Chemistry and Toxicology

Dietrich Hoffmann and Ilse Hoffmann

HISTORICAL NOTES

Early information on the smoking of cigars originates from artifacts of the Mayas of the Yucatan region of Mexico. Smoking of tobacco was part of the religious rituals and political gatherings of the natives of the Yucatan peninsula as shown in the artwork on a pottery vessel from the 10th century (Figure 1) where a Maya smokes a string-tied cigar (Kingsborough, 1825). Five hundred years later, in 1492, when Christopher Columbus landed in America, he was presented with dried leaves of tobacco by the House of Arawaks. Columbus and his crew were thus the first Europeans who became acquainted with tobacco smoking. Early in the 16th century, Cortez confirmed that tobacco smoking was practiced by the Aztecs in Mexico. In addition, tobacco was grown in Cuba, Haiti, several of the West Indian Islands, and on the East coast of North America from Florida to Virginia (Tso, 1990).

The Mayan verb *sikar*, meaning to "smoke," became the Spanish noun *cigarro*. The form of cigar Columbus had first encountered was a long, thick bundle of twisted tobacco leaves wrapped in dried leaves of palm or maize. In 1541, the Cuban cigar appeared in Spain. The first person known to have grown tobacco in Europe was Jean Nicot, the French ambassador to Portugal. He introduced tobacco and tobacco smoke at the royal court of Paris, where Catherine de Medici and her son, King Charles IX, used it to treat migraine headaches (Jeffers and Gordon, 1996). In 1570, the botanist Jean Liebault was the first to grow tobacco in France; he gave the plant the scientific name *Herba Nicotiana*, in honor of Jean Nicot. However, the name tobacco, which is derived from the American Indians' word *tobacco*, remained in common use.

In 1828, the chemists, Posselt and Reimann of the University of Heidelberg, isolated nicotine as the major pharmacoactive ingredient in tobacco. In 1895, Pinner established the chemical structure of nicotine as that of 3-(1-methyl-2-pyrrolidinyl)pyridine.

THE CIGAR

Types and Definitions

There are many types of cigars on the market. The U.S. Department of the Treasury (1996) defines a cigar as "any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco," while a cigarette is defined as "any roll of tobacco wrapped in paper or in any substance not containing tobacco." In North America, and in many parts of Europe, there are at least four types of cigars, namely, little cigars, small cigars (also called cigarillos), regular cigars, and premium cigars (Figure 2). For taxation purposes, the U.S. Department of the Treasury (1996) differentiates only between small cigars, weighing not more than three pounds per thousand (≤ 1.36 g/cigar), and large cigars, weighing more than three pounds per thousand.

Figure 1
A man smoking a Maya's string-tied cigar depiected on a pottery vessel, dated 10th century or earlier, found in Mexico.

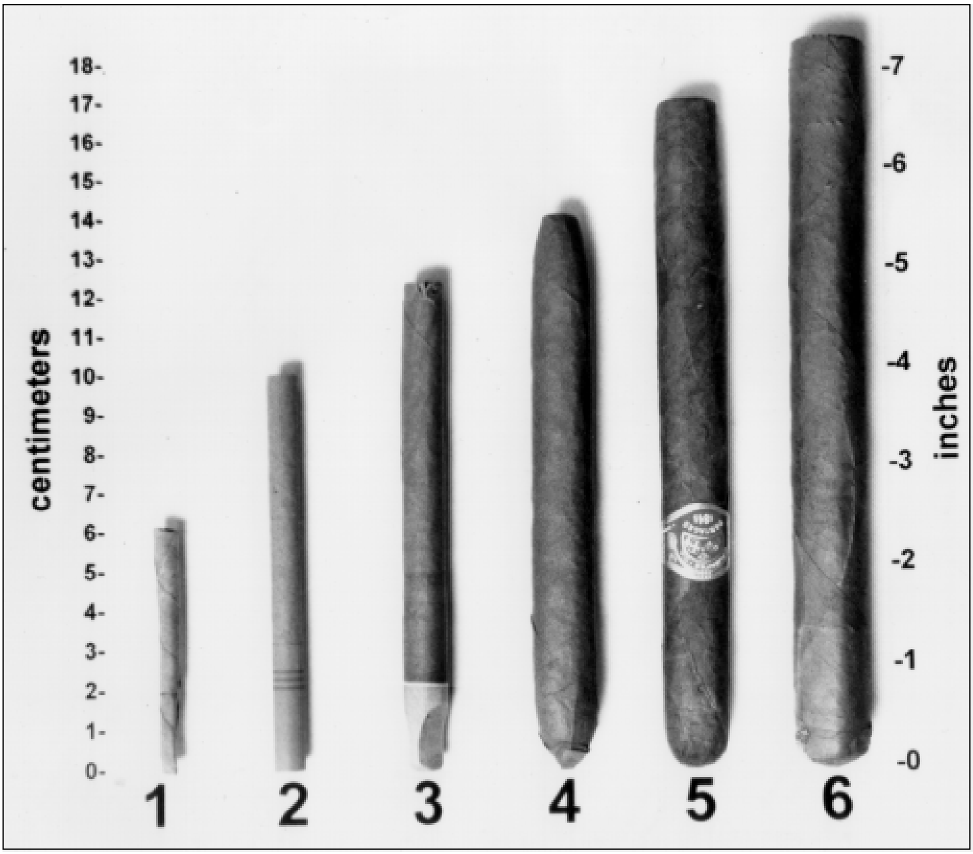
Courtesy of the General Research Division, The New York Public Library, Astor, Lenox, and Tilden Foundaitons.

In general, little cigars contain air-cured and fermented tobaccos. They are wrapped either in reconstituted tobacco or in cigarette paper that contains tobacco and/or tobacco extract. Some little cigars marketed in the U.S. have cellulose acetate filter tips and are shaped like cigarettes (length 70 - 100 mm, weight 0.9 - 1.3 g each; Hoffmann and Wynder, 1972).

The small cigars on the U.S. market have straight bodies, weigh between 1.3 and 2.5 g each, are 70 - 120 mm long, and are open on both ends. To some extent they are comparable to the *stumpen*, a form of cigar primarily smoked in Switzerland and some parts of Germany. In the Far East, small cigars, called cheroots, are made from heavy-bodied burley-type tobacco. The Indian cheroots are produced from light, air-cured tobacco (Voges, 1984). In Denmark and some other parts of Scandinavia, similar types of cigars are also called cheroots but like the small U.S. cigars, they are more akin to the Swiss *stumpen.*

Regular cigars appear on the market in various sizes and shapes. In the U.S., their dimensions are generally 110 - 150 mm in length, up to 17 mm in diameter, and they weigh between 5 and 17 g. Regular cigars are rolled to a tip, on at least one end. Some of them carry a 'banderole,' or decorative foil or paper strip, to indicate the brand's name (Wynder and Hoffmann, 1967; Brunnemann and Hoffmann, 1974a; Schmeltz et al., 1976a and 1976b; Voges, 1984). Many of the regular cigars on the U.S. market are machine-made; others are hand-rolled.

Figure 2
Types of cigars on the U.S. Market in 1996: (1) bidi (imported from India), (2) little cigar with filter tip, (3) small cigar with plastic mouth piece, (4) regular cigar, (5) and (6) premium cigar.



In recent years the popularity of premium cigars has increased in the United States. With diameters ranging from 12 to 23 mm and lengths between 12.7 and 21.4 cm, these cigars carry bands with an imprint of their brand name and/or manufacturer's name or logo. They are imported in large numbers from the Dominican Republic, Honduras, Mexico, Jamaica, and other countries (O'Hara, 1996). In 1996, the two most popular types of premium cigars on the U.S. market were the "Coronas" and the "Lonsdales." The recorded 96 brands of Coronas were between 12.7 and 15.2 cm (5 - 6 inches) long and ranged in price between $1.10 and $8.60 apiece. The 111 recorded brands of Lonsdales were between 15.2 and 17.8 cm (6 - 7 inches) long and sold for $1.50 to $11.00 per cigar (Cigar Aficionado, 1996).

Cigar Tobacco Tobacco belongs to the *Solanaceae* family. Primarily two species, *Nicotiana tabacum* and *Nicotiana rustica,* are used for the manufacture of chewing tobacco, oral and nasal snuff, cigarettes, cigars, and pipe tobacco.

Most of the tobacco products manufactured in North America, Western Europe, and Africa are made of *N. tabacum*. *N. rustica* is predominately used in South America, Russia, the former republics of the U.S.S.R., and Poland; and, to some extent, also in India and Turkey. Within the *N. tabacum* species, four types are commonly used: bright (Virginia), burley (Kentucky), Maryland, and Turkish (oriental) tobaccos. Bright tobaccos are flue-cured by drying with artificial heat; burley and Maryland tobaccos are air-cured; and Turkish tobaccos are sun-cured.

Cigars consist of a filler (the inner part of the cigar), a binder, and a wrapper. The filler, binder, and wrapper of small cigars, regular cigars, and premium cigars are all made with air-cured and fermented tobaccos (Cornell et al., 1979). Since the mid-fifties, the binders and/or wrappers of many of the regular brands (but not of premium brands) are made from reconstituted cigar tobacco (Moshy, 1967). In general, about 85 percent of the weight of a cigar is contributed by the filler, 10 percent by the binder, and 5 percent by the wrapper (Frankenburg and Gottscho, 1952).

The air-curing process of burley and Maryland tobaccos is characterized by slow, gradual drying of the leaf. Usually, the whole tobacco plant is cut off at ground level and hung in sheds or barns. However, in the case of tobaccos used for many regular cigars and premium cigars, the leaves are primed and hung individually on strings in sheds or barns for air-curing. It is important to ensure ample air flow through the barns during this process. Sometimes it is necessary to raise the temperature in the barns using charcoal fires, thereby creating a relative humidity of 65 - 75 percent. During air-curing, tobacco leaves normally reach the yellow stage 10 - 12 days after harvesting, and the brown stage after another 6 or 7 days. To complete the air-curing process requires 30 - 40 days. During this time, 80 - 85 percent of the water content of the leaves is lost. The total nitrogen content is reduced by about 30 percent and the protein-nitrogen content by about 50 percent; however, the percentage of nitrate nitrogen doubles, and the nicotine content remains practically unchanged. Following air-curing, the leaves are aged for up to two years, or even longer. During this time, the nicotine content is reduced by 30 - 50 percent, whereas protein, ammonia, and nitrate nitrogen contents generally remain unchanged (Wolf, 1967).

