materials are applied late in the process. The flavorings normally used (whether natural or chemically compounded) are usually selected from substances generally considered safe to humans even though such definitions do not guarantee that subsequent pyrolytically-produced materials are safe.

Tobacco blends can also be mechanically processed in different ways. For example, leaf tobacco can be shredded to various widths and lengths to control density, burning rates, puff resistance, and other related properties (15). This alteration in tobacco blends produces a cigarette or cigar with a modified chemical composition in both the tobacco product and the resulting smoke as has been described earlier in this chapter.

Cigarette paper can also be manufactured with a variety of additives and with different porosities in order to control burning qualities. High porosity citrate paper used with a standard tobacco blend delivered less tar, but the same nicotine, as a control cigarette. Acetaldehyde, acrolein, formaldehyde, carbon monoxide, and hydrogen cyanide were reduced, but the pH of the smoke was elevated slightly. Low porosity phosphate paper used with the same blend delivered greater quantities of tar and nicotine than did the control cigarettes. Increases were also found for the deliveries of acetaldehyde, acrolein, formaldehyde, carbon monoxide, and hydrogen cyanide, while the pH remained unchanged (15–18).

Most modern cigarettes use filters of various kinds. Over 80 percent of the cigarettes sold in 1977 were filtered, using charcoal filters, mentholated filters, special baffled filters, cellulose acetate, and combination filters. Charcoal filtration reduces some of the toxic gas components; cellulose with absorptive additiv_s tends to remove acidic constituents; and magnesium silicate (when used) removes some of the aldehydes and organic vapors from smoke. Perforating the filter to allow air dilution further reduces the concentration of gas phase components of smoke (10, 11, 22).

Many modifications of cigarettes are possible and the precise ingredients and variations thereof are usually proprietary to manufacturers. However, experimental cigarettes have been prepared using a number of modifications, such as variation of the width of tobacco cut, the use of different parts of the tobacco itself (leaf, stems, fines, etc.), a selection of additives, and different paper porosities. These experimental cigarettes have been prepared by different methods, smoked on smoking machines under standard conditions, and the condensate collected. Subsequent mouse dermal bioassays showed such trends as the following (15–17): (1) Reconstituted tobacco sheets generally resulted in condensates less tumorigenic than standard control cigarettes. (2) High relative paper porosity seemed to decrease carcinogenic activity of condensate on mouse skin. (3) The addition of nitrates to aid combustion did not reduce condensate carcinogenicity as

was originally anticipated. (4) Different shred widths of tobacco did not appear to affect the carcinogenicity of condensate for mouse skin. (5) Cigarettes made from 100 percent tobacco stems resulted in condensate with the lowest carcinogenic activity for mouse skin. (6) In two cases, cigarettes made solely of tobacco leaves produced condensates so toxic that they caused the death of experimental mice before carcinogenicity could be ascertained. (7) The relative petroleum ether solubles in tobacco correlated with condensate carcinogenicity for mouse skin.

Several special processes are also possible in treating tobacco blends; for example, puffing or expanding (adding air or CO_2) and freeze drying. These methods can affect the cigarette weight, puff resistance, nicotine delivery, and in fact, the delivery of many components such as acetaldehyde and acrolein. Since puffing or expanding processes introduce air and effectively reduce the density of the cigarette, they constitute a form of dilution and tend to reduce the output of some substances. The burning rate is also affected, which in turn will change the yield and composition of some pyrolysis products. Freeze drying, for example, reduced nicotine and phenolics significantly in the experimental blend used, but produced about the same amounts of acetaldehyde, acrolein, and formaldehyde as did control blend cigarettes (15-17).

Possible approaches that plant scientists can take to modify tobacco leaf have been reviewed by Tso (26). The main objective of such research is to acquire the desired characteristics which will meet with acceptance of smokers and at the same time produce a less harmful tobacco (25). Modification may involve genetic and cultural modification, nitrogen fertilization technology, leaf and plant population, the physiological stage of topping, and pesticide treatments. Post-harvest modification is also possible, as leaf composition is markedly affected by the curing process, aging, or other treatment of cured leaves.

