent of the nonsmokers identified physicians as the one group that could influence them not to start smoking; 43 percent of the smokers felt that the physician's advice would influence their decision to stop smoking.
4. Health professionals as a group have preceded the general public in improving their smoking habits; they have stopped smoking, moved to less hazardous forms of tobacco, or reduced the amount smoked.
5. Several studies of methodologies used in smoking education reported mixed results, with no method clearly predominating.

Introduction and Summary: References

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14. CONSTITUENTS OF TOBACCO SMOKE.

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Smoke Formalion

The raw material that goes into the making of a cigarette is only a prelude to what happens when the cigarette is smoked. Indeed, the lighted cigarette is a unique chemical factory generating more than 2,000 known compounds by a variety of processes responsive to thermodynamic constraints. The following sections will review the smoke generation process and the effects on smoke composition.

Physico-Chemical Nature of Cigarette Smoke

As a smoker takes a puff from a burning cigarette, he draws the mainstream smoke that issues from the butt end. The aerosol emitted from the burning cone during puff intervals is the sidestream smoke, and is chemically different from mainstream smoke. That portion of the smoke which can be retrained by a Cambridge glass fiber filter (99.9 percent efficient for particles $>0.1 \mu$) is defined as the particulate phase, whereas the portion that passes the filter is termed the gas phase.

Smoke aerosol is a highly concentrated aerosol of liquid particles constituting the "tar." Each particle is composed of a large variety of organic and inorganic chemicals that are dispersed in a gaseous media consisting primarily of nitrogen, oxygen, hydrogen, carbon dioxide, carbon monoxide, and a large variety of volatile and semivolatile organic chemicals in equilibrium with the particulate phase of the tobacco smoke. The smoke aerosol is a continuously changing entity. Aging of the aerosol results in changes in its physical and chemical properties (13).

In order to generate reproducible physical and chemical data for the analysis of cigarette smoke, standard smoking conditions have been set up based on observations of patterns in human smoking. In the United States, these standard conditions prescribe 1 puff per minute, 2-second puff duration, a puff volume of 35 ml, and a butt length of 23 mm in an unfiltered cigarette, or the length of the filter tip, including the overwrap plus 3mm, whichever is greater, in a filtered cigarette. Smoking conditions for cigarettes in other countries (9) and for cigars (46) differ somewhat from the adapted standards for U.S. cigarettes.

Temperature Profiles

Several parameters determine the qualitative and quantitative smoke composition of mainstream and sidestream smoke. The major factors affecting the temperature profiles of the burning cigarette include physical form (length and circumference) of the cigarette, filler materials, tobacco type or blend, tobacco cut, packing density, additives, moisture content, quality of the cigarette paper (porosity, construction, perforation). During puffing, temperatures in the

burning cone reach 900°C with some hot spots on the periphery of the cigarette up to 1,050°. A steep temperature gradient from 880°C to 40°C is observed away from the burning center extending over the next 3 centimeters of the tobacco column (65, 100). On the basis of this temperature profile, three major reaction zones are defined: the high temperature zone (900–600°C) which is free of oxygen (immeasurable) and contains up to 8 volume percent of hydrogen and 15 volume percent of carbon monoxide, the oxygen-depleted pyrolysis-distillation zone (600–100°C), and the low-temperature zone (<100°C) with up to 12 volume percent of oxygen. Within these three zones, the actual mainstream smoke formation occurs by hydrogenation, pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation. The exit temperature of the mainstream smoke at the cigarette butt ranges from 25 to 50°C, depending on the butt length.

The sidestream smoke is generated during smoldering of the cigarette at peak temperatures inside the glowing cone of up to 800°C but reaches ambient temperatures at a distance of a few centimeters from the burning cone.

Material Balance

The amount of tobacco consumed during puffing and smoldering depends on the static burning temperature and on the same parameters which determine the mainstream smoke formation. An indicator for the release of sidestream smoke is the static burning rate between puffs which generally ranges from 5 to 7 mm of tobacco column per minute. It has been shown that between 55 and 70 percent of the tobacco of a cigarette is burned between puffs and thus serves as a source for the formation of sidestream smoke and ashes. The mainstream smoke effluent of a cigarette smoked to a 30 mm butt length amounts to about 500 mg (Tables 12 and 13, and reference 4). Of the 55 mm tobacco column, about 300 mg is consumed for the generation of mainstream smoke (and ashes) and about 500 mg for the formation of sidestream smoke (and ashes).

The interrelationships involved in cigarette smoke may be described by the general equation described recently by Gori (25).

$$\begin{aligned} & \text{Weight of ash produced during puffs} \\ & + \text{Mainstream TPM weight} \\ & + \text{Mainstream gas phase weight} \\ & - \text{Mainstream entrained gas weight} \\ & - \text{Mainstream combustion oxygen weight} \\ & = \text{Weight of cigarette burned during puffs} \end{aligned}$$

TABLE 12.—Percent distribution of cigarette smoke*

Material	Weight (mg/cigarette)	Weight of total effluent (%)
Particulate matter (inc. cond. H ₂ O)	40.6	8.2
Nitrogen (67.2 vol %)	295.4	59.0
Oxygen (13.3 vol %)	66.8	13.4
Carbon dioxide (9.8 vol %)	68.1	13.6
Carbon monoxide (3.7 vol %)	16.2	3.2
Hydrogen (2.2 vol %)	0.7	0.1
Argon (0.8 vol %)	5.0	1.0
Methane (0.5 vol %)	1.3	0.3
Water vapor (relative humidity=0.6)	5.8	1.2
C ₂ –C ₆ hydrocarbons	2.5	0.5
Carbonyls	1.9	0.4
Hydrogen cyanide	0.3	0.1
Other known gaseous materials	1.0	0.2
Total	505.6	101.2
Measured total effluent	500	100

*55 mm nonfilter cigarette, 30 mm butt length, 10 puffs of 38.9 ml volume each.
SOURCE: Keith, G.H. (52).

TABLE 13.—Percent distribution of cigarette smoke*

Material	Weight (mg/cigarette)
TPM (wet)	40.6
Nitrogen	295.4
Oxygen	66.8
Argon	5.0
Carbon dioxide	68.1
Carbon monoxide	16.2
Water vapor	5.8
C ₂ –C ₆ hydrocarbons	2.5
Carbonyls	1.9
Other (gaseous)	3.3
	505.6

*55 mm cigarette, 30 mm butt length, 10 puffs of 38.9 ml volume each.
SOURCE: Gori, G.R. (25).

Mainstream Smoke Aerosol

The undiluted smoke as it leaves the cigarette butt contains up to 5 x 10¹⁰ heterogeneous particles per ml with round and spheric forms ranging in diameter between 0.2 and 1.0 μ and a median particle diameter of about 0.4 μ (13, 51). The smoke aerosol is slightly charged with about 10¹² electrons per gram of smoke; about 55 percent of the particles contain one or more charges (51). The pH of the total smoke effluent of a cigarette is primarily determined by the tobacco. For a

blended U.S. cigarette, the pH of the mainstream smoke varies between 5.5 and 6.2, and that of the sidestream smoke ranges between 6.5 and 7.5, depending on the puff number measured. In the case of cigarettes made exclusively from Burley or black tobacco, or in the case of cigars, the pH for mainstream smoke varies between 6.5 and 8.5 (highest values for last puffs) and for sidestream smoke between 7.5 and 8.8 (8). Cigarette smoke has reducing activity which increases with puff number (79).

Chemical Composition of Tobacco Smoke

To facilitate the analysis of the tobacco smoke, the smoke is separated into a gas phase and a particulate phase in the following way: the particulate phase is defined as that portion of the smoke collected on a conventional Cambridge filter pad (99.9 percent efficient for particles more than 0.1μ), and the gas phase is the portion that passes through the Cambridge filter.

Gas Phase

Carbon Monoxide and Carbon Dioxide

More than 90 percent of the weight of the total mainstream smoke effluent is given by the gas phase with nitrogen and oxygen already comprising more than 70 percent. Of the remaining gas phase components, carbon dioxide and especially carbon monoxide have been studied in great detail. These compounds are primarily formed by oxidation of the tobacco constituents in the high temperature zone and by decarboxylation in the pyrolysis and distillation zone and in the low temperature zone. Both CO and CO₂ increase linearly with ascending puff number. Leaves from the lower stalk positions generate significantly less CO and CO₂ than do leaves from the upper stalk positions of the same tobacco plant (6). The mainstream smoke of U.S. commercial cigarettes contains between 1.8 and 17.0 mg of CO (1.5–5.5 volume percent) and between 10 and 60 mg of CO₂ (8.5–14.5 volume percent) (6, 30, 74). Especially low CO values have been reported for cigarettes with perforated filter tips (27). A study with a limited number of commercial cigarettes from England indicates that filter cigarettes without perforated filter tips may contain as much, if not slightly more, CO than nonfilter cigarettes (98). Levels of sidestream smoke CO may be three times as high as those levels in mainstream smoke, and CO₂ may be up to eight times as high. The CO and CO₂ values for the smoke of cigars are significantly higher than those for cigarette smoke, primarily because of the relatively unporous cigar wrapper (6).