To become cigar tobacco, the leaves need to be fermented. After about 1 year of storage and aging, the leaves are placed in special rooms for fermentation at about 45°C and a relative humidity of 60 percent. After 3 - 5 weeks, the leaves are removed from the rooms, repacked, and returned. The repacking process is repeated several times to induce “sweating.” The baled leaves are occasionally slightly moistened. The temperature in the center of the bales may reach up to 58°C. During the fermentation, chemical and bacterial reactions lead to the formation of carbon dioxide, ammonia, water, and various volatile compounds. Carbohydrates in the leaves are reduced by 50 - 70 percent, organic acids by up to 30 percent, and a major portion of the polyphenols is degraded. The degradation of polyphenols during curing causes the browning of the leaves; whereas during fermentation, their degradation ensures the oxygenation of several leaf components. The pH of the fermented tobacco is slightly alkaline (Wolf, 1967; Wiernik et al., 1995). During curing and fermentation of air-cured tobacco, nitrate is partially reduced to nitrite, primarily by microbal action. This contributes to the *N*-nitrosation of nicotine, converting it into the highly carcinogenic, tobacco-specific *N*-nitrosamines (TSNA), *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Burton et al., 1992; Hoffmann et al., 1994; Wiernik et al., 1995).

Manufacture of Cigars

Cigars consist of filler, binder, and wrapper; all of which are air-cured and fermented. In recent decades, some brands of regular cigars (though not premium cigars) have used reconstituted cigar tobacco as binder, wrapper, or both (Moshy, 1967; Halter and Ito, 1980). Cigars are either hand-rolled (Jeffers and Gordon, 1996) or machine-made (Van der Boor, 1996). The flavor and aroma of cigars and their smoke are, in large measure, the results of precisely controlled fermentation of the tobacco. Most little cigars are machine-made, much like cigarettes, except that fermented cigar tobacco, not blends of cured tobaccos are used (20, 30, or 50 cuts per inch); the little cigars have wrappers which contain tobacco.

CHEMISTRY OF CIGAR TOBACCO

Processed tobacco contains at least 3,050 different compounds. Table 1 lists the major groups of compounds that have been identified in tobacco (Roberts, 1988). Most of these are already present in the green tobacco leaf, others are formed during curing, aging, and fermentation. Although only a portion of the 3,050 compounds has been identified specifically in cigar tobacco, one may assume that the full spectrum of compounds is present in cigar tobacco, albeit in many cases, at different levels of concentration than are present in cigarette tobaccos. Exceptions to the qualitatively comparable constituents of cigar and cigarette tobaccos are agents such as pesticides, that are applied to tobacco during cultivation of the plant, and agents that are added during the processing of the tobaccos.

In the case of the insect control agents, the last reports on organic chlorinated hydrocarbons were published in the 1960s. DDT concentration was significantly higher in cigar tobacco (10.0 - 53.0 µg/g) than in cigarette tobacco (2.0 - 6.0 µg/g), whereas DDD and endrin concentrations in cigar tobaccos (10 - 15 µg/g and 0.0 - 0.5 ppm) and cigarette tobaccos (12 - 23 µg/g and < 0.5 - 2 ppm) were comparable (Lawson et al., 1964). However, in the seventies, chlorinated pesticides were banned for use on tobacco; thus, their concentrations in U.S. tobacco declined by > 98 percent by 1994 (Djordjevic et al., 1995b). An overview of the pesticides currently applied to U.S. tobacco plants and a discussion of their residues on tobacco was presented by Sheets (1991).

In general, flavor additives are not applied to cigar tobacco which is quite different from the treatment of tobacco formulated for cigarettes, especially in the case of filter cigarettes designed to yield low nicotine emission (Doull et al., 1994; Hoffmann and Hoffmann, 1997). It is also different from pipe tobacco formulation (LaVoie et al., 1985) and possibly from the formulation of tobacco for small cigars. Furthermore, it is unlikely that plasticizers are

Table 1
Compounds identified in tobacco and smoke

Functional Groups	No. in Tobacco	No. in Smoke	No. in Tobacco and Smoke
Caboxylic Acids	450	69	140
Amino Acids	95	18	16
Lactones	129	135	39
Esters	529	456	314
Amines & Imines	205	227	32
Anhydrides	10	10	4
Aldehydes	111	106	48
Carbohydrates	138	30	12
Nitriles	4	101	4
Ketones	348	461	122
Alcohols	334	157	69
Phenols	58	188	40
Amines	65	150	37
Sulfur Compounds	3	37	2
N-Heterocycles:			
Pyridines	63	324	46
Pyrroles & Indoles	9	88	3
Pyrazines	21	55	18
Non-aromatics	13	43	7
Polycyclic Aromatics	1	36	0
Others	4	50	2
Ethers	53	88	15
Hydrocarbons:			
Saturated Aliphatics	58	113	44
Unsaturated Aliphatics	338	178	10
Monocyclic Aliphatics	33	138	25
Polycyclic Aliphatics	55	317	35
Miscellaneous	112	110	19
Inorganics & Metals	105	111	69

Source: D.L. Roberts, 1988

used for manufacturing small, regular and premium cigars which do not contain reconstituted tobacco, whereas plasticizers (e.g., glyceryl triacetate, triethylene glycol diacetate) are applied to filter tips in the production of little cigars. When reconstituted tobacco is chosen as a binder and/or wrapper for regular cigars, such cigars will contain plasticizers and other tobacco treatment products in addition to humectants, adhesives, and/or inorganic additives (Moshy, 1967).

Distinct quantitative differences between cigar and cigarette tobaccos are primarily related to the long aging and fermentation process of cigar tobacco. Table 2 shows some of the distinct differences for a select number of compounds as they occur in cigar tobacco and in the four major types of cigarette tobaccos. Cigar tobacco contains only traces of polyphenols

Table 2
Comparison of some selected components in the tobacco of cigars and of four cigarette Tobacco Types (% of dry weight of tobacco)

	Type of Tobacco				
Component	Cigar	Burley	Maryland	Bright	Oriental
Nitrate	1.4 - 2.1	1.4 - 1.7	0.9	< 0.15	< 0.1
pH	6.9 - 7.8	5.2 - 7.5	5.3 - 7.0	4.4 - 5.7	4.9 - 5.3
Reducing Sugars	0.9 - 2.7	1.5 - 3.0	1.2	7.0 - 25.0	5.5
Total Polyphenols	< 0.1	2.0	1.6	5.1	4.5
Nicotine	0.6 - 1.7	2.0 - 2.9	1.1 - 1.4	1.2 - 1.9	1.1
Paraffins	0.3 - 0.32	0.34 - 0.39	0.34 - 0.41	0.24 - 0.28	0.37
Neophytadiene	0.4 - 0.8	0.4	0.40	0.3	0.2
Phytosterols	0.14 - 0.16	0.3 - 0.39	0.38	0.3 - 0.45	0.26
Citric Acid	5.5 - 6.0	8.22	2.98	0.78	1.03
Oxalic Acid	3.3 - 3.6	3.04	2.79	0.81	3.16
Maleic Acid	1.5 - 1.8	6.75	2.43	2.83	3.87

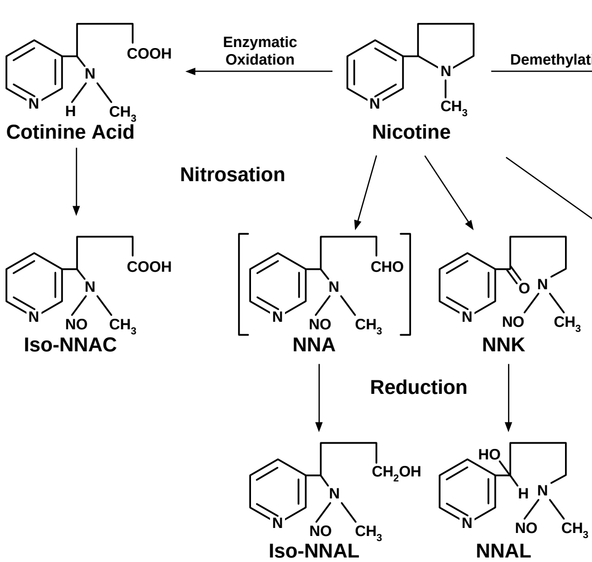
References: Wolf, 1967; Hoffmann and Wynder, 1972; Schmeltz et al., 1976a and 1976b; Tso, 1990.

(< 0.1 percent; Table 2) compared to cigarette tobaccos (1.6 - 5.1 percent). The nitrate content of cigar tobacco is relatively high (1.4 - 2.1 percent versus. < 0.1 - 1.7 percent in U.S. cigarette tobacco blends) and the amounts of phytosterols are lower in cigar tobacco (0.14 - 0.16 percent versus. 0.26 - 0.45 percent). In respect to the nitrate content,
the pH of a suspension of tobacco in water, and the percentage of reducing sugars, cigar tobacco is comparable to the two types of air-cured cigarette tobaccos, namely, burley and Maryland (Wolf, 1967; Hoffmann and Wynder, 1972; Tso, 1990; Schmeltz et al., 1976a and 1976b).