Other Tobacco Products

In contrast to cigarettes (see discussion on types and classes of tobacco) cigars are normally made of filler tobacco (bulk of cigar), binder tobacco (used to hold the shape), and wrapper tobacco (the outside layer or covering) (30). Wrappers are now being made increasingly from reconstituted tobacco products. Cigar tobaccos are generally air-cured, aged, and fermented. Pipe tobacco may be pure Burley or a blend of Burley with other tobaccos. A considerable amount of sweeteners and other additives is used to create a pleasing aroma and taste. Chewing tobacco is made of tobacco leaf (usually Burley, cigar, and bright) and is heavily sweetened. Snuff is powdered and flavored tobacco (usually dark air-cured and fire-cured).

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Summary

Tobacco has been cultivated and consumed in the civilized world for more than 300 years. It is an important economic crop and demands high production inputs, including energy. The United States is well known for its high quality tobacco and the application of modern technology to tobacco production. Extensive knowledge in tobacco science has been accumulated by intensive research effort, especially during the past 20 years. Recent advances in various areas of research related to tobacco and tobacco smoke have provided adequate basic information for improvement of production.

In plant research, there are means available for genetic, cultural, and post-harvest modification. Also, a new homogenized leaf curing process makes it possible to extract soluble proteins and to improve the smoking material at the same time.

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Smoke Formation

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, additives), and the filter (fiber material, plasticizer, draw resistance, 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-depleter 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*).

Weight of ash produced during puffs
+ Mainstream TPM weight
+ Mainstream gas phase weight
− Mainstream entrained gas weight
− Mainstream combustion oxygen weight
—————————————————————
= Weight of cigarette burned during puffs

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TABLE 12.—Percent distribution of cigarette smoke*

Material	Weight (mg/cigarette)	Weight of total effluent (%)
Particulate matter (inc. cond. H_2O)	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

*85 mm nonfilter cigarettes, 30 mm butt length, 10 puffs of 38.9 ml volume each.
SOURCE: Keith, C.H. (52).

TABLE 13.—Typical mainstream smoke mixture*

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

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

Mainstream Smoke Aerosol

The undiluted smoke as it leaves the cigarette butt contains up to 5 x 10^9 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 10^{12} 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 0.1 μ), 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 CO_2 increase linearly with ascending puff number. Leaves from the lower stalk positions generate significantly less CO and CO_2 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 CO_2 (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 CO_2 may be up to eight times as high. The CO and CO_2 values for the smoke of cigars are significantly higher than those for cigarette smoke, primarily because of the relatively unporous cigar wrapper (6).

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Nitrogen Oxides

Tobacco smoke is known to contain nitric oxide (NO) and trace amounts of nitrogen dioxide (NO_2) and nitrous oxide (N_2O). 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 NO_2 (64a); however, upon aging, NO in the smoke is quickly oxidized to NO_2 (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 µg 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 µg ammonia (as the ammonium ion) per cigarette and between 68 and 135 µg 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 ciliatoxic agent in cigarette smoke; however, its selective

reduction by charcoal filters, among other things, diminishes the inhibition of lung clearance of the cigarette smoke to a significant 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).

14—40

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,H-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_{12} 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: $\geq$ 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

cigarettes accounted for less than 40 percent of the total market in 1957 and comprise nearly 90 percent of today's market. Several parameters influence the "tar" yields of cigarettes. These include tobacco type, use of reconstituted tobacco sheets and expanded tobacco, packing density, cigarette paper, and filter tips. The effects of these and other factors are discussed in the next section.