Nitrogen Oxides

Tobacco smoke is known to contain nitric oxide (NO) and trace amounts of nitrogen dioxide (NO₂) and nitrous oxide (N₂O). The alkali nitrates in tobacco are the major precursors for the nitrogen oxides in the smoke (100). With the possible exception of the last few puffs of a cigarette, fresh mainstream smoke does not contain NO₂ (64a); however, upon aging, NO in the smoke is quickly oxidized to NO₂ (although the half lifetime of NO in cigarette smoke is about 10 minutes). In concentrated smoke, aging leads to the formation of nitrites (96). Nitrogen oxides can be reduced in the mainstream smoke of cigarettes and little cigars with the aid of charcoal-containing filter tips (91). The concentration of NO in the smoke of U.S. commercial cigarettes varies between 5 and 800 μ g per cigarette (1, 27, 72).

Ammonia

The major precursors for ammonia in the mainstream and sidestream smoke of tobacco products are alkali nitrate and protein (48). The nitrate in tobacco is reduced to nitrogen and ammonia in the burning cone with a high yield in sidestream smoke. The mainstream smoke of U.S. commercial tobacco products contains between 22 and 130 μ g ammonia (as the ammonium ion) per cigarette and between 68 and 135 μ g ammonia per little cigar (7, 33). The ratio of ammonia in sidestream smoke to that in mainstream smoke ranges from 1:40 to 1:70. The sidestream smoke of cigars is even richer in ammonia, with amounts up to more than 1 mg per cigar.

Volatile N-Nitrosamines

Another type of compound for which the yield is largely determined by the nitrate content of the tobacco is that of nitrosamines, many of which are known animal carcinogens (57). To date eight volatile nitrosamines have been identified in tobacco smoke with dimethylnitrosamine (DMN), diethylnitrosamine (DEN) and nitrosopyrrolidine (NPY) as the major representatives (76). The unaged (freshly generated) smoke of three U.S. cigarettes without filter tips contained 13 to 65 ng of DMN, 15 to 50 ng of DEN, and 11 to 34 ng of NPY (11). Cellulose acetate filter tips retain volatile nitrosamines selectively, whereas charcoal filter tips do not exhibit such selective removal. Unaged sidestream smoke contains 10 to 40 times higher concentrations of volatile nitrosamines than the mainstream smoke of the same cigarette.

Hydrogen Cyanide and Cyanogen

Amino acids and protein are the major precursors for hydrogen cyanide (HCN), cyanogen, and nitriles in tobacco smoke (49). HCN is the major ciliotoxic agent in cigarette smoke; however, its selective

reduction by charcoal filters, among other things, diminishes the inhibition of lung clearance of HCN in the smoke of U.S. commercial degree. The concentration of HCN in the smoke of U.S. commercial cigarettes varies between 10 and 400 μg per cigarette with low values for low "tar" cigarettes and cigarettes with charcoal filter tips (27, 72). Sidestream smoke (SS) contains significantly less HCN than mainstream smoke (MS) with SS/MS ratios between 0.006 and 0.37 (12, 49). Tobacco smoke also contains small amounts of cyanogen (CN_2) with concentrations varying between 10 and 20 μg /cigarette (12). Since (CN_2) hydrolyzes easily to cyanide and cyanate, it can contribute to the hydrogen cyanide concentration in the smoke. In the case of cigar smoke, this can amount to 10 to 30 percent of the measured HCN.

Volatile Sulfur Compounds

This class of gas-phase compounds is of special interest because of its high reactivity. Sulfur-containing volatiles are highly sensitive to flame photometric detectors, and nanogram amounts of sulfur compounds can be rapidly determined even in the presence of great excesses of other gases. Guerin and Horton determined 28 sulfur compounds in the gas phase of cigarette smoke (29, 43). Typical cigarette deliveries of the major sulfur constituents include 85 μg of hydrogen sulfide, 35 μg of carbonylsulfide, 2 μg of carbon disulfide, and 3 μg of sulfur dioxide (43). The authors also observed an "aging effect" during the first 30 seconds after smoking, even when Teflon® sampling loops and columns were used instead of conventional stainless steel tubes. During "aging," the composition of the mixture of the sulfur components in the smoke shifts significantly from low molecular compounds (such as hydrogen sulfide) toward high molecular weight sulfur components.

Volatile Nitriles

The major precursors for volatile nitriles in tobacco are amino acids and protein similar to those for hydrogen cyanide (50). The most widely studied nitrile is acetonitrile (CH_3CN). Its concentration in the smoke of one cigarette varies between 100 and 250 μg . So far a total of 13 aliphatic nitriles and 20 aromatic nitriles have been identified in tobacco smoke, many of which occur in the gas phase (76). Pyridine-3-carbonitrile and possibly some aliphatic and aromatic nitriles may be formed from nicotine and other tobacco alkaloids during smoking. Recently one volatile smoke nitrile has been reported as carcinogenic in the experimental animal and is considered as a possible occupational carcinogen (64). Acetonitrile has been reported in much higher concentration in sidestream smoke than in mainstream smoke (1:3.9).

Other N-Containing Volatile Compounds

To date, more than 600 N-containing compounds have been identified in tobacco smoke; several of them are volatile (76). Of these, aliphatic and aromatic nitrohydrocarbons and nitrophenols have been studied in some detail. The concentration of the major representative, nitromethane, varies between 0.5 and 1.0 μg per cigarette and nitrobenzene between 10 and 25 ng per cigarette. These compounds are formed primarily from NO_2 and C_2H -radicals in the hot zones of burning tobacco products; thus concentration of the nitro compounds is governed by the nitrate content of the tobacco. Little is known about the tumorigenic potential of nitrohydrocarbons and nitrophenols, although it should be considered that the aromatic nitrohydrocarbons and possibly nitrophenols are reduced *in vivo* to the corresponding amines, some of which are known carcinogens. Recently 2-nitropropane (0.2-2.0 μg /cigarette) has been reported to induce hepatomas in mice (24).

Tobacco has long been known to contain aliphatic and aromatic amines, with methylamine (4.6 μg /cigarette) and aniline (1.2 μg /cigarette), as representative examples, present in the highest concentrations. In the blended U.S. cigarette with a smoke pH around 6, the major portion of the volatile amines may be protonated and thus found in the particulate phase. In recent years, several amines, especially the volatile secondary amines including pyrrolidine, have been discussed as precursors for carcinogenic N-nitrosamines. Since nitrosamines as well as both types of their precursors, NO_2 and amines, have been found in much higher concentrations in the smoke of nitrate-rich cigarettes (48), the concept of smoke amines as potential precursors for nitrosamines has been supported. Aniline and possibly other volatile amines are present in significantly higher concentration in sidestream smoke than in mainstream smoke (1:30) (67).

Three other N-compounds with tumorigenic activity in the experimental animal have been reported in tobacco smoke. These are hydrazine (30 μg /cigarette), 1,1-dimethylhydrazine (100 ng /cigarette), and urethane (20-38 ng /cigarette). The hydrazines are not formed from the maleic hydrazide, the major U.S. tobacco sucker growth inhibitor, but both are transferred from tobacco during smoking and are also pyrosynthesized. Urethane is primarily formed during smoking. As with other compounds with the amino group (ammonia and amines), more hydrazine is found in sidestream smoke than in mainstream smoke (1:3).

Volatile Hydrocarbons

The highest concentration of organic compounds found in the gas phase are the hydrocarbons (88). Methane (200-1,000 μg /cigarette), ethane (100-600 μg /cigarette), and propane (50-300 μg /cigarette) are

the major representatives of 15 identified saturated aliphatic hydrocarbons. Out of the 15 volatile olefins that have been identified with certainty, ethylene (50-200 µg/cigarette) and propene (50-250 µg/cigarette) are the major representatives. Of the seven volatile dienes identified, butadiene-1,3 (35 µg/cigarette) and isoprene (50-800 µg/cigarette) are of interest insofar as they can react in the hot zones with dienophiles leading to formation of cyclohexenes which are dehydrogenated to aromatic hydrocarbons. The tobacco terpenes serve as major precursors for isoprene and butadiene and possibly for the other dienes. Cigarette smoke is also known to contain acetylene (≈20 µg per cigarette), propyne (≈5 µg/cigarette), and the cyclic aliphatic hydrocarbons cyclopentene (≈5 µg/cigarette) and cyclohexane (≈3 µg/cigarette). So far, about 20 aromatic hydrocarbons have been identified in gas phase tobacco smoke (77). These volatile compounds are partially pyrosynthesized from cyclic terpenes and cellulose. Toluene amounts to 20-200 µg/cigarette and benzene to 15-100 µg. Of interest also are the chemically reactive smoke compounds styrene (≈10 µg/cigarette) and alkylated styrenes.