During the processing of tobacco, especially during air-curing and aging, nitrate is partially reduced to nitrite (Burton et al., 1992; Hoffmann et al., 1994; Wiernik et al., 1995). Nitrite is a strong *N*-nitrosating agent of secondary and tertiary amines. Consequently, during these stages of tobacco processing, *N*-nitrosamines are formed (Hoffmann et al., 1994). In tobacco, we distinguish between volatile nitrosamines (VA), nonvolatile nitrosamines (NVA), nitrosamino acids (NA), and tobacco-specific *N*-nitrosamines (TSNA). The latter group is of significance for several reasons. TSNA are formed by *N*-nitrosation of nicotine and of the minor *Nicotiana* alkaloids, nornicotine, anatabine, and anabasine (Figure 3). Among the seven TSNA, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N′*-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are strong carcinogens in mice, rats, hamsters, and mink. *N′*-Nitrosoanabasine (NAB) is weakly carcinogenic, while *N′*-nitrosoanatabine (NAT), 4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol (iso-NNAL), and 4-(methylnitrosamino)-4-(3-pyridyl)butyric acid (iso-NNAC) are inactive in carcinogenesis assays (Hoffmann et al., 1994). Furthermore, in the

Figure 3

Formation of tobacco-specific N-nitrosamines. Iso-NNAC, 4-(methylnitrosamino)-4-(3-pyridyl)-butyric acid; NNA, 4-(methylnitrosamino)-4-(3-pyridyl) butyric aldehyde; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; NAT, N′-nitrosoamatabine; NAB, N′-nitrosoanabasine; iso-NNAL, 4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol; NNA, 4-(methylnitrosamino)-4-(3-pyridyl)-1-(3-pyridyl)-1-(3-pyridyl)-1-butanol



Source: Hoffmann et al., 1994.

smoke of a nonfilter cigarette, about 45 percent of NNN originates by transfer from the tobacco, whereas the remainder is pyrosynthesized during smoking (Hoffmann et al., 1977). Between 23 percent and 35 percent of the NNK in smoke originates from the tobacco by transfer (Adams et al., 1983). NNN in cigar tobacco is present at levels of 3.0 - 10.7 µg/g, in the tobacco of little cigars at 11.1 - 13.0 µg/g, in tobacco of nonfilter cigarettes at 1.5 - 2.2 µg/g, and in tobacco of filter cigarettes at 5.0 - 6.6 µg/g. NNK levels in the four tobacco types are 1.2 - 1.3 µg/g, 3.5 - 4.5 µg/g, 0.5 - 0.8 µg/g, and 0.4 - 1.0 µg/g, respectively (Brunnemann et al., 1983). During fermentation of cigar tobacco, a small portion of nicotine is converted into 2,3-dihydronicotine, which easily forms 4-methylamino-1-(3-pyridyl)-1-butanone (Frankenburg et al., 1958). The latter, a secondary amine, is rapidly *N*-nitrosated to NNK. This compound and the higher nitrate levels in cigars may explain why more NNK is formed in little and regular cigars than during the processing of cigarette tobacco.

Table 3 presents data obtained in a comparative study of the concentrations of nicotine, nitrate, volatile nitrosamines (VNA), nonvolatile nitrosamines (NVNA), and TSNA in cigar and cigarette tobacco (Brunnemann et al., 1983). All seven of the VNA identified are carcinogenic in mice, rats, and/or hamsters. The nonvolatile nitrosoproline is neither carcinogenic in rats nor in hamsters, while *N*-nitrosodiethanolamine (NDELA) does cause cancer in

Table 3
Nicotine nitrate and N-nitrosamines in the tobacco of U.S. cigars little cigars, and nonfilter and filter cigarettes (ng/g)

Compound	Little Cigars	Nonfilter Cigars	Filter Cigarettes	Cigarettes
Nicotine, %	1.10	1.66 - 1.72	1.81 - 2.05	1.45 - 2.04
Nitrate, %	1.98	0.74 - 0.89	0.7 - 1.08	0.81 - 1.23
Volatile Nitrosamines				
Nitrosodimethylamine	n.dt.	43	250 - 280	n. dt. - 6.7
Nitrosodiethylamine	3.2	11	n. dt. - 47	n. dt. - 2.0
Nitrosodi-n-propylamine	11.8	nd	n. dt.	n. dt. - 2.3
Nitrosodi-n-butylamine	0.9	nd	n. dt. - 65	n. dt.
Nitrosopiperidine	22	nd	5.5 - 13.3	n. dt. - 7.0
Nitrosopyrrolidine	20	19	n. dt. - 4.9	n. dt. - 9.9
Nitrosomorpholine	44	nd	3.7 - 4.1	n. dt. - 10.0
Non-Volatile Nitrosamines				
Nitrosodiethanolamine	108	420	115	194
Nitrosoproline	1130	nd	880 - 1200	1450 - 2300
Tobacco-Specific Nitrosamines				
N^1-Nitrosonornicotine	2940	4500	1830 - 1960	1940 - 3200
Total TSNA	4780	9300	3610 - 4090	3730 - 8900

Abbreviations: nd, not determined; n. dt., not detected.
Source: Brunnemann and Hoffmann, 1981; Brunnemann et al., 1983.

mice, rats, and hamsters. The concentrations of the VNA and TSNA are somewhat higher in cigar tobaccos than in cigarette tobaccos. Since the nitrate content of the tobaccos of the little cigars tested was not exceptionally high (0.74 - 0.89 percent), other factors must be correlated with these high NDELA and TSNA values.

As already mentioned, tobacco also contains nitrosamino acids. The noncarcinogenic *N*-nitrosoproline and *N*-nitrosopipecolic acid belong to this group. In addition, cigarette tobaccos were found to contain the carcinogenic *N*-nitrososarcosine, 3-(methylnitrosamino)propionic acid, and 4-(methylnitrosamino)butyric acid (Djordjevic et al., 1989). Cigar tobacco has not yet been analyzed for these nitrosamino acids.

Cigar tobaccos, like other types of processed tobaccos, contain at least 28 metals and more than ten metalloids (Wynder and Hoffmann, 1967; Iskander et al., 1986). Their concentrations range from 5,300 to 97,000 µg calcium/g tobacco to trace amounts, as in the case of mercury (0.05 µg/g tobacco) (Wynder and Hoffmann, 1967; Andren and Harriss, 1971). Most of the metals and metalloids are essential elements for the tobacco plant. Others, such as lead, arsenic, and mercury, are trace contaminants. Small portions, at most a few percent of the metals and metalloids, transfer from the tobacco into the smoke. Among those that transfer into the smoke and are thus inhaled, the International Agency for Research on Cancer (1987) considers arsenic, beryllium, chromium, nickel, and cadmium as human carcinogens (IARC, 1993a, 1993b).

Like all types of tobacco, cigar tobacco contains, or may contain, radioactive elements such as radium-226 and polonium-210 at concentrations ranging from 0.1 - 0.47 and 0.18 - 0.46 pCi/g cigar tobacco respectively) (Tso et al., 1966a). Phosphate fertilizers are the major source of these radioelements (Tso et al., 1966b); minor contributions come from airborne particles carrying lead-210 and polonium-210. These particles are trapped by the trichomes on the undersides of the tobacco leaves (Martell, 1974). A minor amount of polonium-210 transfers into the mainstream smoke and is thus inhaled by the smokers. The U.S. National Council on Radiation Protection and Measurement (1987) ascribes about 1 percent of the risk for lung cancer after 50 years of cigarette smoking to the role of polonium-210 inhaled as a tobacco smoke constituent.

CHEMISTRY AND ANALYSIS OF MAINSTREAM CIGAR SMOKE

Smoking Conditions

It is one of the objectives of tobacco-related research to design smoking devices that can simulate human smoking patterns under reproducible conditions. Smoking instruments that are widely accepted today are piston-type machines which generate puff profiles that simulate the puff profiles of smokers (Wynder and Hoffmann, 1967). For the smoking of cigarettes by machines, the U.S. Federal Trade Commission (FTC) (Pillsbury et al., 1969) adopted and modified a method that was initially devised by Bradford et al. in 1936. This method employs, as standard smoking conditions, one puff per minute, of two-seconds duration with a volume of 35 ml; the butt length is 23 mm for nonfilter cigarettes and filter length plus overwrap, plus 3 mm, for filter cigarettes (Table 4). The U.K., Germany, and the Cooperative Center for Scientific Research Relative to Tobacco (Centre De Cooperation Pour Les Recherches Scientifiques Relatives Au Tabac, CORESTA) in Paris, France, developed similar standard smoking parameters (Brunnemann et al., 1976a). The FTC smoking schedule has also been employed for the determination of "tar," nicotine, carbon monoxide, and other smoke constituents in the mainstream smoke of little cigars (Hoffmann and Wynder, 1972; Schmeltz et al., 1976a).

In the course of smoke-uptake analyses, it soon became clear that the employed machine-smoking conditions do not simulate the smoking habits of consumers of filter cigarettes; most certainly they are not even close to the average smoking parameters observed for smokers of filter cigarettes delivering low levels ≤(1.2 mg/cigarette, according to the FTC method) of nicotine (Russell, 1980a; Herning et al., 1981; Fagerström, 1982; Haley et al., 1985). With a recently developed "tobacco smoke inhalation testing system," it has been shown that smokers of cigarettes with low nicotine yields ≤(1.2 mg/cigarette according to FTC method) titrate nicotine uptake by taking, on average, 12 ± 2.7 puffs per cigarette (FTC 10) with average puff

[1]The scientific definition of "tar" is the total particulate matter collected by a Cambridge filter after subtacting moisture and nicotine. (SG Report 1972, Chapter 9)

Table 4
Standard conditions for machine smoking of cigars, cigarettes, and pipe

Parameters	Cigars (CORESTA)[2]	Cigarettes (FTC)[1,4]	Pipes (CORESTA)[3]
Weight	2.5 - 8.0 g	0.9 - 1.1 g	1.2 g (filling)
Puff:			
Frequency	1/40 seconds	1/60 seconds	1/20 seconds
Duration (sec.)	1.5	2	2
Volume (ml)	40	35	50
Butt length (mm)	33	23 nonfilter	1.0 g burned

[1]Pillsbury et al., 1969; [2]International Committee for Cigar Smoking, 1974; [3]Miller, 1963; [4]Little cigars are smoked as cigarettes.

volumes of 52 ± 5.7 ml (FTC 35 ml), puff durations of 1.7 ± 0.24 seconds (FTC 2.0 seconds), every 28.5 ± 10.3 seconds (FTC 58 seconds). When operated with the same parameters that were determined for individual smokers, a smoking machine produced smoke yields per cigarette of 28 - 40 mg "tar" (FTC 11 - 14 mg) and 2.1 - 2.5 mg nicotine (FTC 0.9 - 1.0 mg). Smoke emissions of the carcinogenic B*a*P were 23.2 - 25.5 ng (FTC 11.9 - 21.9 ng) and those of NNK were 30.1 - 33.9 ng (FTC 14.4 - 14.9 ng) per cigarette (Djordjevic et al., 1995a).

Today, more than 97 percent of all cigarettes in the U.S. have filter tips (Creek et al., 1994) and about 75 percent of these give FTC-measured nicotine yields of ≤ 1.2 mg/cigarette. The FTC data for "tar," nicotine, and carbon monoxide are, therefore, of limited usefulness and can, at most, compare relative smoke yields of commercial cigarettes generated under the FTC standardized smoking conditions.

Rickert et al. (1985) examined the delivery of "tar," nicotine and CO per liter of smoke for different tobacco products. They found that the mean yields per liter of smoke were highest for small cigars followed by hand-rolled and manufactured cigarettes and were lowest for large cigars. Total delivery was greatest for large cigars because of their larger amount of tobacco.