The sidestream smoke of cigarettes has been determined in specially designed chambers which are under constant slow airflow during the collection procedure. In this case, the particulate matter is retained and measured on Cambridge fiber filter discs (100). For nonfilter cigarettes, the "tar" ratio in mainstream and sidestream smoke varies from 1:1.4 to 1:1.2; for low "tar" filter cigarettes this ratio can shift considerably in favor of sidestream smoke. The quantitative compositions of the two "tars," however, differ widely (as noted later in this section).

In 1972, the FTC reported "tar" yields for U.S. little cigars to range from 16.5 to 47.8 mg (92). All cigars weighing less than 1.36 g are considered "little cigars." When the tobacco of little cigars is wrapped in cigarette paper, the tar yield remains the same as or only slightly lower than that of little cigars with normal wrappers. This observation is quite different from that made for the CO yield. Here, the paper wrapper leads to a 30 to 50 percent CO reduction. Large cigars puffed under standard cigar-smoking conditions generally deliver more "tar" than cigarettes and little cigars because of their higher weight. Compared on the basis of gram-to-gram tobacco consumed, the cigar "tar" yield, however, is only 20 to 30 percent that of a cigarette (75, 100).

Nicotine and Minor Tobacco Alkaloids

Nicotine and the compounds derived from it contribute significantly to the organoleptic nature and toxicity of tobacco smoke and are considered a major factor in tobacco habituation. As in the case of "tar," the FTC reports the nicotine values for the smoke of U.S. cigarettes semiannually (0.05–2.50 mg)(23). The sales-weighted average of nicotine in the smoke of U.S. cigarettes has decreased from 2.5 mg in 1957 to 1.1 mg in 1976 (97). Similar observations were made for products of other countries (99). Figures 15 and 16 describe the trends of tar and nicotine in the United States.

The nicotine values for the smoke of U.S. little cigars were reported by the FTC in 1972 to vary between 0.52 and 3.11 mg (92). In general, the yield of nicotine in the smoke of a cigar is considerably higher than that in the smoke of a cigarette. However, on a per-gram-tobacco-smoked basis (or for a given smoke volume), the nicotine yield is significantly lower for cigars (20 to 40 percent) (75, 100). When one considers the physiological effects of nicotine, however, the comparison of the nicotine content of cigarette smoke with that of cigar smoke can