Volatile Alcohols

A number of volatile alcohols are known to occur in cigarette smoke (85). These include methanol (50-25 µg/cigarette), ethanol (≈2 µg/cigarette), n-propanol (≈4 µg/cigarette), and at least 10 other volatile alcohols. The alcohols are of interest because they can react in the hot zone with a number of thermally activated smoke compounds under formation of esters, ethers, urethanes and others.

Volatile Aldehydes and Ketones

Volatile aldehydes and ketones are of special interest as inhibitors of ciliary movement and lung clearance (85). So far about 15-20 volatile saturated and unsaturated aldehydes and about 10 volatile ketones have been identified. The major representatives are formaldehyde (10-50 µg/cigarette), acetaldehyde (100-1,500 µg/cigarette), and acrolein (20-150 µg/cigarette); formaldehyde and acrolein are the most ciliotoxic organic volatiles in the smoke besides hydrogen cyanide. They can be selectively reduced in cigarette smoke by charcoal filter tips. The smoke from cigarettes with charcoal filters and ventilated cigarettes is significantly less ciliotoxic than are other types of smoke.

Table 14 lists the major toxic agents in the gas phase of cigarette smoke. The third group of compounds listed in the 1972 Surgeon General's report—including acetaldehyde, acetone, acetonitrile, acrylonitrile, ammonia, benzene, butylamine, carbon dioxide, crotonitrile, dimethylamine, ethylamine, formaldehyde, hydrogen sulfide, methacrolein, and methylamine—was considered as "suspected contributors to the health hazards of smoking" (93).

TABLE 14.—Major toxic agents in the gas phase of cigarette smoke¹ (unaged)

Agent ²	Biological Activity ³	Concentration in 1 Cigarette	
		Range Reported	U.S. Cig ⁴
Dimethylnitrosamine ⁵	C	1 - 200 ng	13 ng
Ethylmethylnitrosamine ⁵	C	0.1 - 10 ng	1.8 ng
Diethylnitrosamine ⁵	C	0 - 10 ng	1.5 ng
Nitroacetylnitrosamine ⁵	C	2 - 42 ng	11 ng
Other Nitrosamines (4 compounds) ⁵	C	0 - 20 ng	?
Hydrazine ⁵	C	24 - 43 ng	32 ng
Vinyl Chloride ⁵	C	1 - 16 ng	12 ng
Urethane ⁵	TI	10 - 35 ng	30 ng
Formaldehyde ⁵	CT, CoC	20 - 90 µg	30 µg
Hydrogen Cyanide ⁵	CT, T	30 - 200 µg	110 µg
Acrolein ⁵	CT	25 - 140 µg	70 µg
Acetaldehyde ⁵	CT	18 - 1400 µg	800 µg
Nitrogen Oxides (NO, ⁶ NO ₂) ⁵	T	10 - 600 µg	350 µg
Ammonia ⁵	TT ⁶	10 - 150 µg	60 µg
Pyridine ⁵	TT ⁶	9 - 83 µg	10 µg
Carbon Monoxide ⁵	T	2 - 20 mg	17 mg
Acrylonitrile ⁵	C	3.2 - 15 µg	10 µg
2-Nitropropane ⁵	C	0.73 - 1.21 µg	0.92 µg

¹May also contain such carcinogens as arsine, nickel carbonyl, and possibly volatile chlorinated olefins and nitroolefins.

²Nitropropane and acrylonitrile, both present in cigarette smoke, have been found to induce hepatomas in rats. Acrylonitrile is a suspected human carcinogen.

³Biological activities: C carcinogen; BC bladder carcinogen; TI tumor initiator; CoC co-carcinogen; CT ciliotoxic agent; T toxic agent.

⁴35 mm cigarette without filter tip bought on the open market 1973-76.

⁵NO, > 95% NO, rest NO₂.

⁶Not toxic in smoke of blended U.S. cigarettes because pH < 6.5 and therefore ammonia and pyridines are present only in protonated form.

SOURCE: (100) (101, 102), (103, 104).

Particulate Phase Total Particulate Matter

Depending on the makeup of the cigarette, the wet particulate matter that issues with the mainstream smoke from the butt end amounts to 0.2 to 9.0 percent of the weight of the mainstream smoke. The U.S. Federal Trade Commission (FTC) issues reports semiannually on the "tar" content of all U.S. commercial cigarettes. In those reports "tar" is defined as total particulate of mainstream smoke, minus water and nicotine, and is determined by smoking cigarettes under standard conditions in a 20-channel machine (68). For U.S. commercial cigarettes, the latest report lists "tar" values between 0.5 and 35.0 mg and nicotine values between 0.05 and 2.50 mg (23). Between 1957 and 1976, the sales-weighted average "tar" content for U.S. cigarettes decreased from about 39 mg to 17 mg (97). Similar "tar" reductions have been reported in other countries (99). This trend is largely due to the increased marketing of filter cigarettes. In the United States, filter

μg/cigarette) and cigars (NNN, 3.2 to 5.5 μg/cigarette; NNK, 1.9 to 4.2 μg/cigarette), as well as in the sidestream smoke of cigarettes (NNN, 1.7 to 6.1 μg; NNK, 0.41 to 0.60 μg) and cigars (NNN, 0.9 to 17.0 μg; NNK, 0.8 to 16.0 μg). Again, as for other smoke compounds depending on the reduction of nitrogen oxides in the burning cone, tobacco-specific nitrosamines are found in higher amounts in sidestream than in mainstream smoke (38).

The transfer rate of ¹⁴C-labelled NNN into mainstream smoke was determined for a U.S. blended nonfilter cigarette and was found to be about 11 percent (38a). This finding indicates that about 50 percent of the NNN in the smoke originates by transfer from tobacco and the other half was pyrosynthesized from nicotine during smoking. The nonvolatile nitrosamines are of special interest because they are the only tobacco-specific carcinogens thus far identified.

In the United States, about 70 to 80 percent of all tobaccos are treated during cultivation with the sucker growth inhibitor, maleic hydrazide (MH-46). Since this chemical is water-insoluble, it is solubilized as a diethanolamine formulation. During curing, the diethanolamine residue on tobacco is nitrosated to the carcinogenic N-nitrosodiethanolamine (74, 76). As an alternative, the potassium salt of MH has been used to impart water solubility. Although no data are presently available, it is possible that residues of pesticides with amino groups give rise to nitrosamines in tobacco and its smoke (e.g., carbarbyl)(20). This area needs to be investigated.

Aromatic Amines

Aromatic amines have been discussed as one possible factor in the association of cigarette smoking with bladder cancer (16). So far, two known human bladder carcinogens have been identified in trace amounts in cigarette smoke. These are β-naphthylamine (1-2 ng/cigarette) and 4-aminobiphenyl (0.8-2.4 ng/cigarette). These amines may serve as indicators of the concentration of other potential carcinogens in tobacco smoke, since most aromatic amines are pyrosynthesized by the same mechanism and have been isolated from tobacco smoke, although not yet fully identified (66, 67). Furthermore, a safe level of exposure for human bladder carcinogens has not been established (73, 93). Tobacco smoke also contains a number of alkylated o-toluidines, of which only the parent compound has been tested so far and found to be carcinogenic in the experimental animal (73).

Sidestream smoke of cigarettes contains significantly higher amounts of aromatic amines than mainstream smoke. For example, the mainstream smoke of a nonfilter cigarette was found to contain 160 ng of o-toluidine, 1.7 ng of β-naphthylamine, and 4.6 ng of 4-aminobiphenyl. The amounts of these amines in the sidestream smoke of the same cigarette were 3,000 ng, 67 ng and 140 ng, respectively (67). Since tobacco smoke may also contain the highly mutagenic amino-β-

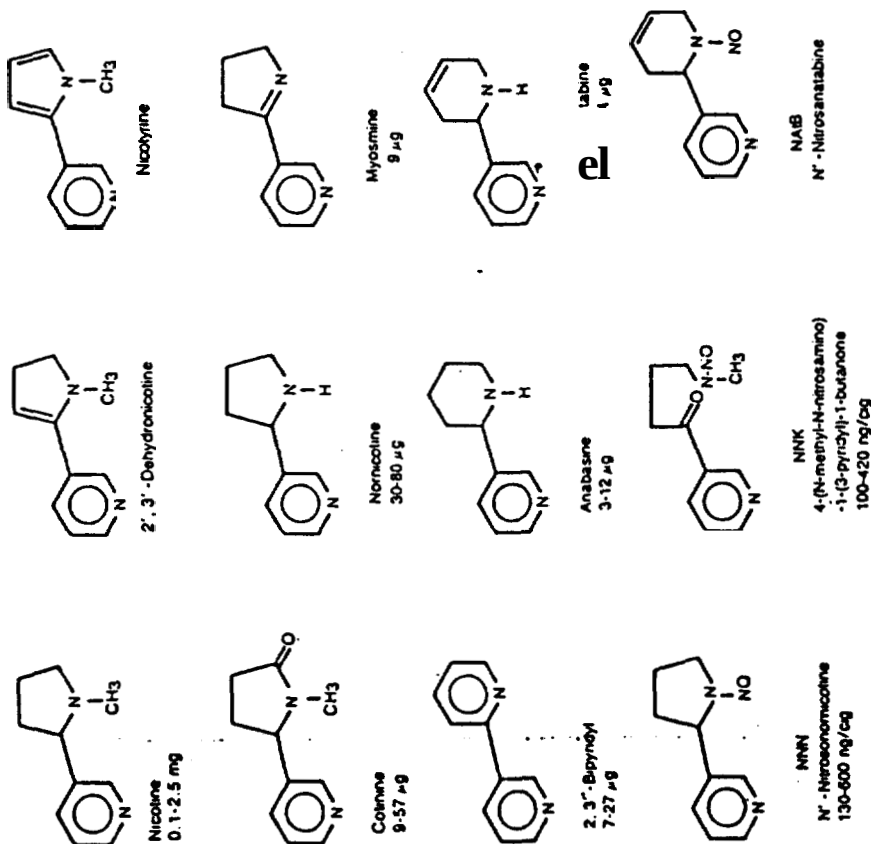


FIGURE 3.—Common tobacco alkaloids and tobacco-specific nitrosamines in cigarette smoke. Numbers are values for mainstream smoke of a cigarette).

carbolines which can be pyrosynthesized from tryptophan (87), further studies are needed before one can evaluate the contribution of aromatic amines to tobacco carcinogenesis.