So far, only a study by Miller (1963) has been concerned with a standardized method for pipe smoking. The pipe is filled with 1.2 g tobacco and is smoked by taking five puffs per minute, of two-seconds duration and a 50-ml volume per puff. Miller also determined nicotine in the tobacco and the smoke yields of the tobaccos from a filter cigarette (1.58 percent nicotine) and two pipe tobaccos (1.52 percent and 1.30 percent nicotine), all smoked in a pipe bowl. Then, smoking 1.0 g of the tobacco from a filter cigarette under the pipe smoking conditions, he found 59.5 mg "tar," 7.15 mg nicotine, and 1.36 vol. % CO, whereas the pipe tobaccos gave 53.3 and 56.4 mg "tar", 5.18 and 6.12 mg nicotine, and 1.04 and 1.10 vol% CO. When the filter cigarette tobacco was smoked in a cigarette with such standard cigarette-smoking conditions, the yields for the 1 g of tobacco smoked were: 24.1 mg "tar,"

*Mainstream smoke (MS) is the smoke a smoker draws into his mouth from the butt end or mouth piece of a cigar, cigarette, or pipe. Sidestream smoke (SS) is the smoke emitted form the burning cone of a cigar or cigarette, or pipe during the interval between puffs. (SG Report 1979 Chapter 14)

1.63 mg nicotine, and 4.89 vol% CO. Clearly, pipe smoking produces much higher yields of "tar" and nicotine per gram of tobacco than cigarette smoking.

It has been reported that with increasing number of puffs per given cigar, and also with increasing puff volume per given unit of time (puff velocity), the amount of tobacco burned rises linearly (Rice and Scherbak, 1976). CORESTA developed a standard smoking method for cigars with the following parameters: one puff of 20 ml volume is taken during 1.5 seconds every 40 seconds. The cigars are smoked to a butt length of 33 mm. In 1974, the International Committee for Cigar Smoke Study of CORESTA chose these smoking parameters as an average of the observations made on cigar smokers in France, Germany, the U.S., and the U.K. The smoke yields for cigars reported in the literature since 1974 are based on the CORESTA method (Table 4). However, for smoke analyses of little cigars, the cigarette-smoking parameters of the FTC are applied. To date, the testing of the actual smoking parameters of cigar smokers by a computer-assisted instrument has not been reported. Table 4a presents the dimensions and yield characteristics of cigarettes, little cigars, large cigars, and premium cigars smoked under these standardized machine smoking conditions.

Physicochemical Nature of Cigar Smoke

Tobacco smoking, like the burning of all organic matter, is a process of incomplete combustion governed by several in air factors relating to the combustibility of certain leaf components (such as laminae, ribs, and stems), insufficient supply of oxygen, and the existence of a temperature gradient in the burning cone.

At least three types of reactions occur simultaneously during smoking: pyrolysis, pyrosynthesis, and distillation. The process of tobacco burning leads to thermal degradation, in which organic matter is broken down into smaller molecules (pyrolysis). The newly formed fragments, or radicals, are often unstable and may recombine with identical and/or other radicals to form components that were not originally present in tobacco. This process is called pyrosynthesis. Distillation of certain compounds from the tobacco into the smoke is the third process occurring during smoking. Compounds such as nicotine and some low-molecular-weight terpenes participate in this third process. They decompose only partially (Osdene, 1976). Some of the metals transfer into the smoke stream while entrained in microfragments of ash (Wynder and Hoffmann, 1967). It has been suggested that the presence of high-molecular-weight pigments and other high-molecular-weight components in tobacco smoke is due to the sharp thermal gradient behind the burning cone which leads to cellular rupture, thereby expelling these compounds into the smoke stream where they form the nuclei of the smoke particles (Stedman et al., 1966).

The smoke from a burning tobacco product is divided into the mainstream smoke and the sidestream smoke. The heat produced during the burning of one gram of tobacco is estimated to be 4.5 - 5.0 kcal. The temperature in the burning cone of a cigar reaches 930°C, in that of a cigarette up to 910°C; it

Table 4a

Smoke yields of leading U.S. cigarettes[a] without and with filter tips, little cigars with filter tips, cigars[b], and premium cigars[b] 1997

Parameters	Pall Mall Non-filter Cigarettes	Marlboro Filter Cigarettes	Swisher Sweets Little Cigars	King Edward Cigars	Macanudo Premium Cigars
Length (mm)	85	85	100	138	176
Weight (g)	1.1	1.0	1.24	8.06	8.01
Puff (No)	11	10	18.5	89.7	119.4
Total Smoke (L)	0.385	0.35	0.4	1.8	2.4
"Tar" (mg)	26	16	24	37	44
CO (mg)	18	14	38	96	97
Nicotine (mg)	1.7	1.1	3.8	9.8	13.3
BaP (ng)	20	16	26.2	96.0	97.4
NNN (ng)	280	200	595	1225	1225
NNK (ng)	160	130	310	1200	1145

[a]The cigarettes were smoked under FTC conditions: 1 puff/min, 35 ml, 2-second puff duration butt length NF, 23 mm; F., 29 mm. (FTC) Pillsbury et al., 1969

[b]Little cigars, cigars; and premium cigars were smoked under the conditions of the International Committee for Cigar Smoke Study (ICCSS): 1 puff/40 seconds, 20 ml, 1.5-second puff duration, butt length 33 mm. Values are averages of 3 runs. (ICCSS) International Committee for Cigar Smoke Study, 1974.

Abbreviations: BaP, Benzo (*a*) pyrene; NNN, N^1-nitrosonornicotine; NNK, 4-(methylnitrosamino) -1-(3-pyridyl)-1-butanone.

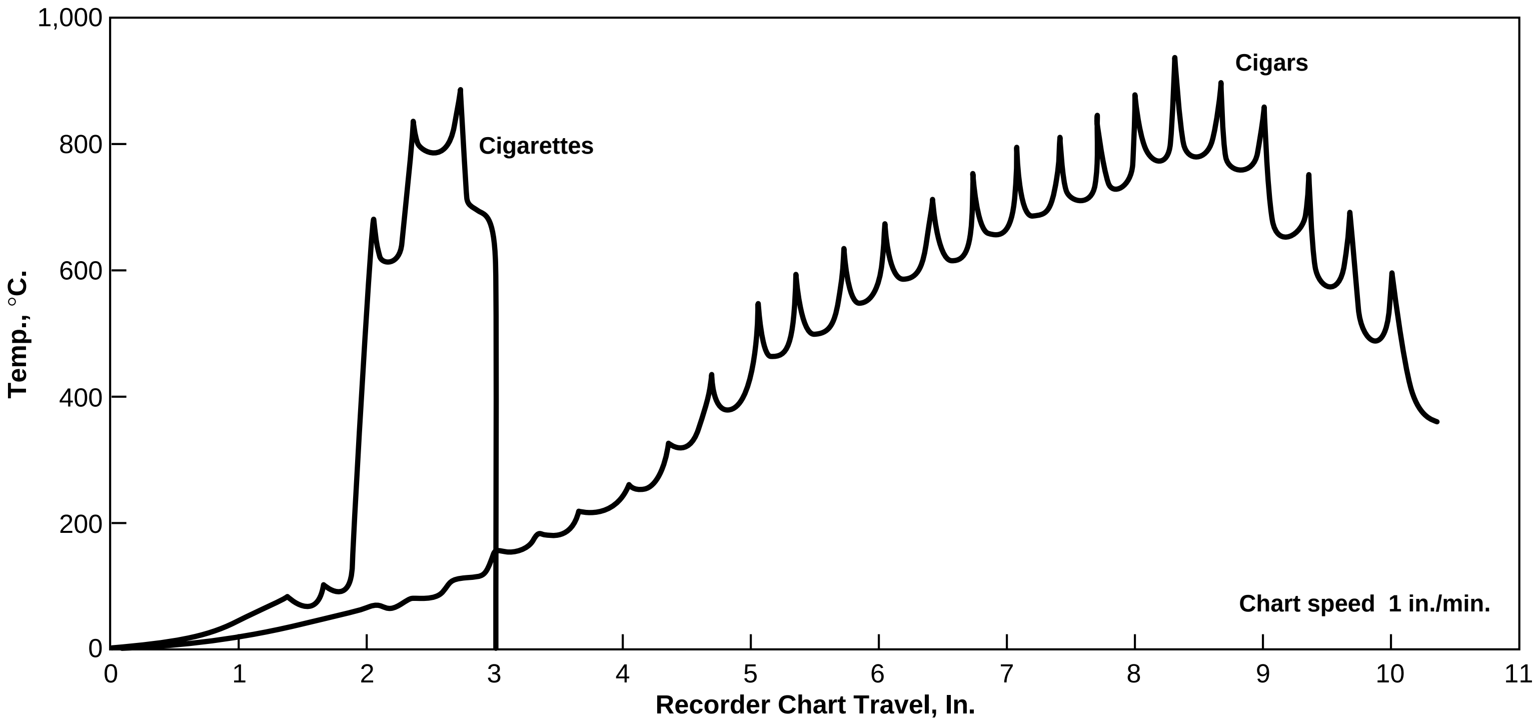
Source: Unpublished data Hoffmann, D. American Health Foundation

decreases to 820°C between puffs (Figure 4) (Touey and Mumpower, 1957a; 1957b). Taking four puffs per minute with volumes of 10, 15, or 20 ml, Adams (1968) reported that peak temperatures of 1,117°C and 1,290°C occur during smoking of small cigars and 1,139°C and 1,160°C have been measured for large cigars. Using cigar tobacco in a cigarette, peak temperatures of 944°C and 970°C were recorded (Table 5).

The temperature of the mainstream smoke emitting from the mouthpiece with early puffs from cigars and cigarettes lies only a few degrees above room temperature (25° - 30°C). The temperature of subsequent puffs rises gradually above 50°C and can even reach 75°C with the last puff of a cigar that is smoked down to 10 mm (Borowski and Seehofer, 1962).

In general, the pH of the whole smoke of cigars increases from the early puffs when it is ~ 6.5, to ~ 8.0 for the last (35th) puff. The pH of the puffs of small cigars increases from 6.5 to 7.4 (14th puff), that of little cigars from pH 6.5 to 7.5 (9th puff), and that of cigarettes decreases from pH 6.0 to 5.7 (11th puff) (Table 5). This phenomenon is of major significance, since above pH 6.0 the smoke contains unprotonated (free) nicotine. Thus, the last puff of a cigar with a pH of 8.0 contains about 50 percent unprotonated

Figure 4
Temperature profiles in the burning cones of cigarettes and cigars



Source: Touey and Mumpower, 1951a.