be misleading. In cigarette smoke, with the exception of French black tobacco cigarettes, nicotine is present in a protonated form, whereas in cigar smoke, nicotine is partially present in the more easily absorbed unprotonated form (2, 8, 34).
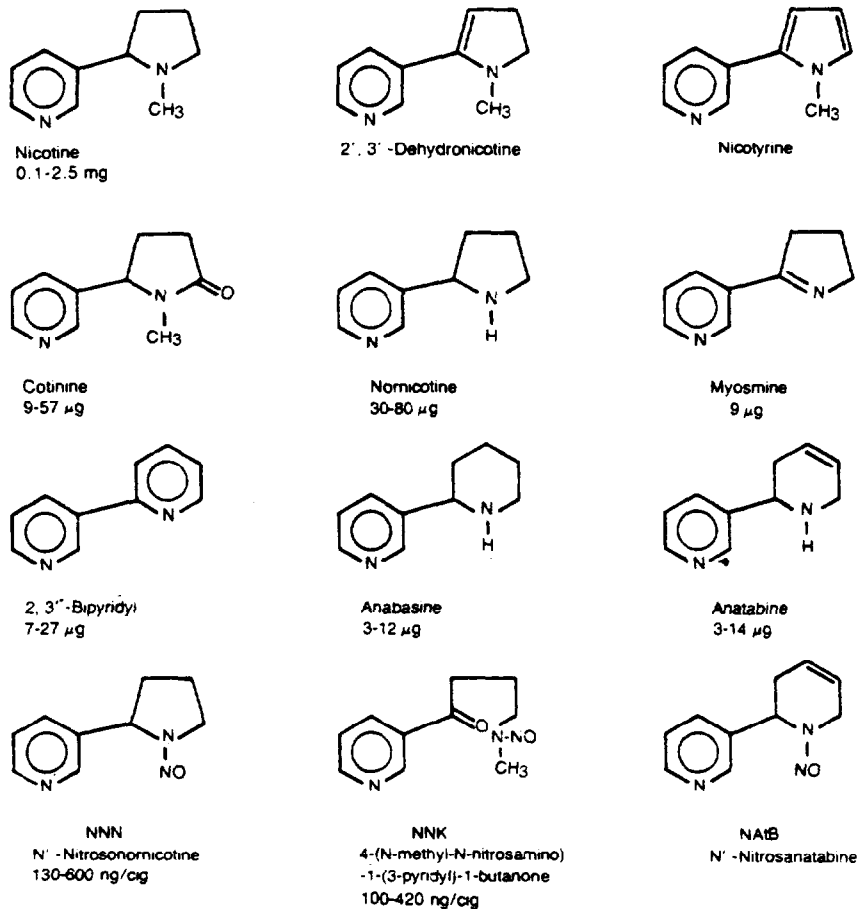
Depending on the *Nicotiana tabacum* variety, the nicotine content of the processed leaf can vary between 0.2 and 5.0 percent of the dry weight. The nicotine content of smoke tobaccos, however, varies generally between 1.0 and 2.0 percent, with values below 1.0 percent reported for certain low "tar" cigarettes. Because of the pharmacological effect of nicotine and its relatively high concentration in the tobacco, it is important to study the fate of tobacco nicotine during smoking. Studies with ^{14}C-labelled nicotine have shown that, in the case of the blended U.S. cigarette, 14 to 22 percent of the nicotine was transferred unchanged into mainstream smoke and 20 to 30 percent was found unchanged in the sidestream smoke (47, 80). Four to eight percent of the radioactivity in the mainstream smoke particulate matter was given by decomposition products of ^{14}C-nicotine. The major decomposition products identified were myosmine, bipyridyl (Figure 3), and pyridines. Despite the high transfer rate of intact nicotine into mainstream smoke and the low yield of (non-tumorigenic) decomposition products, one cannot exclude a contributory role of the thermal decomposition of nicotine towards the tumorigenicity of cigarette smoke. So far, it has been shown that nicotine may yield traces of the carcinogenic dibenzacridines, a dibenzocarbazole (93, 100), and tobacco specific nitrosamines (38).

The structural formulas of nicotine and of other tobacco alkaloids and of tobacco specific nitrosamines are presented in Figure 3, together with their concentrations in the mainstream smoke of cigarettes.

Nonvolatile N-Nitrosamines

During curing and fermentation of tobacco, specific nitrosamines can be formed by nitrosation of alkaloids, as was shown by identification of N'-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosoanatabine (NAtB) in processed tobacco leaves. The yield of these compounds depends on the concentration of the nitrate and alkaloids in the leaf. In the case of cigarette tobacco, NNN and NNK were found in concentrations between 0.3 and 7.0 ppm and 0.1 and 0.4 ppm, respectively. The reported values for cigar tobacco were for NNN, 3 to 45 ppm, and for NNK, 2 to 36 ppm. Since chewing of tobacco has been associated with an increased risk of cancer of the oral cavity and esophagus, high values of nitrosamines in chewing tobacco and snuff are of more than academic interest (NNN 2 to 90 ppm) (35, 38).

NNN, NNK, and NAtB have also been identified in the mainstream smoke of cigarettes (NNN, 0.14 to 3.70 µg/cigarette; NNK, 0.11 to 0.42

Nicotine
0.1-2.5 mg

2', 3'-Dehydronicotine

Nicotyrine

Cotinine
9-57 µg

Nornicotine
30-80 µg

Myosmine
9 µg

2, 3"-Bipyridyl
7-27 µg

Anabasine
3-12 µg

Anatabine
3-14 µg

NNN
N'-Nitrosonornicotine
130-600 ng/cig

NNK
4-(N-methyl-N-nitrosamino)
-1-(3-pyridyl)-1-butanone
100-420 ng/cig

NAtB
N'-Nitrosanatabine

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

14—46

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 ^{14}C-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., carbaryl)(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-