Alkanes and Alkenes

The coating of leaves with "waxes" is an almost universal phenomenon throughout the plant kingdom (100). The waxy layer of tobacco leaves is primarily composed of alkanes, alkenes, terpenes, esters, phyosterols, and alkaloids (85). The tobacco specific alkane fraction of the wax layer is made up of *n*-, iso-, anteiso- $C_{25}H_{52}$ to $C_{30}H_{60}$ paraffin hydrocarbons. The most abundant hydrocarbon is *n*-(and iso-) hentriacontane ($C_{31}H_{64}$), which amounts to 30 to 40 percent of the total alkanes. Trace amounts of hydrocarbons have also been found from $C_{25}H_{52}$ to $C_{31}H_{64}$. The content of the crystalline alkanes amounts to 0.24 to 0.43 percent of the dry weight of the leaves.

Mainstream smoke of nonfilter cigarettes contains between 0.7 and 1.2 mg of nonvolatile alkanes, depending on the type of tobacco leaves used as cigarette filler. When diluents such as reconstituted tobacco sheets, stems, or expanded tobacco are incorporated into the cigarette blend, the content of nonvolatile alkanes decreases accordingly. These nonvolatile hydrocarbons are retained by filter tips to the same degree as "tar" in general.

Studies with ^{14}C -labelled *n*-dotriacontane have shown that about 25 percent of the radioactivity is recovered in the mainstream smoke and 75 percent in the sidestream smoke. Of the radioactivity in the mainstream smoke, about 95 percent was given by the unchanged C_{32} hydrocarbon and 0.7 percent by $CO + CO_2$ and the rest by C_1 to C_{10} compounds. *N*-dotriacontane did not contribute in any measurable degree to the benzo(a)pyrene content in mainstream and sidestream smoke (47).

So far, only a limited number of studies have been concerned with the unsaturated hydrocarbons (C_{10} to C_{22}) in the mainstream smoke particulate matter, because they amount to less than 0.02 percent of the "tar." It appears that the nonvolatile acids, esters, and ketones in the leaf serve as precursors for the alkenes in the smoke.

The alkanes and alkenes appear to play no major role in tobacco toxicity and carcinogenesis other than to influence the resorption of smoke carcinogens. In studies on mouse skin, this effect was seen as an inhibition of resorption, which delayed latency of tumor development and diminished tumor yield.

Tobacco Isoprenoids

Tobacco and its smoke contain a large spectrum of isoprenoids; many of them can be regarded as tobacco-specific constituents (85). They are important because they contribute to the organoleptic nature of

tobacco smoke and thereby add to the consumer acceptability of specific tobacco products. The increasing volume of cigarettes with reduced and low "tar" yield and the desire to produce tobacco substitutes have given renewed impetus to chemical research on tobacco flavor components, especially on tobacco isoprenoids, during the last decade.

Primarily four types of terpenoids are found in tobacco: the carotenoids and acyclic isoprenoids; the cytoplasmic triterpenoids and phytosterols; the diterpenoids, which are biosynthesized in the trichomes; the glandular hair of the leaves; and the cyclic sesquiterpenoids and monoterpenoids (Figure 4) (85). The concentration and nature of these terpenoids in the leaf are not just dependent on plant genetic factors and growth conditions but also on the curing and fermentation processes that lead to the final tobacco product.

For the details on the chemistry and organoleptic nature of individual tobacco terpenes, the reader should refer to the specific scientific literature (81, 82, 85, 100). At present, several hundred isoprenoids have been isolated from tobacco. During smoking, some of these compounds, especially the more volatile ones, are transferred partially intact and appear also in the mainstream smoke as thermally rearranged or oxidized decomposition products. Although it has been demonstrated that the tobacco terpenoids represent an important part of smoke flavor, little is known about their contribution to the toxicity or tumorigenic properties of tobacco products. Some authors have considered it possible that certain cyclic tobacco isoprenoids may be active as tumor promoters (36), while others have shown that cyclic terpenes, upon pyrolysis, form relatively high concentrations of carcinogenic polycyclic hydrocarbons (100). At best, the data at hand are inconclusive. Therefore, intensified research is needed on the possible contribution of isoprenoids to smoke toxicity and tumorigenicity. The importance of such a program is underscored by the fact that, today, flavoring agents derived from tobacco and mixtures of plant extracts are added to tobacco in order to make low "tar" cigarettes acceptable to the consumer.

Benzenes and Naphthalenes

During all incomplete combustions of organic matter, small amounts of aromatic hydrocarbons are formed. Like other plant materials, tobacco already contains a number of compounds with the benzene ring structure, such as hemicellulose, plant phenols and polyphenols, certain amino acids, and a few terpenes (e.g., aromatized menthanes) (82, 85, 100). In addition, benzenes are pyrosynthesized from C,H-radicals and by diene-synthesis reactions with subsequent dehydrogenation during burning of the tobacco. It is, therefore, not surprising that cigarette smoke contains more than two dozen benzene hydrocarbons, with toluene (20 to 150 $\mu g/cigarette$) and benzene itself (10 to 100 μg) as the

most abundant compounds of this type. Most benzene compounds are considered to be semivolatile and thus are present in both the gaseous and the particulate phase.

Concern has been expressed in recent years about the possible risk of leukemia for workers who have been exposed to benzene. This concern has led to a standard of 10 ppm as a threshold limit for benzene in the working atmosphere. Although some prospective and retrospective studies have reported a somewhat higher risk of leukemia for cigarette smokers, these data remain unconfirmed and no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked.

In model studies with ^{14}C -labelled precursors, Badger and his group showed that the probability of pyrosynthesis of polycyclic aromatic hydrocarbons decreases with the number of condensed rings (9); thus, tobacco smoke contains less naphthalene (2.0 to 3.5 $\mu\text{g}/\text{cigarette}$) than toluene (20 to 150 $\mu\text{g}/\text{cigarette}$) (6, 85, 100). Other naphthalenes identified in cigarette smoke are ethylnaphthalenes, dimethylnaphthalenes, and trimethylnaphthalenes. Neutral tobacco smoke condensate fractions, which contain naphthalene and methylnaphthalenes and are free of three-ring and higher polycyclic hydrocarbons, are inactive as carcinogens, co-carcinogens, and tumor initiators, as are the pure compounds (77, 78). There has been some indication that naphthalenes may induce lymphomas in mice; however, this finding needs confirmation.

Polynuclear Aromatic Hydrocarbons (PAH)

Fractionation studies with tobacco "tar" have shown that only those neutral fractions and subfractions in which the PAH are enriched induce tumors on mouse skin and the bronchial epithelium of rats and sarcomas in the connective tissues of rats (40, 83, 100). Minute subfractions (<0.002 percent) of the "tar," containing only four-, five-, and six-ring PAH, are the only fractions which show activity as tumor initiators upon application in low doses. PAH alone, however, account for only a small portion of the carcinogenicity of tobacco "tar." These observations, and the fact that a significant reduction of PAH in the smoke leads to a concomitant reduction of the tumorigenicity of the total "tar" on mouse skin, are the major reasons for the extensive chemical analytical studies and identification of tumorigenic PAH (83, 100). More than 100 individual four-ring and higher polycyclic hydrocarbons have been identified to date. These include the classical carcinogens benzo(a)pyrene, dibenz(a,h)anthracene, and dibenzo(a,h)pyrene as well as other PAH. The levels of carcinogenic PAH in tobacco smoke are well below their practical threshold as complete mouse skin carcinogens, but their role in tobacco smoke condensate is definitely that of a tumor initiator.