Table 5
Comparison of some physicochemical parameters of the mainstream smoke of cigars and cigarettes

Parameters		Cigars	Little Cigars	Cigarettes
pH[1]	3rd Puff	6.5	6.5	6.0
	Last Puff	8.0	7.4	5.7
Temperature[2]				
	During puffing, range, °C	1139° - 1160°	n. a.	944 - 970
	Between puffs, °C	820	n. a.	800
Reducing Activity[3] (units of DCIP)				
	Particulate Phase	45.0	n. a.	108.3
	Gas Phase	10.1	n. a.	4.9

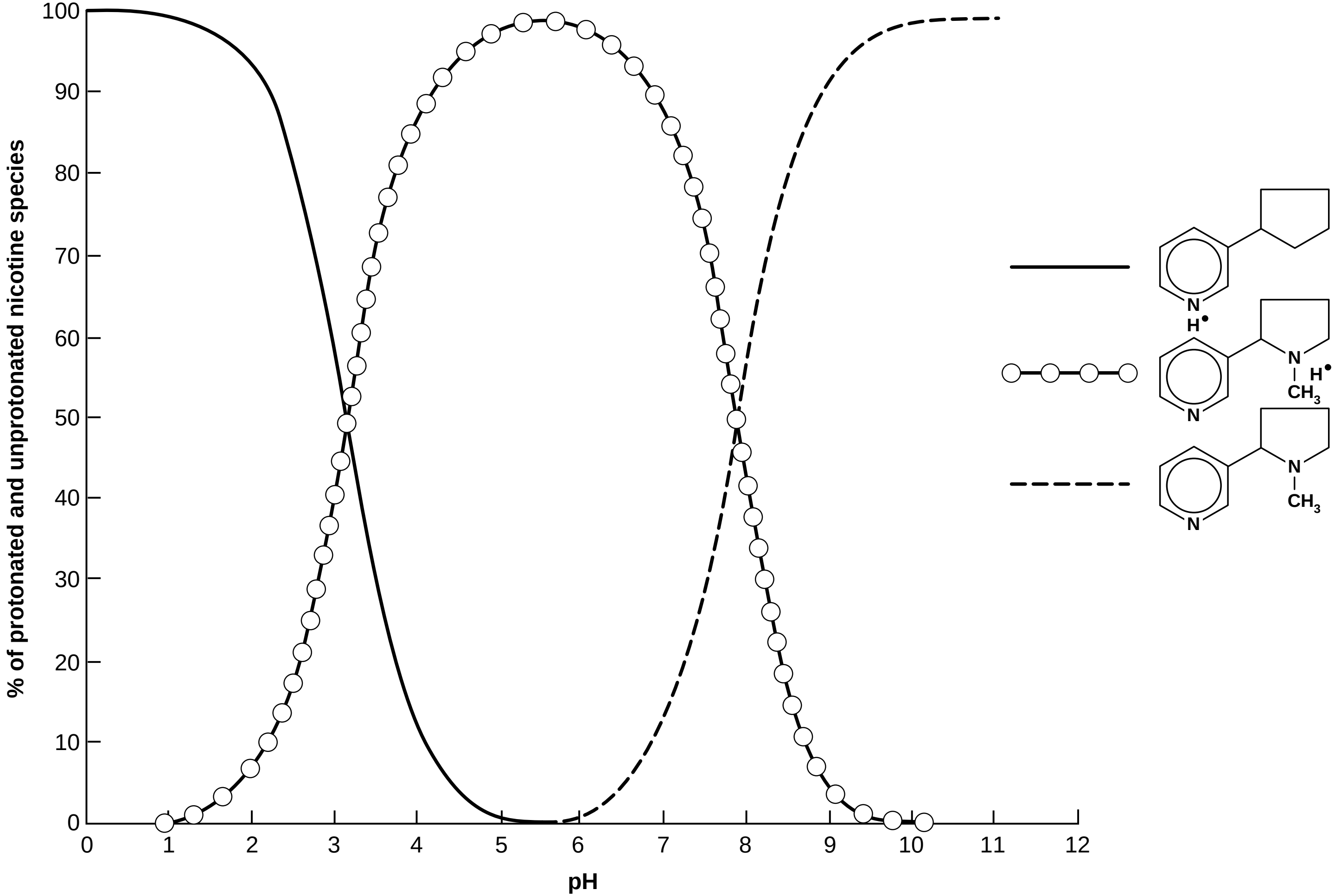
n. a., not available.
[1]Brunnemann and Hoffmann, 1974a; [2]Adams, 1968; [3]Bilimoria and Nisbet, 1972.

nicotine in the vapor phase; that of a small cigar, at pH 7.4, about 30 percent unprotonated nicotine; and the last puff of a little cigar, at pH 7.5, has about 32 percent unprotonated nicotine. On the other hand, the smoke of the U.S. blended cigarette does not contain unprotonated nicotine when tested under current FTC smoking conditions (Figures 5 and 6) (Brunnemann and Hoffmann, 1974a). Unprotonated nicotine is present in the vapor phase of the inhaled smoke; protonated nicotine resides in the particulate phase. Unprotonated nicotine is absorbed through the mucous membrane of the oral cavity and delivers a dose of the pharmacoactive agent, that “satisfies” the primary cigar smoker without his inhaling the smoke (Armitage and Turner, 1970).

The smoke of fresh (unaged) mainstream smoke of a U.S. blended, nonfilter cigarette contains about 5×10^9 spherical droplets with a particle-size distribution of 0.1 - 1.0 micron (maximum around 0.2 micron) (Keith and Derrick, 1961). Slightly less than half of the particles are neutral, whereas most of the particles carry only one electrical charge and these are evenly divided between those with negative and those with positive charges (Norman and Keith, 1975). There is a lack of published data on particle concentration and particle size distribution in cigar smoke and also on the electrical charges of cigar smoke particles.

All tobacco smoke products exhibit significant reducing activity. Studies using the reduction of 2,4-dichloroindophenol as a marker of the reducing potential of tobacco smoke have shown that cigarette smoke has a significantly higher reducing potential than cigar or pipe smoke. In cigarette smoke, about 96 percent of the reducing activity of the total smoke

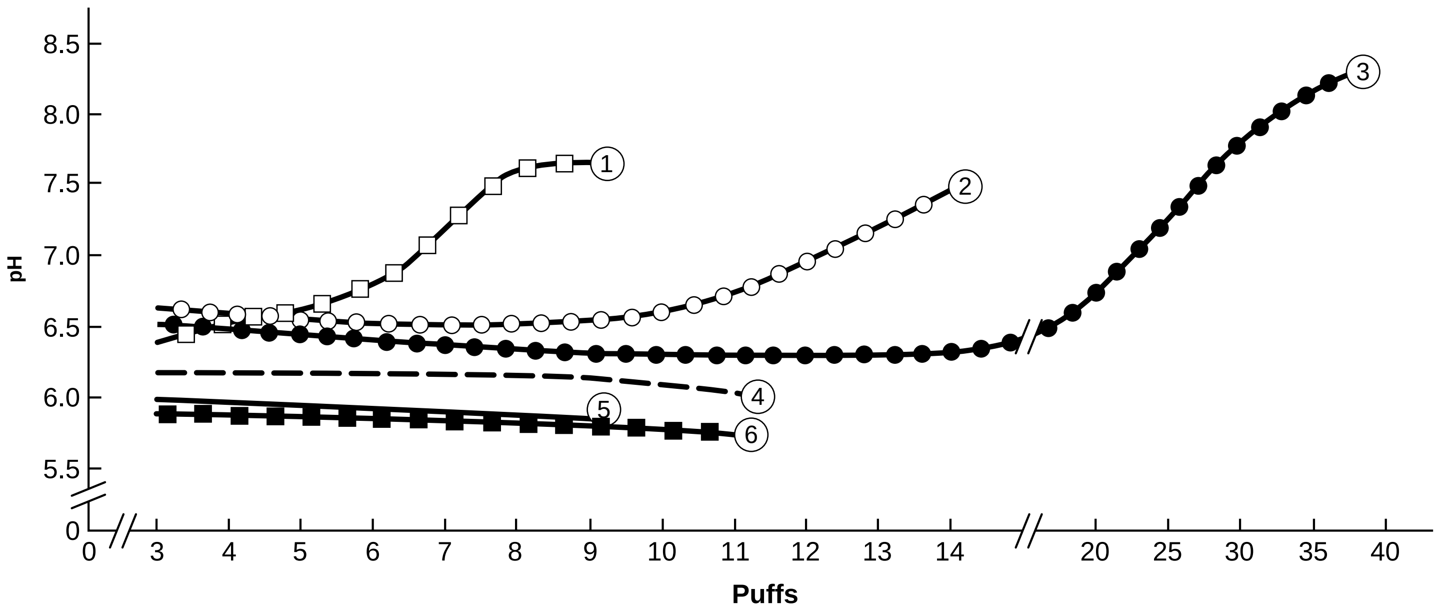
Figure 5
Degree of protonation of nicotine in relation to pH.



Source: Brunnemann and Hoffmann, 1974.

Figure 6

pH of total mainstream smoke of various tobacco-products



(1) little cigar I
(2) little cigar II
(3) cigar
(4) Kentucky reference cigarette
(5) blended filter-tipped cigarette (85 mm)
(6) blended cigarette without filter (85 mm)

Source: Brunnemann and Hoffmann, 1974a and 1974b.

resides in the particulate phase, while in cigar smoke, 82 percent is found in the particulate phase (Table 5) (Bilimoria and Nisbet, 1972).

Chemical Composition of Cigar Smoke

Gas Phase*

Tobacco smoke contains more than 4,000 individual components; about 500 of these occur in the gas phase. The major gas-phase constituents in cigar smoke are 51.8 - 54.6 volume% nitrogen (for cigarettes, 55 - 72 vol%), 4.1 - 4.2 vol% oxygen (9.2 - 14.3 vol%), 15.5 - 16.7 vol% carbon dioxide (6.9 - 13.4 vol%), and 9.7 - 12.7 vol% carbon monoxide (1.9 - 6.3 vol%) (Boyd et al., 1972). These comparisons strongly indicate that the combustion during puff drawing from cigars is even less complete (oxygen 4.1 - 4.2 vol%; CO, 1.9 - 6.3 vol%) than that during cigarette smoking. A primary reason for the low concentration of O_2 and the high concentration of CO in cigar smoke is the lack of porosity of the cigar binder and wrapper compared to that of cigarette paper. The porosity of cigarette paper accelerates the delivery of oxygen into the tobacco column and the diffusion of certain gaseous components (e.g., CO, CO_2, NO) through the paper into the environment.