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, phytosterols, and alkaloids (*85*). The tobacco specific alkane fraction of the wax layer is made up of n-, iso-, anteiso-$C_{24}H_{50}$ to $C_{34}H_{70}$ 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 $C_{12}H_{26}$ to $C_{23}H_{48}$. 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_{32}) 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
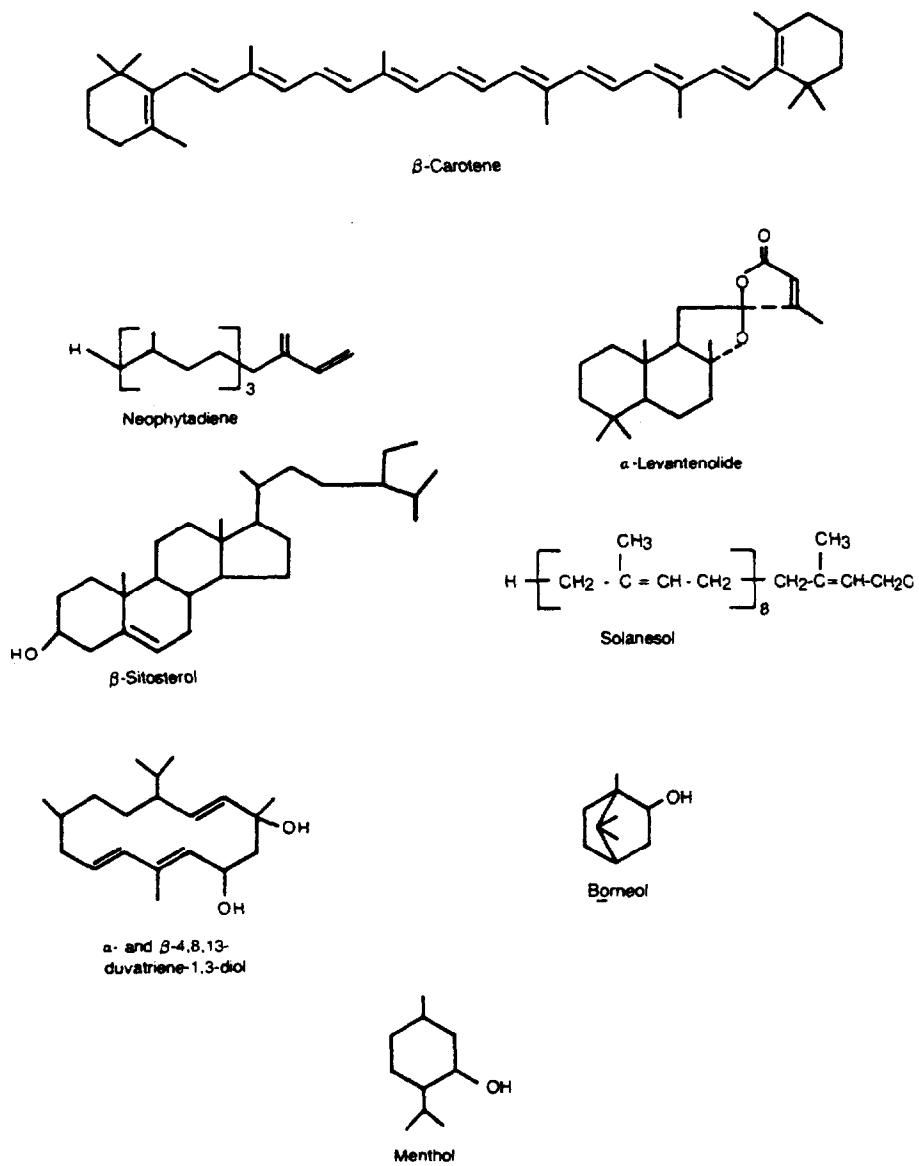
14—48

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 (21, 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 polycylic 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 μg/cigarette) and benzene itself (10 to 100 μg) as the

β-Carotene

Neophytadiene

α-Levantenolide

β-Sitosterol

Solanesol

a- and β-4,8,13-
duvatriene-1,3-diol

Borneol

Menthol

FIGURE 4.—Tobacco isoprenoids.