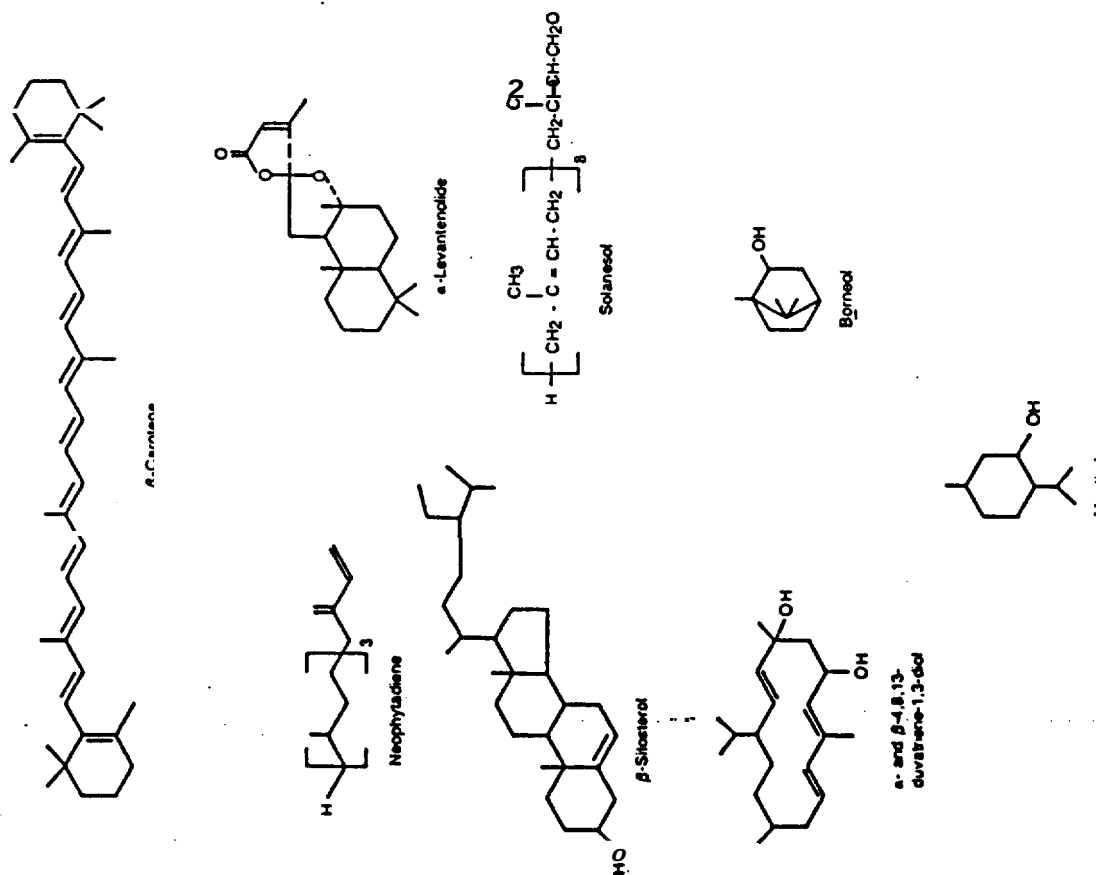


FIGURE 4.—Tobacco isoprenoids.

Certain PAH are not active when tested as complete carcinogens, but they are active as tumor initiators or as co-carcinogens when applied as such. A major characteristic for a tumor initiator is that it merely induces a dormant tumor cell, thus not eliciting tumors in epithelial tissues unless the tissue is exposed to a promoting agent. Promoters are active only in tissues previously treated with a tumor initiator. A co-carcinogen is a chemical which is neither a tumor initiator nor a complete carcinogen; it is, however, typically capable of significantly increasing the carcinogenic response towards a low dose of a carcinogen. Figure 5 presents the structural formulas of several carcinogenic PAH, tumor-initiating PAH and co-carcinogenic PAH. Table 15 lists the concentrations of some of the active PAH in cigarette smoke. Since it has been demonstrated that most, though not all, of the PAH are pyrosynthesized from C₂H₂-radicals by the same mechanism and from unspecific precursors, carcinogenic BaP has often been used as an indicator of the concentration of tumorigenic PAH in the smoke of a given cigarette and cigar. The concentration of BaP in "tar" of cigarettes made primarily from tobacco lamina has served as an indicator of the carcinogenic potential of the smoke particulates on mouse skin.

N-Heterocyclic Hydrocarbons (Aza-Arenes)

Although the nicotine-free basic portion of tobacco smoke is inactive as a complete carcinogen, it contains traces of carcinogenic aza-arenes. This group includes dibenz(a,h)acridine and dibenz(a,j)acridine (Figure 6). Another aza-arene with carcinogenic activity is dibenz(c,g)carbazole, which is found in the neutral portion (100). Van Duuren and coworkers have shown in model studies that nicotine can serve as precursor for these carcinogenic aza-arenes (94). So far, the basic portion of tobacco smoke has not been found to be carcinogenic (40). Mutagens thus far identified in cigarette smoke are: quinoline (MS 1.7 µg/cigarette; SS 18 µg/cigarette), all seven isomeric methylquinolines (MS 0.7 µg/cigarette; SS 8 µg/cigarette), benzo(f)quinoline (MS 0.01 µg/cigarette; SS 0.1 µg/cigarette), phenanthridine (MS 0.01 µg/cigarette; SS 0.01 µg/cigarette), and benzo(h)quinoline (MS 0.01 µg/cigarette; SS 0.1 µg/cigarette) (84, 88). Quinoline induces hepatomas when fed in high doses to rats (19, 37, 83).

Phenols

The weakly acidic fraction of cigarette smoke condensate is active as both a tumor promoter and co-carcinogen (13, 100). It contains volatile phenols, polyphenols, cyclopentenols, fatty acids, and pyridinols (Figure 7). Among these, the catechols are of special interest as co-carcinogens (95). At present, however, the major tumor promoters and co-carcinogens in the weakly acidic fraction need identification.

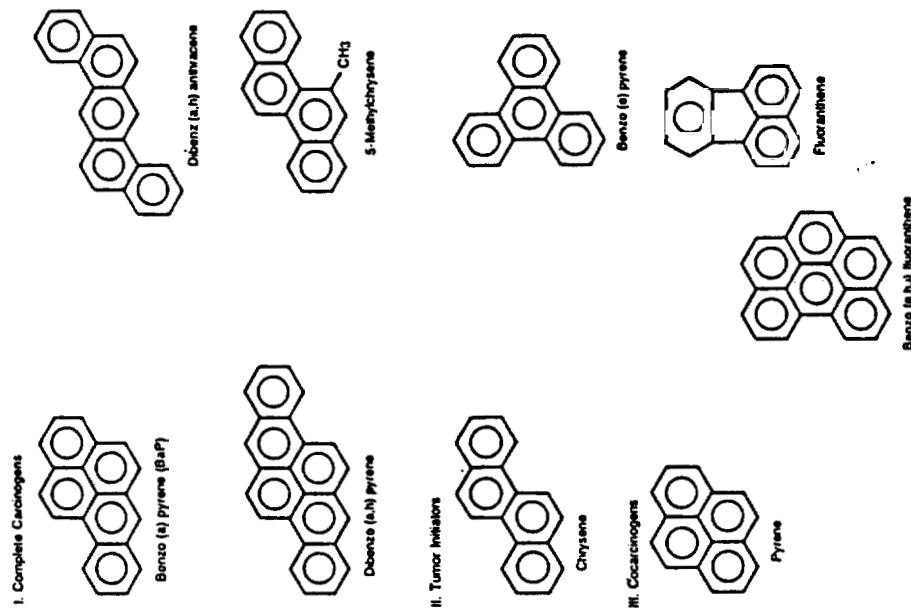


FIGURE 5.—Some tumorigenic PAH in tobacco smoke.

TABLE 15.—Tumorigenic PAH in cigarette smoke¹

PAH	Relative activity as complete carcinogen ²	ng/cig
I. Active as tumor initiators		
Benzo(a)pyrene	++	10-50
5-Methylchrysene	++	0.6
Dibenz(a,h)anthracene	+	40
Benzo(b)fluoranthene	+	30
Benzo(j)fluoranthene	+	60
Dibenz(a,h)pyrene	+	pp ³
Dibenz(a,j)pyrene	+	4
Indeno(1,2,3-cd)pyrene	+	pp ³
Benzo(c)phenanthrene	+	40-70
Benzo(a)anthracene	+	40-60
Chrysene	- (-+)	5-40
Benzo(c)pyrene	+	7
2-, 3-Methylchrysene	-	10
1-, 6-Methylchrysene	+	30
2-Methylfluoranthene	?	40
3-Methylfluoranthene	?	40
Dibenz(a,c)anthracene	?	pp ³
II. Active as co-carcinogens		
Pyrene	-	50-200
Methylpyrenes	-	50-300
Fluoranthene	-	100-250
Benzo(a,h)perylene	-	60

¹Incomplete list.²Relative carcinogenic activity on mouse skin.³Present, but no quantitative data available.

SOURCE: Hoffman, D. (49).