Table 6 presents select volatile components in the smoke of cigars, little cigars, and cigarettes. Remarkably, the concentrations of nitrogen oxides (NO_x) and ammonia are significantly higher in cigar smoke than in cigarette smoke. Formation of nitrogen oxides and ammonia is primarily linked to the nitrate content of the cigar tobacco, the incomplete combustion, and the lack of porosity of cigar binders and wrappers. The amounts of ammonia reported in the smoke of cigars and cigarettes may not only originate from the ammonia produced in the reducing atmosphere of the burning cone but can also, to a minor extent, come from amides which partially decompose in the sulfuric acid that is used for trapping the ammonia from the smoke (Brunnemann and Hoffmann, 1975). In the smoke of cigars, up to 0.8 percent is present as free ammonia at pH levels between 6.8 and 7.2; whereas cigarette smoke contains only up to 0.01 percent of free ammonia at a pH between 5.3 and 5.6 (Figure 7) (Sloan and Morie, 1976). The higher quantities of free ammonia contribute to the pungency of cigar smoke.

Cigar smoke also contains a large number of volatile amines (Pailer et al., 1969). However, there is a lack of quantitative data. The levels of volatile *N*-nitrosamines are also higher in cigar smoke than in cigarette smoke, again primarily because of the higher nitrate content of the cigar tobacco compared to that of cigarette tobacco. Furthermore, cigar smoke contains a large spectrum of volatile agents, such as volatile olefins, dienes (1,3-butadiene, isoprene, etc.), volatile nitriles, and halogenated hydrocarbons.

* The classification of the tobacco smoke aerosol into gas phase and particulate phase is based on the separation of the smoke that occurs when it is drawn through a Cambridge glass fiber filter CM-113. Fifty percent of the components are from the gas phase and pass through the filter. That portion of the smoke which is trapped on the filter consists of particulate phase components. These are arbitrary definitions, they do not fully reflect the conditions prevailing in undiluted, unaged smoke; however, they serve as guidelines.

Table 6
Components in mainstream smoke of cigars and cigarettes: gas phase (values are given for 1.0 g tobacco smoked)

Component	Cigars	Non-filter Cigarettes	Little Cigars	Filter Cigarettes	Ref.
Carbon monoxide, mg	39.1 - 64.5	16.3	22.5 - 44.9	19.1	1-3
Carbon dioxide, mg	121 - 144	61.9	47.9 - 97.9	67.8	1-3
Nitrogen oxides (NO_x), µg	159, 300	160	45, 150	90 - 145	1
Ammonia, µg	30.5	95.3	200, 322	98	4
Hydrogen cyanide, µg	1,035	595	510, 780	448	2
Vinyl chloride, ng	n.a.	17.3, 23.5	19.7, 37.4	7.7 - 19.3	5
Isoprene, ng	2,750 - 3,950	420, 460	210 , 510	132 - 990	1.6
Benzene, µg	92 - 246	45, 60	n.a.	8.4 - 97	1,6-8
Toluene, µg	n.a.	56, 73	n.a.	7.5 - 112	1,7
Pyridine, µg	49 - 153	40.5	61.3	27.6, 37.0	9
2-Picoline, µg	7.9 - 44.6	15.4	17.0	14.8, 15.6	9
3-+4-Picoline, µg	17.9 - 100	36.1	32.9	12.6, 20.2	9
3-Vinylpyridine, µg	7.0 - 42.5	29.1	21.2	102, 192	9
Acetaldehyde, µg	1,020	960	850, 1,390	94.6	2
Acrolein, µg	57	130	55, 60	87.6	2
N-Nitrosodimethylamine, ng	n.a.	16.3 - 96.1	555	7.4	10
N-Nitrosopyrrolidine, µg	n.a.	13.8 - 50.7	24.5	6.6	10

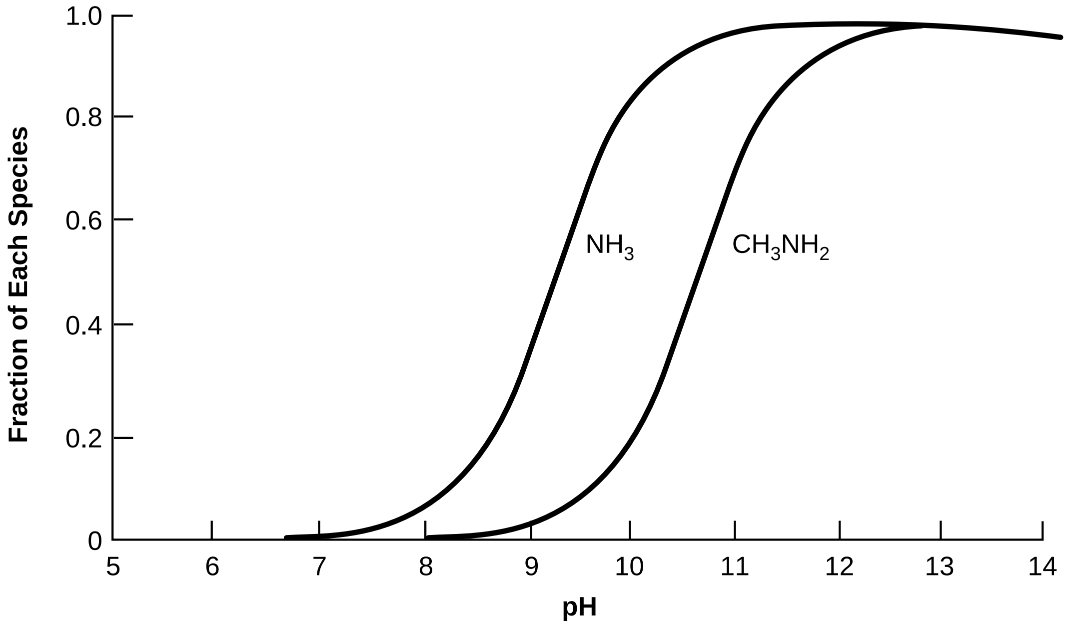
n.a., data not available.
References: (1) Wynder and Hoffmann, 1967; (2) Hoffmann et al., 1973; (3) Brunnemann and Hoffmann, 1974b; (4) Brunnemann and Hoffmann, 1975; (5) Hoffmann et al., 1976; (6) Brunnemann et al., 1990; (7) Osman and Barson, 1964; (8) Appel et al., 1990; (9) Brunnemann et al., 1978; (10) Brunnemann et al., 1977b.

However, the available literature offers few quantitative data for cigar smoke, except for a report on the presence of vinyl chloride (Hoffmann et al., 1976).

Particulate Phase The particulate phase of tobacco smoke contains at least 3,500 individual components (Roberts, 1988). Most of our knowledge about the physicochemical nature and composition of tobacco smoke derives from studies on cigarette smoke.

Only limited research has been done on the chemical composition of cigar smoke. One would expect cigar smoke chemistry to be qualitatively similar to that of cigarette smoke, except for differences caused by the use of additives, by the pH effects, and by the lower concentrations of oxygen available to support combustion. Cigar smoke may contain components that derive from additives incorporated into reconstituted tobacco sheets, and these may be different from additives used in reconstituted tobacco formulations for cigarettes (Moshy, 1967; Halter and Ito, 1980). The tobacco of low-yielding cigarettes is often treated with flavor additives (Doull et al., 1994). Such flavor additives are generally not used for cigars except for some little cigars with filter tips.

Figure 7
Fraction of free ammonia and methylamine vs. pH.



Source: Sloan and Morie, 1976.

Quantitative similarities are seen when one compares the smoke yields of cigars and cigarettes per gram tobacco smoked (Table 7). This is the case for the smoke yields of volatile phenols and polynuclear aromatic hydrocarbons (PAH), compounds primarily pyrosynthesized during smoking. However, "tar" yields per gram of cigar tobacco burned are somewhat higher because the nonporous cigar binder and wrapper make the combustion less complete than that of cigarette tobacco combustion of which is facilitated by highly porous cigarette paper (Rickert et al., 1985). Also, cigars have larger diameters than cigarettes which further hinders more complete combustion. The nicotine yields in the mainstream smoke of cigars are also generally higher than in the mainstream smoke of cigarettes because the latter contain a tobacco blend, while most cigars are made solely from burley tobacco that delivers a weakly alkaline smoke with a high proportion of unprotonated nicotine.

The significantly lower yields of long-chain paraffin hydrocarbons in cigar smoke compared to cigarette smoke can, in part, be explained by the loss of such hydrocarbons during fermentation of the cigar tobacco (Wolf, 1967). The low yields of the long-chain hydrocarbons in cigar smoke are likely also attributable to the very intense "cracking" of these compounds during smoking. The high yield of *N*-nitrosodiethanolamine seen in the smoke of little cigars was probably related to the treatment of the tobacco of these little cigars with the sucker growth inhibitor MH-30, maleic hydrazide

Table 7
Components in the mainstream smoke of cigars and cigarettes: particulate phase (values are given for /g tobacco smoked)

Smoke Component	Cigars	Non-filter Cigarettes	Little Cigars with Filter	Filter Cigarettes	Ref.
"Tar" (FTC), mg	38.0 - 40.6	16.0 - 36.1	17.4 - 31.8	8.0 - 20.3	1,2,3
Nicotine, mg	2.9 - 3.1	1.7 - 2.65	0.6 - 1.8	0.6 - 1.4	1,2,3
Tridecane, µg	1.2	14.3			4,5
Pentadecane, µg	0.8	14.3			4,5
Eicosane, µg	0.8	27.4			4,5
Docosane, µg	0.6	26.2			4,5
Cholesterol, µg		27.5	49.0[a]		6
Camposterol, µg		53.4	57.4[a]		6
Stigmasterol, µg		97.5	152[a]		6
β-Sitosterol, µg		74.1	82.5[a]		6
Phenol, µg	24 - 107	96 - 117	37.0	19.0 - 33.2	2,7
o-Cresol, µg	19 - 21	22 - 26	4.3	4.2 - 6.8	2,7
m- and *p*-Cresol, µg	19 - 62	50 - 58	18.0	17 - 23.3	2,7
Catechol, µg		318	129 - 169	178	8
Formic acid, µg	109 - 121	400			9
Acetic acid, µg	286 - 320	900			9
Quinoline, µg	2.0 - 4.1	1.67	0.66	0.62	10
Naphthalene, ng		3,900 - 5,000	1,780		11
1-Methylnaphthalene, ng		1,390 - 1,760	1,110		11
2-Methylnaphthalene, ng		1,720 - 2,130	1,470		11
Acenaphthene, ng	16	50			12,13
Anthracene, ng	119	109			12,13
Pyrene, ng	176	125			12
Fluoranthene, ng	201	125			12
Benz(*a*)anthracene, ng	39 -92.5	92	44.3	40.6	12
Benzo(*a*)pyrene, ng	30 - 51	47 - 58.8	25.7	26.2	12
N-Nitrosodiethanolamine, ng	5.7	4.6	700	38	13
N^1-Nitrosonornicotine, ng	820	300	7,100	390	14
NNK, ng	4.90	140	5,400	190	14
N^1-Nitrosoamabasine	4.90	410	2,200	460	14
Copper, ng	40 - 160	< 10 - 100			15
Lead, ng	160 - 280	100 - 510			15
Cadmium, ng	2.0 - 38	16 - 82			15
Zinc, ng	360 - 2,500	120 - 920			15
Nickel, ng	2,500 - 7,000	300 - 600			16,17

[a] Small cigar without filter.
[b] N^1-Nitrosoanatabine contains 10 - 15% N^1-nitrosoanabasine.