14—50

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 (*3*); thus, tobacco smoke contains less naphthalene (2.0 to 3.5 μg/cigarette) than toluene (20 to 150 μg/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.

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. Promotors 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 C,H-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 dibenzo(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.
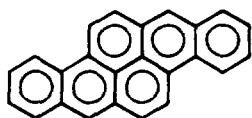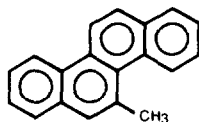
14—52

I. Complete Carcinogens
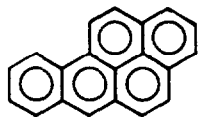
Benzo (a) pyrene (BaP)
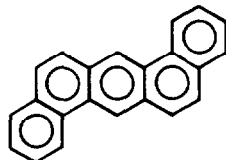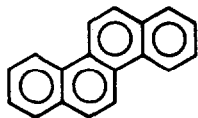
Dibenz (a,h) anthracene
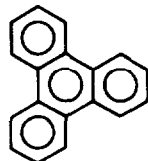
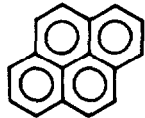Dibenzo (a,h) pyrene

5-Methylchrysene

II. Tumor Initiators
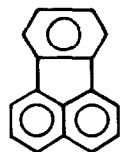
Chrysene

Benzo (e) pyrene

III. Cocarcinogens

Pyrene

Fluoranthene

Benzo (g,h,i) fluoranthene

FIGURE 5.—Some tumorigenic PAH in tobacco smoke.

TABLE 15.—Tumorigenic PAH in cigarette smoke[1]

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
Dibenzo(a,h)pyrene	+ +	pr[3]
Dibenzo(a,j)pyrene	+ +	pr[3]
Indeno(1, 2, 3-cd)pyrene	+	4
Benzo(c)phenanthrene	+	pr[3]
Benz(a)anthracene	+	40–70
Chrysene	- (+ ?)	40–60
Benzo(e)pyrene	- (+ ?)	5–40
2-, 3-Methylchrysene	+	7
1-, 6-Methylchrysene	–	10
2-Methylfluoranthene	+	30
3-Methylfluoranthene	?	40
Dibenz(a,c)anthracene	?	pr[3]
II. *Active as co-carcinogens*		
Pyrene	–	50–200
Methylpyrenes	–	50–300
Fluoranthene	–	100–260
Benzo(g,h,i)perylene	–	60

[1]Incomplete list.
[2]Relative carcinogenic activity on mouse skin.
[3]Present, but no quantitative data available.
SOURCE: Hoffman, D. (40).

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
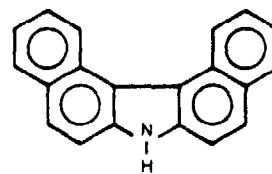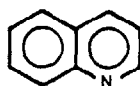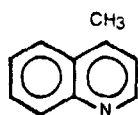
FIGURE 6.—Carcinogenic aza-arenes in tobacco smoke.
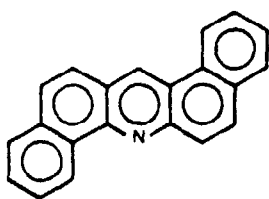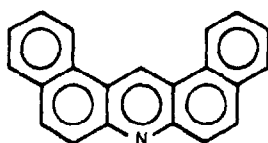
Dibenz (a.h) acridine

Dibenz (a.j) acridine

Dibenzo (c.g) carbazole

Quinoline

4-Methylquinoline

Phenanthridine