Catechol is the phenol with the highest concentration in the smoke of cigarettes. In the mainstream smoke of a plain cigarette it varies from 160 to 500 µg, and in the mainstream smoke of a filter cigarette it ranges from 60 to 200 µg (10, 100). Smoke also contains a number of alkylated catechols, hydroquinone, resorcinol, and volatile phenols. The latter group appears to contribute only to a minor extent to the tumor-promoting activity of the weakly acidic portion. Compared to mainstream smoke, sidestream smoke of cigarettes contains less catechol (SS/MS 0.7-0.8) and more volatile phenols (SS/MS 2-3). It appears that the major precursors for the smoke catechols reside in the "wax" layer of the tobacco leaf and that the major precursors for the smoke phenols are the tobacco carbohydrates.

Extensive investigations in several laboratories have demonstrated highly selective filtration of semi-volatile phenols from cigarette smoke by cellulose acetate filter tips (52, 61). Because of their low

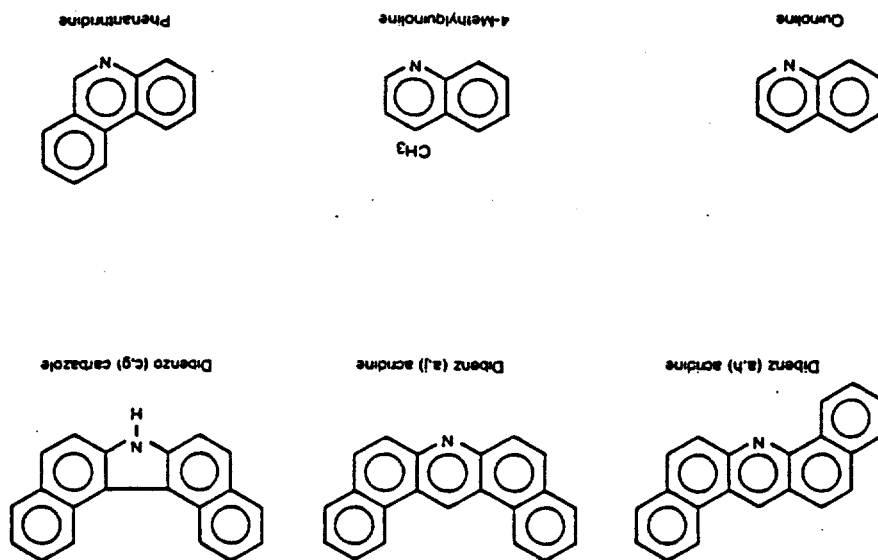


FIGURE 6.—Carcinogenic aza-arenes in tobacco smoke.

TABLE 16.—Major phenols in cigarette smoke

Phenol	Nonfilter	Filter	Remarks ¹
Phenol	50-130	10-50	1
<i>o</i> -Cresol	20-40	7-20	1
<i>m</i> - + <i>p</i> -Cresol	40-70	15-25	1
2,4-Dimethylphenol	15-25	5-12	1
Catechol	160-500	60-200	2
3-Methylcatechol	15-25	10-20	2
4-Methylcatechol	15-25	10-20	2
Hydroquinone	50-120	N.D. ²	-
Resorcinol	15-20	N.D.	-
Eugenol	3-10	N.D.	-
Isoeugenol	8-20	N.D.	-
Scopoletin	140-280	N.D.	-
Chlorogenic Acid	N.D.	N.D.	-
Rutin	N.D.	N.D.	-
β -Naphthol	0.5-2	N.D.	-

¹Remarks: 1 - Tumor promoting agent on mouse skin;
2 - Cocarcinogen on mouse skin;
- - Inactive or not tested.
²N.D. - Quantitative data not determined.
SOURCE: Keith, C.H. (57), Merle, G.P. (61).

vapor pressure, no selective reduction by filter tips was observed for catechols (Table 16).

Cyclopentanediols found as constituents of the weakly acidic portion of tobacco smoke are considered important flavor compounds in tobacco smoke. Their concentrations are highest in the smoke of Oriental tobaccos, less in Burley and the least in flue-cured varieties (9:2:1) (26). It appears that these compounds are not toxic.

Carboxylic Acids

A considerable number of carboxylic acids are present in tobacco and tobacco smoke. More than 50 of these have been identified thus far in smoke, accounting for 4 to 7 percent of the particulate matter. The composition of the fraction of volatile carboxylic acids (C_1 to C_4) is a determining factor in the flavor of tobacco varieties. Oriental tobaccos, for example, have a high proportion of β -methylvaleric acid and also contain hydroxyderivatives of valeric- and β -methylvaleric acid. Flue-cured tobaccos are often high in acetic acid, whereas benzoic acid predominates in Burley tobaccos. The non-volatile fatty acids in tobacco range from C_8 - C_{24} with highest concentrations of palmitic acid (C_{16}), C_{18} -acids, stearic, oleic, linoleic and linolenic acids. These range from 0.01 to 0.7 percent in dry tobacco leaf and from 1 to 3 percent in the tar. The highest fatty acid concentrations are found for Turkish tobacco and its smoke.

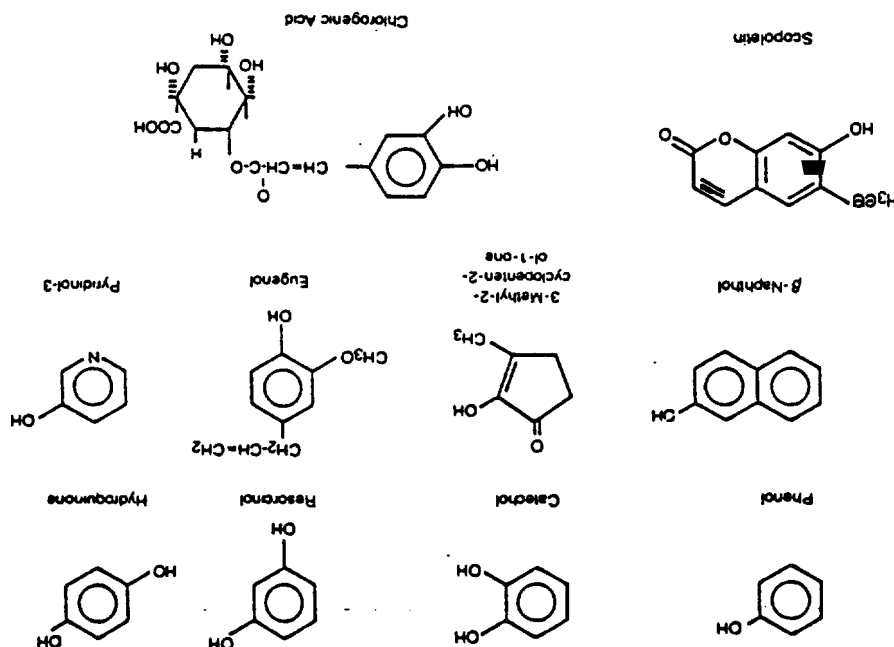


FIGURE 7.—Weakly acidic compounds in cigarette smoke.

TABLE 17.—Free fatty acids in cigarette smoke

Acid	μg/l g Tobacco smoked ¹				
	Turkish 1	Bright	Maryland	Burley	Blend
Palmitic	284	197	107	55	152
Stearic	90	74	43	33	75
Oleic	108	39	32	21	58
Linoleic	146	113	52	50	96
Linolenic	329	310	66	52	240
Total (mg)	0.96	0.73	0.30	0.21	0.62
Wet TPM (mg)	37.2	37.6	26.4	20.1	32.3
5 fatty acids					
% of TPM (wet)	2.6	1.95	1.14	1.06	1.9

¹Moisture content of the tobacco
SOURCE: Hoffman, D. (46).

Transfer rates of unchanged fatty acids from tobacco into mainstream smoke can be up to 20 percent, especially for the saturated fatty acids of C₁₆-C₁₈ chain length. Lower transfer rates are observed for the C₁₈ unsaturated fatty acids—oleic, linoleic, and linolenic acid. Comparative concentrations of the major fatty acids in the smoke of various cigarettes are presented in Table 17.

Although high concentrations of fatty acids play a role as tumor promoters in model studies with BaP it appears that these fatty acids are of lesser importance in tobacco carcinogenesis. About two dozen hydroxy-γ-lactones of C₄ to C₈-acids have been identified in tobacco smoke. They probably arise from tobacco leaf carbohydrates by thermal degradation (87). γ-Lactones have not been fully examined for their biological significance in tobacco carcinogenesis. However, several of these compounds are known alkylating agents and as such induce sarcomas in rats (54).

Metallic Constituents

Minerals and other inorganic compounds in the tobacco plant derive from soil, fertilizers, or agricultural sprays. The most prominent metal ions in tobacco are Ca + +, Mg + +, K +, and Na +. During combustion, the bulk of metallic constituents remain in the ashes, but some compounds are vaporized or transferred into the smoke stream. With the growing sophistication of analytical techniques, the list of trace amounts of metals is increasing. Presently, 76 metals, including Bi, Si, As, Se, and Te, excluding the post-uranium metals, have been detected in cigarettes. Of these, 30 have been identified in the smoke (Table 18) (63).