References: (1) Hoffmann et al., 1963; (2) Wynder and Hoffmann, 1967; (3) Hoffmann and Wynder, 1972; (4) Spears et al., 1963; (5) Osman et al., 1965; (6) Schmeltz et al., 1975a; (7) Osman et al., 1963; (8) Brunnemann et al., 1976; (9) Schmeltz and Schlotzhauer, 1961; (10) Dong et al., 1978; (11) Schmeltz et al., 1976a; (12) Campbell and Lindsey, 1957; (13) Brunnemann and Hoffmann, 1981; (14) Hoffmann et al., 1979a; (15) Franzke et al., 1977; (16) Sunderman and Sunderman, 1961; (17) Stahly and Lard, 1977.

diethanolamine. Since 1980-1981, due to an official ban, the use of MH-30 on tobacco has been greatly reduced (Brunnemann and Hoffmann., 1991a).

As to be expected, the smoke of cigars contains significantly higher amounts of the carcinogenic, tobacco-specific *N*-nitrosamines (TSNA) than cigarette smoke (Table 7). A major reason for the elevated levels of TSNA in cigar smoke is the relatively high concentration of nitrate in cigar tobacco. During curing and fermentation, nitrate is partially reduced to nitrite, an important precursor for the *N*-nitrosation of amines, including alkaloids like nicotine; nitrate constitutes up to 2.0 percent of the cigar tobacco (Table 3). The nitrosamines formed from nicotine are NNK and NNN (Figure 3). The latter is also formed in high yields from nornicotine (Hoffmann et al., 1994). In laboratory animals, NNK and NNN are metabolically activated by α-hydroxylation which results in the formation of unstable α-hydroxy nitrosamines. These decompose to yield alkylating agents that react with the nuclear DNA *in vitro* and also *in vivo* (Hecht and Hoffmann, 1989; Hecht, 1996). Lesions formed by this reaction give rise to tumors in the target organs. NNN elicits carcinoma of the esophagus in rats. In explants of human esophageal tissue, NNN is also (-hydroxylated, although to varying extents. The degree of α-hydroxylation of NNN varies between individuals and is likely related to phenotypic differences (Castonguay et al., 1983). In this regard, it is of interest to recall that the risk for cancer of the esophagus among cigar smokers is comparable to that of cigarette smokers (Kahn, 1966; Schottenfeld, 1984; U.S. Department of Health and Human Services, 1989) (Chapter 4).

Like most plants, tobacco contains a number of metal ions; a small percentage of these transfers into the mainstream smoke of tobacco products. The reported transfer rates into cigar smoke were for lead 2.0 - 6.6 percent (cigarette smoke 3.4 - 19.7 percent), for zinc 1.0 - 8.5 percent (cigarette smoke 0.6 - 4.6 percent), for cadmium 0.3 - 2.3 percent (cigarette smoke 1.1 - 7.3 percent), and for copper 0.1 - 0.8 percent (cigarette smoke 0.3 - 1.1 percent) (Franzke et al., 1977). The high transfer rate of nickel into tobacco smoke ((20 percent) has been explained by the formation of the volatile nickel carbonyl (bp 43°C) (Sunderman and Sunderman, 1961; Stahly and Lard, 1977). Cigar tobacco was reported to contain between 1.1 and 4.9 (g nickel per gram tobacco. In inhalation studies, nickel carbonyl ($Ni[CO]_4$) induced a few pulmonary tumors in rats; upon intravenous injection of this compound, 19 out of 20 rats developed lung tumors (International Agency for Research on Cancer, 1990).

SIDESTREAM SMOKE AND ENVIRONMENTAL TOBACCO SMOKE

Sources of Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) is the term used to describe indoor air pollutants derived from burning tobacco products. The major contributor to ETS is the sidestream smoke (SS) that originates between puffs from smoldering cigars, cigarettes, or pipes. Lesser contributions to ETS come from the smoke emitted at the butt end of a burning cigar or cigarette and/or from the mouthpiece of a pipe stem, and also from gases diffusing through cigarette paper. Exhaled smoke also contributes to ETS.

It has been known for a long time that the alkaline cigar SS is irritating to eyes, ears, and throats of people, especially in enclosed environments with limited ventilation, such as offices and other workplaces and conveyances.

The ph levels of cigar Tobacco and of its smoke are slightly alkaline (Wolf, 1967; Brunnemann and Hoffmann, 1974a). This contributes to the unpleasant odor of cigar butts, which contain partially unprotonated, readily volatilizing ammonia, pyridine, methyl- and ethylpyridines, 3-vinylpyridine, 2,4-, 2,6-, and 3,s-dimethylpyridines as well as allylalcohol, ethylmercaptan, volatile phenols, aliphatic nitriles, and benzonitrile (Peck et al., 1969; Adler et al., 1971).

The Physicochemical Nature of Sidestream Smoke

SS is primarily formed in the burning cones and hot zones of cigars, cigarettes, and pipes between the drawing of puffs. The smoldering tobacco releases more of many compounds into the SS than into mainstream smoke (MS).

This applies especially to those agents that are preferably formed in reducing atmospheres, namely ammonia, aliphatic and aromatic amines, and volatile *N*-nitrosamines (Table 8). When SS is generated, several compounds result from the degradation of tobacco constituents of low volatility. These include benzene, toluene, 3-vinylpyridine (from the *Nicotiana* alkaloids), and polynuclear aromatic hydrocarbons (PAH). Smoke components that are formed by oxidation, such as catechol and hydroquinone, are released into SS in significantly lower amounts than into MS (Schmeltz et al., 1975a,b; Schmeltz et al., 1979; Klus, 1990; Guerin et al., 1992).

Because of the release of relatively large quantities of ammonia, the pH of the SS of cigarettes is neutral (MS slightly acidic) and that of cigars is alkaline (Figure 8; see Figure 6 to compare with the pH of MS). Therefore, the SS of both cigarettes and cigars contains a greater proportion of unprotonated nicotine and ammonia than the MS (Figures 5 and 7; Brunnemann and Hoffmann, 1974a; Morie, 1972).

Few physicochemical parameters of cigar SS are available in the accessible literature (Table 9). It is likely that they are generally similar to those of cigarette SS. Under standardized machine-smoking conditions (FTC method) (Pillsbury et al., 1969), the generation of MS from cigarettes requires, on average, 10 puffs of 35 ml each and a total of 20 seconds, while the formation of SS occurs over 550 seconds. During these periods, 347 mg tobacco are burned to generate MS and 411 mg tobacco are burned to produce SS. In the MS of a nonfilter cigarette one finds 10.5×10^{12} particles; in the SS, 35×10^{12} particles (Scassellati-Sforzolini and Savino, 1968); the particle sizes range from 0.1 to 1.0 µm in MS and from 0.01 to 0.8 µm in SS, with means of 0.4 µm and 0.32 µm, respectively (Carter and Hasegawa, 1975; Hiller et al., 1982). Ingebrethsen and Sears (1985) reported that particle size declines in line with the degree of dilution of SS by air. Diluting SS from 226 $\mu g/m^3$ to 26 $\mu g/m^3$ and down to 1.4 $\mu g/m^3$ reduces the median diameter from 0.210 to 0.196 and to 0.185 µm, while the percentage of particles with diameters <0.10 µm increases from about 39 to 54, and to 73 percent of the

Table 8
Distribution of select constituents in fresh, undiluted mainstream smoke and diluted sidestream smoke from nonfilter cigarettes

Constituent	Amount in MS	Range in SS/MS
Vapor phase		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Carbonyl sulfide	18-42 µg	0.03-0.13
Benzene	12-48 µg	5-10
Toluene	100-200 µg	5.6-8.3
Formaldehyde	70-100 µg	0.1-≅50
Acrolein	60-100 µg	8-15
Acetone	100-250 µg	2-5
Pyridine	16-40 µg	6.5-20
3-Methylpyridine	12-36 µg	3-13
3-Vinylpyridine	11-30 µg	20-40
Hydrogen cyanide	400-500 µg	0.1-0.25
Hydrazine	32 ng	3
Ammonia	50-130 µg	40-170
Methylamine	11.5-28.7 µg	4.2-6.4
Dimethylamine	7.8-10 µg	3.7-5.1
Nitrogen oxides	100-600 µg	4-10
N-Nitrosodimethylamine	10-40 ng	20-100
N-Nitrosodiethylamine	ND-25 ng	<40
N-Nitrosopyrrolidine	6-30 ng	6-30
Formic acid	210-490 µg	1.4-1.6
Acetic acid	330-810 µg	1.9-3.6
Methyl chloride	150-600 µg	1.7-3.3
Particulate phase		
Particulate matter	15-40 mg	1.3-1.9
Nicotine	1-2.5 mg	2.6-3.3
Anatabine	2-20 µg	<0.1-0.5
Phenol	60-140 µg	1.6-3.0

Constituent	Amount in MS	Range in SS/MS
Catechol	100-360 µg	0.6-0.9
Hydroquinone	110-300 µg	0.7-0.9
Aniline	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine	1.7 ng	30
4-Aminobiphenyl	4.6 ng	31
Benz[*a*]anthracene	20-70 ng	2-4
Benzo[*a*]pyrene	20-40 ng	2.5-3.5
Cholesterol	22 µg	0.9
γ-Butyrolactone	10-22 µg	3.6-5.0
Quinoline	0.5-2 µg	8-11
Harman	1.7-3.1µg	0.7-1.7
N'-Nitrosonornicotine	200-3,000 ng	0.5-3
NNK	100-1,000 ng	1-4
N-Nitrosodiethanolamine	20-70 ng	1.2

(continues)

Table 8 *(continued)*

Cadmium	100 ng	7.2
Nickel	20-80 ng	13-30
Zinc	60 ng	6.7
Polonium-210	0.04-0.1 pCi	1.0-4.0
Benzoic acid	14-28 µg	0.67-0.95
Lactic acid	63-174 µg	0.5-0.7
Glycolic acid	37-126 µg	0.6-0.95
Succinic acid	110-140 µg	0.43-0.62

National Research Council, 1986.