TABLE 18.—Metals in cigarette smoke particulate

Metal	(μg/cig)	Metals for which good quantitative data are not available	
		70	Si
K	1.3		Ca
Na	0.36		Ti
Zn	0.24		Sr
Pb	0.22		Tl
Al	0.19		Po ²
Cu	0.12 ¹		
Cd	0.080 ¹		
Ni	0.070		
Mg	0.052		
Sb	0.042		
Fe	0.012 ¹		
As	0.006		
Te	0.004		
Bi	0.004		
Hg	0.003		
Mn	0.0018		
La	0.0014		
Sc	0.0014		
Cr	0.0012		
Ag	0.001		
Se	0.0002		
Co	0.0002		
Ca	0.0002		
Au	0.00002		

¹Cigarettes other than the University of Kentucky Reference cigarette

²Levels expressed in terms of radioactivity

SOURCE: Norman, V. (67).

With respect to tobacco carcinogenesis, special interest has focused on As and Ni. The continued trend toward replacement of arsenical sprays with other pesticides has been reflected in progressively lower arsenic contents of leaf and smoke. Between 1940 and 1950, arsenic values in the dry leaf of up to 50 to 60 ppm were reported for U.S. tobaccos (37). The last published data for U.S. tobaccos range between 0.5 and 0.9 ppm (28). Between 7 and 18 percent of the total arsenic in tobacco reappears in the mainstream smoke of cigarettes. Studies with ⁷⁴As-labelled cigarettes have shown that, depending on the individual's smoking patterns, 2.2 to 8.6 percent of the arsenic in cigarette tobacco is transferred into the respiratory tract. About 50 percent of the inhaled arsenic is eliminated within 10 days, primarily in urine; the remainder is either deposited in body tissues or is exhaled or otherwise eliminated (41).

All forms of nickel (metal, oxide, sulfide, salts, and carbonyl) tested in the experimental animal were found to be carcinogenic. In nickel factories, primarily in those converting nickel sulfide to nickel oxide,

workers have a high risk for cancer of the nasal cavity and cancer of the lung. In cigarette tobacco, 2.0 to 6.2 μg Ni per cigarette were reported; other tobacco products contained between 0.5 and 8.5 μg per gram. In South Africa, nickel values of 52 and 88 μg per gram of Swazi snuff were reported as a possible contributing factor in the high incidence rate of cancer of the nose and in accessory sinuses in male Bantus (5). During smoking, 10 to 20 percent of the nickel in the tobacco is transferred into the mainstream smoke (62). In one study, tentative evidence indicated that most of the nickel transferred into the mainstream smoke (≈ 10) is present in the gas phase (≈ 8 percent) (90). This and a model study suggest that nickel is present in the gas phase of tobacco smoke as nickel carbonyl. $\text{Ni}(\text{CO})_4$ is highly carcinogenic in the respiratory tract of rats. It induces epidermoid carcinomas and adenocarcinomas of the lung (89).

Several forms of cadmium are carcinogenic in the experimental animal. Two studies suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer (45). In mainstream smoke, concentrations are 9–70 ng Cd per cigarette (45). It has been suggested that a heavy smoker retains about 1.5 μg of Cd per day and that he may accumulate up to 0.5 mg through inhalation.

Radioactive Compounds

Two types of radioactive compounds have been reported in tobacco and tobacco smoke. These are the α -particle emitting elements of the disintegrating radium and thorium series and the β -emitters. In the latter group, potassium-40 is the most abundant in tobacco products (100). A sample of 100 U.S. and Canadian cigarettes was found to contain 2,120 and 2,295 pCi of ^{40}K -derived β -activity, respectively. The β -activity from ^{40}K in the mainstream smoke of 100 cigarettes was 15.9 and 9.4 pCi, corresponding to a transfer rate of 0.75 percent and 41 percent, respectively. ^{40}K is a soft emitter with E_{max} of 1.3 MeV.

The presence of radioelements ^{226}Ra , ^{210}Pb , and ^{210}Po in tobacco products (e.g., from fallout, natural background) have been of special interest and concern (69). The general range of ^{210}Po in 1 g of U.S. tobacco leaf varies from 0.15 to 0.45 pCi. In the smoke of one U.S. cigarette, ^{210}Po values of between 0.03 and 0.07 pCi were reported. The average ^{210}Po content was ≈ 0.036 pCi per cigarette or ≈ 2.6 pCi of ^{210}Po per 1 g smoke condensate with a ^{210}Pb : ^{210}Po ratio of 0.66 ± 0.23 (42). ^{210}Pb has a half-life of 22 years and decays by emission of two β -particles to ^{210}Po ; the latter decays by α -emission with a half-life of 138.4 days. Preliminary studies indicate that most of the ^{210}Pb is concentrated in the nonvolatile and insoluble portion of the particulate matter of cigarette smoke (58).

Analysis of human tissues demonstrated that the lung, blood, and liver of smokers contain a higher concentration of ^{210}Po than do those of nonsmokers. It has been calculated that a smoker's intake of ^{210}Po is

reflected within several days by the observed excess burden of 3–10 pCi of ^{210}Pb and ^{210}Po in the lungs. Based on the measured concentration of ^{210}Po in epithelial samples, Little and Radford estimated a maximum radiation dose of ≈ 200 rem per 25 years to the lower lobe bifurcations of the lung (56); however, others have estimated a far lower effective radiation dose (14, 70).

After multiple intratracheal installations of ^{210}Po in Syrian golden hamsters, a dose-dependent increase was observed in epidermoid carcinoma and adenocarcinoma in the peripheral lung fields (55). Simultaneous and multiple intratracheal instillation of benzo(a)pyrene (total dose 4.5 mg) and ^{210}Po (total dose 50,000 pCi) on the same carrier induced twice the number of tumors expected from the additive effect of either carcinogen alone (59).

Agricultural Chemicals

As in the case of arsenical pesticides, a significant reduction in the use of chlorinated hydrocarbon insecticides on tobacco has occurred during the last decade. This is reflected in the reduction of such insecticide residues as DDD, DDT, endrin, and endosulfan on tobacco (Figure 8). Whereas in 1968 70.2 percent of all U.S. flue-cured auction-marketed tobaccos contained more than 10 ppm of DDT, in 1972 there was no tobacco of the same type containing levels above 10 ppm of DDT. In the latter year, 73.1 percent of the tobaccos marketed contained only 0.1 to 0.49 ppm of DDT (17). DDD values declined from levels of ≥ 10 ppm in 97.6 percent of the 1968 crop to levels no higher than 0.1 to 0.49 percent in 63.9 percent of the tobaccos marketed in 1972. Again, there was no tobacco with levels of DDD above 10 ppm in 1972. Similar reductions of insecticide residues on tobacco were reported for endrin, dieldrin, and endosulfan (17, 30). A further gradual decrease of these pesticides in tobacco is expected. During smoking, 11 to 18 percent of DDT and DDD are transferred without change of structure from tobacco into the mainstream smoke of cigarettes. DDE, DDM, and 4,4'-dichlorostilbene (Figure 8), an immediate decomposition product of DDT and DDM resulting from elimination of HCL and molecular rearrangement, are also detected in mainstream smoke (39). One study showed that levels of chlorinated hydrocarbon insecticides in adipose tissues of smokers were not elevated above those in nonsmokers (18). Other pesticide residues found on some U.S. tobaccos are parathion (up to 0.03 ppm), carbaryl (up to 1.5 ppm), endosulfan (up to 2.9 ppm), and toxaphene (0.7 to 3.4 ppm) (30).

Some of the chlorinated hydrocarbon insecticides and the isomeric impurities present in the technical preparations, e.g., o,p'-DDD, are possible or known carcinogens in experimental animals. One of the co-carcinogens is 4,4'-dichlorostilbene, formed by pyrolysis from DDT and DDD (40). As discussed earlier, the carbaryl residue on tobacco may give rise to a carcinogenic nitrosamine. Similarly, maleic hydrazide and

its soluble salts have been mentioned. Present evidence is not uniformly clear as to whether pure MH is mutagenic or carcinogenic, though the weight of the evidence suggests it is mutagenic. (22, 32).

Tobacco Additives

Tobacco products are refined by the addition of additives, humectants, tobacco casings, and flavor-enhancing compounds. The most widely used humectants are propanediol, glycerol, diethylene glycol, triethylene glycol, and D-sorbitol (100). Humectants amount to 2 to 4 percent of the original tobacco weight for cigarettes. Analyses of 18 U.S. cigarette brands showed ranges of 0.46 to 2.24 percent of propylene glycol and 1.7 to 3.15 percent of glycerol in the tobaccos (15). Smoke analyses demonstrated that in filter cigarettes 9.9 percent and in nonfilter cigarettes 12.6 percent of the propylene glycol in tobacco reappear unchanged in the mainstream smoke. The glycerol transfer rate into the mainstream smoke of filter and nonfilter cigarettes was 12 and 14 percent, respectively. The smoke of humectant-treated cigarettes had increased amounts of acetaldehyde and acetone (53). Transfer of humectants into the mainstream smoke is probably significantly greater in pipe smoking than in cigarette smoking because of the former's higher puff frequency (60).

The use of humectants in tobacco products has raised concern as to their effects on smoke toxicity. Formation of volatile aldehydes and ketones, including acrolein, from combustion of such humectants would add to the ciliotoxicity of tobacco smoke. The glycols, especially diethylene glycol, are suspected to influence the smoker's risk for bladder cancer (44).

Pipe tobaccos may contain up to 30 percent of casing agents. These are primarily sugars, starches, humectants, and plant extracted isoprenoids. These casing agents influence the flavor of the tobacco smoke, as well as the burning rate of the tobacco, and thus affect smoke toxicity. When cigarette tobacco contained 5 percent or higher levels of sugar additives, the resulting smoke was higher in furfural, nicotine, and tar content than the smoke from an identical cigarette without the sugar casing (36).

The flavor of cigarette smoke is also affected by the curing, aging, and blend of tobaccos used. Considerations such as acreage yield and tobacco prices during the last decade have resulted in changes of leaf aroma affecting the tobacco blends and thus the smoke flavor. More importantly, however, the trend toward low-tar, low-nicotine cigarettes and toward a reduction of undesirable volatile smoke compounds has brought about major changes in the smoke flavor of cigarettes. The use of rolled stems and reconstituted tobacco sheet admixed with leaf lamina and the use of effective filter tips are major factors inducing changes in smoke flavor. All of these developments have led to increased use of flavor additives, especially for low-tar, low-nicotine

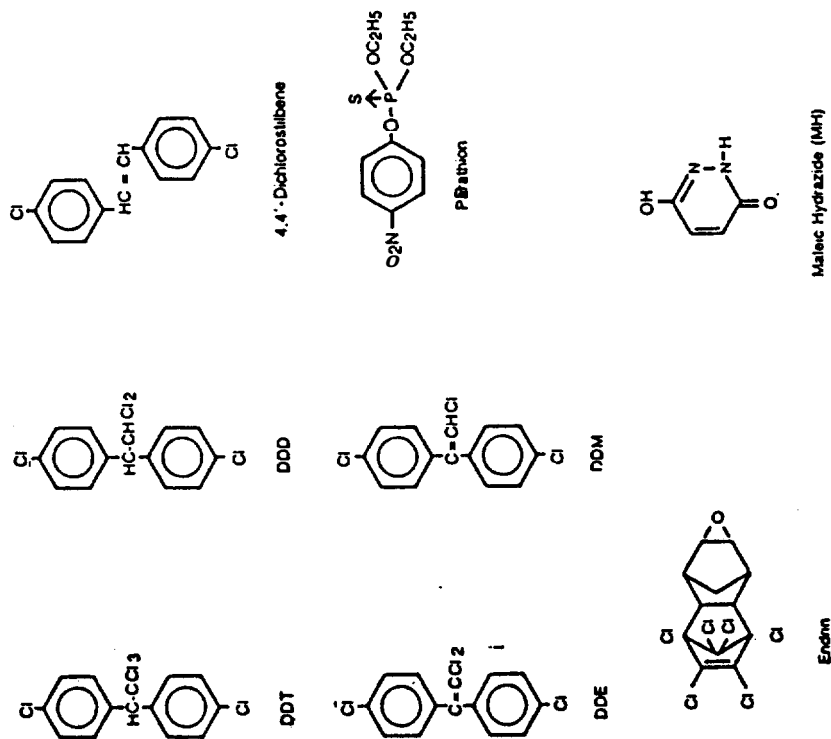


FIGURE 8.—Residues of agricultural chemicals in tobacco and cigarette smoke.

TABLE 19.—Harmful constituents of cigarette smoke particulate matter

I. Compounds judged most likely to contribute to the health hazards of smoking: ¹	
Nicotine	50-2,500 µg/cig
II. Compounds judged as probable contributors to the health hazards of smoking:	
Cresols (all 3 isomers)	500-35,000 µg/cig
Phenol	9-202 µg/cig
III. Compounds judged as suspected contributors to the health hazards of smoking:	
DDT	0-0.77 µg/cig
Hydroquinone	83 µg/cig
Pyridine	25-218 µg/cig
Endrin	0-0.06 µg/cig
Nickel compounds	0-0.58 µg/cig

¹Values from May 1978 FTC list
²"Tar" contains the polynuclear aromatic hydrocarbons which are "generally accepted as being responsible for a substantial portion of the carcinogenic activity of the total "tar". "Tar" also contains β-naphthylamine, a known human bladder carcinogen for which there is no known safe level of human exposure.
 SOURCE: U.S. Public Health Service (93).

cigarettes. In fact, these new cigarettes require flavor corrections by additives in order to be acceptable to the consumer. Tobacco extracts as well as nontobacco flavors, such as licorice, coca, fruit, spices, and floral compositions, are used. More recently, suggestions for synthetic flavor additives for cigarette tobaccos are increasing in the patent literature. At present, the selection of tobacco flavor additives from the GRAS (Generally Regarded As Safe) List or from natural extracts and the screening of their smoke decomposition products for toxicity or other biological activity are not required by law and are done voluntarily by manufacturers.

Toxic and Carcinogenic Agents—A Summary

The report of an expert panel on the "harmful constituents of cigarette smoke" classified the harmful and possibly harmful smoke compounds into the following categories: (1) contributors, (2) probable contributors, and (3) suspected contributors to the health hazard of smoking (93).

The constituents of the particulate matter are listed according to this classification in Table 19. Since 1970, when the harmful smoke constituents were so defined, much progress has been made toward the identification of toxic and especially of tumorigenic agents in cigarette smoke. The identified tumorigenic agents and their quantities in cigarette smoke are listed in Table 20. The majority of co-carcinogenic agents in cigarette smoke remain to be identified.

The increased risk for cigarette smokers of cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette

TABLE 20.—Known tumorigenic agents in cigarette smoke particulates

Compound	µg/cig	Compound	µg/cig
I. Tumor Initiators		II. Co-carcinogens	
Benz(a)pyrene	0.01-0.05	Pyrene	0.05-0.2
Other PAH ¹	0.3-0.4	Other PAH ²	0.5-1.0
Dibenz(a,h)acridine	0.003-0.01	1-Methylindoles	0.8-
Other Aza Arenes	0.01-0.02	9-Methylcarbazoles	0.14-
Urethane	0.035	4, 4-Dichlorostilbene	0.5-1.5
		Catechol	200-500
		Alkylcatechols	10-30
III. Organ Specific Carcinogens			
N-Nitrosomethylamine	0.14-3.70		
4-(N-Methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone	0.11-0.42		
N-Nitrososarcosine	+ ³		
Polonium-210	0.03-0.07pCi		
Nickel Compound	0-5.8		
Cadmium compounds	0.01-0.07		
β-Naphthylamine	0.001-0.022		
4-Aminobiphenyl	0.001-0.002		
O-Toluidine	0.16		

¹For details see Table 15

²For details see Table 15

³Concentrations unknown

SOURCE: U.S. Public Health Service (93).

smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic amines and N-nitrosamines.

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Physiological Responses to Cigarette Smoke

Previous editions of this report have examined acute and chronic effects of cigarette smoke. Starting with epidemiological evidence and buttressed by clinical and pathological findings, the role of cigarette smoke has been implicated in numerous disease processes in humans.

Since smoke is such a complex mixture of elements, experimental work in humans must be augmented by animal studies in order to define the specific role of particular smoke components. Inhalation studies (33) must be designed to closely mimic smoke exposure in the human population and provide data relating to: (1) understanding the physiological or biochemical mechanism of action of whole cigarette smoke or individual smoke components, (2) understanding of pathogenesis and early identification of endpoints which are predictive in nature, and (3) screening potentially less hazardous cigarette models to differentiate their relative influence on physiological or pathological endpoints.

Bioassays must be designed with appropriate exposure modes, since cigarette smoke-related diseases in man are usually chronic and involve a history of prolonged interaction between smoke components and target tissue.

Animal Smoke Inhalation Exposure Methodology

Smoke Generation

Exposure systems for tobacco smoke can be classified as active or passive, depending upon the system used for generating cigarette smoke.

Active exposure systems require the animal to generate the smoke by drawing air through a lighted cigarette to simulate what happens to the human smoker. McGill, et al. (30) used a water-reward system to train baboons to puff on lighted cigarettes and to inhale cigarette smoke. Once the animals were trained to take puffs of a specific duration, it was possible to control the animal's smoking behavior by manipulating the water reward per puff. The effectiveness of this system was shown by the fact that the animals remained in good health throughout the period of training and were able to achieve blood carboxyhemoglobin levels similar to those of human smokers.

However, since most experimental animals will not cooperate as well as baboons, passive devices in which smoke is generated by a machine are commonly used. Passive exposure systems can then be further classified as continuous or intermittent. A continuous system is one which smokes a series of cigarettes at one time by using one or two rotating discs or turrets to position the cigarettes at a smoking port where the puff is usually drawn by a vacuum pump. By designing the system so that a cigarette on one turret is being smoked while a