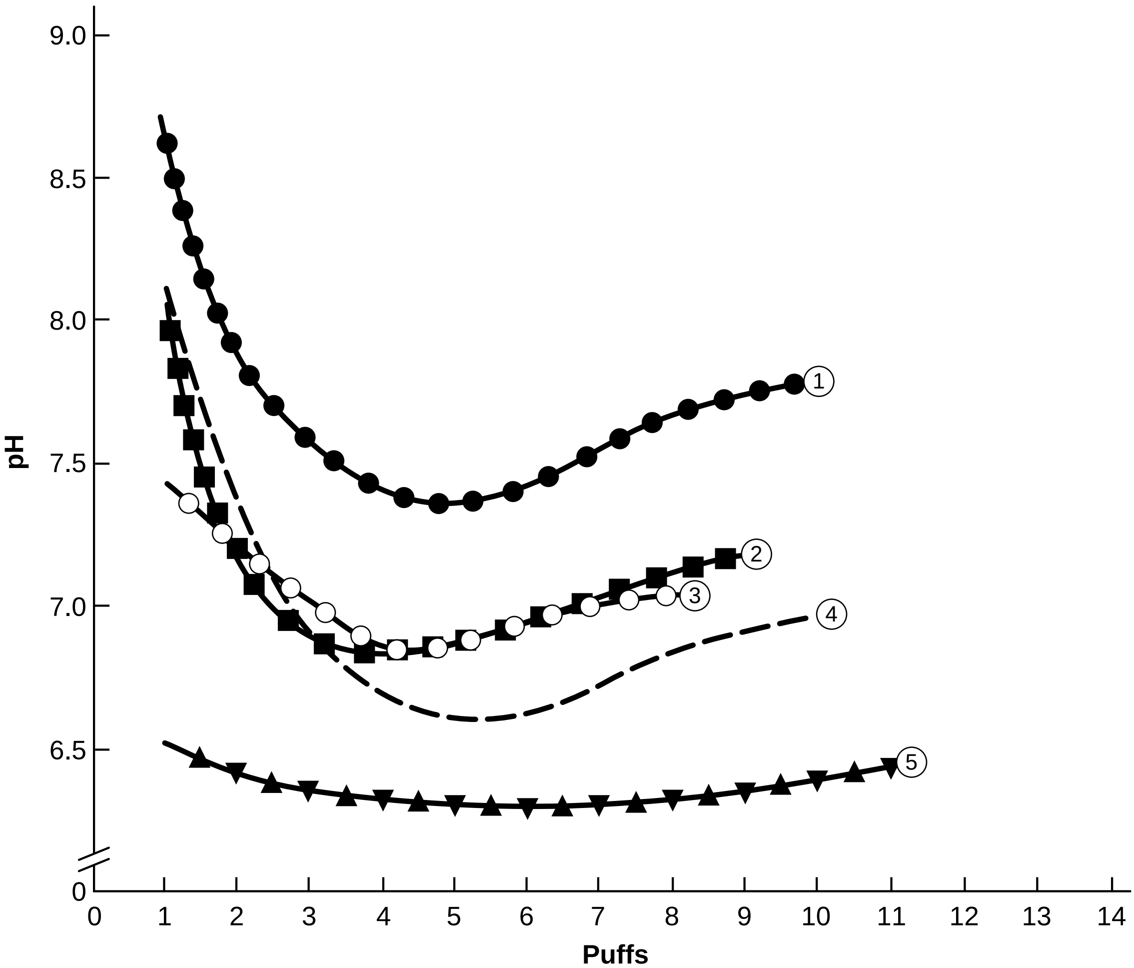
total ETS particles. In respect to particle sizes in the MS and SS of cigars, it is likely that similar parameters prevail; however, precise data are currently not available.

Environmental Tobacco Smoke

The tobacco smoke released into the environment from a burning cigarette, cigar, or pipe, and the exhaled smoke (that portion not retained by the smoker) is usually diluted by air several hundred-fold and often a thousand-fold before the ETS-polluted aerosol is inhaled (International Agency for Research on Cancer, 1986; U.S. Department of Health and Human Services, 1986; National Research Council, 1986; Guerin et al., 1992). However, to date only one model study with cigar smoke as a source for ETS has been reported (Nelson et al., 1997). It involved the concurrent smoking of three cigars of one brand by three men over a 10-minute period in a 45 m^3 chamber. The environmental conditions were static, i.e., there was neither air supply nor recirculation of the air in the chamber. Table 10 compares ETS data from this model study with the data from a model study with six cigarette smokers located for 10 minutes in the same chamber under identical (static) chamber conditions (Nelson et al., 1996 and 1997). Clearly, the smoking of three cigars by three smokers during 10 minutes polluted the air significantly more with CO (16.9 to 25.3 ppm), nitrogen oxides (412 to 520 ppb), nicotine (168 to 450 $\mu g/m^3$), and respirable suspended particulate matter (RSP; 1,520 to 5,770 $\mu g/m^3$) than the smoking by six cigarette smokers which generated 0.629 to 0.782 ppm CO, 226 to 461 ppb nitrogen oxides, 49 to 61 $\mu g/m^3$ nicotine, and 1,170 to 1,960 $\mu g/m^3$ RSP (Table 10). The greater degree of ETS pollution generated by the three cigar smokers can be explained, at least in part, by the fact that these cigar smokers burned cumulatively between 21.4 g and 33.9 g of tobacco while the six cigarette smokers burned only between 3.77 g and 4.69 g tobacco during the same time. This model study documents clearly what has been assumed, namely that cigar smokers pollute enclosed environments to a significantly higher degree than cigarette smokers. Studies of the levels of CO produced under actual cigar smoking conditions are described in Chapter 5 (Repace et al., 1998).

ETS differs from freshly generated mainstream smoke in a number of ways. The conditions under which MS is formed are very different from

Figure 8
pH of total sidestream smoke of various tobacco-products



(1) little cigar I
(2) little cigar II
(3) French (black tobacco) cigarette
(4) Kentucky reference cigarette
(5) blank (air)

Source: Brunnemann and Hoffmann, 1974a and 1974b.

those prevailing during SS formation, and the latter is the main contributor to ETS. The pH of SS is different from that in the MS of cigars and cigarettes (Figures 6 and 8), reflecting the presence of free ammonia and creating major differences in the degree of unprotonated nicotine (Figures 5 and 7). In addition, with the higher degree of air dilution of SS, more nicotine evaporates from the particulate phase into the vapor phase. Eudy et al. (1986) reported that 90 - 95 percent of the nicotine is present in the vapor phase of

Table 9

Some selected compounds in the sidestream smoke of cigars, little cigars, nonfilter cigarettes and filter cigarettes (values are given for 1 g tobacco burned)

Compound	Cigars	Nonfilter Cigarette	Little Cigar with Filter Tips	Filter Cigarette	Ref.
Ammonia, mg		7.18 (44)	9.34 (47)	7.14 (13)	1
		6.11 (64)	12.9 (40)		
Hydrogen cyanide, µg		134 (0.85)	114 (0.17)	167 (0.37)	2
				141 (0.30)	
Pyridine, µg	665 - 800 (5013)	420 (10)			3
2-Picoline, µg	170 - 255 (6-20)	160 (10)			3
3- and 4-Picoline, µg	600 - 930 (–51)	380 (13)			3
3-Vinylpyridine, µg	595 - 900 (14-80)	800 (28)			3
NDMA, ng	473 (6.4)	930 (50)	2,280 (412)	950 (129)	4,5
NEMA, ng	15 (1.4)	74 (30)	97 (15)	129 (95)	4,5
NDEA, µg		72.6 (35.3)	29 (26)	56 (89)	4,5
NPYR, µg	128 (10.5)	410 (27.3)	922 (32)	758 (89)	4,5
Cholesterol, µg		23.6 (0.9)	9.5 (0.6)[a]		
Campesterol, µg		32.5 (0.)	12.5 (0.8)[a]		6
Stigmasterol, µg		67.0 (0.7)	11.8 (0.8)[a]		6
β-Sitosterol, µg		35.0 (0.5)	9.8 (0.8)[a]		6
NNN, µg	4.27 (5.2)	2.13 (7.1)	1.14 (0.16)	0.19 (0.48)	7
NNK, µg	4.03 (8.3)	0.63 (3.7)	1.05 (0.15)	0.24 (1.3)	7
NAB, µg		0.34 (0.82)	0.71 (0.34)	0.19 (0.41)	7

Numbers in parentheses SS/MS.
[a]Little cigar without filter.

References: (1) Brunnemann and Hoffmann, 1974; (2) Brunnemann et al., 1977a; (3) Brunnemann et al., 1978; (4) Brunnemann et al., 1977b; (5) Brunnemann and Hoffmann, 1991; (6) Schmeltz et al., 1975a and 1975b; (7) Hoffmann et al., 1979.

ETS. The particle mass median diameter in ETS is significantly smaller than the particle diameter of inhaled MS (Carter and Hasegawa, 1975; Ingebrethsen and Sears, 1985). Furthermore, even compounds with relatively high molecular weight, such as the paraffin hydrocarbons $C_{25}H_{52}$ to $C_{34}H_{70}$, have been found to be present in the vapor phase of ETS to a significant degree (Ramsey et al., 1990).

Exhaled smoke may also contribute more to the particulate than to the vapor phase of ETS (Baker and Procter, 1990).

The time elapsing between generating and inhaling mainstream smoke is only fractions of seconds or, at most, seconds; thus, chemical reactions between constituents of freshly generated MS are limited compared to reactions during the aging of ETS, which may go on for periods up to a few hours and may be influenced by various atmospheric conditions. Certain ETS constituents may react with other materials in an enclosed environment, or components may be absorbed by textiles or by the surfaces of furniture.

Table 10

Contribution of cigar and cigarette smoke to environmental tobacco smoke model studies in a 45 m^3 room operated in the static mode[a]

	Cigars [b]						Cigarettes [c]			
ETS - component	C	F	D	B	E	A	FF	FFLT	ULT	100
Tobacco burned, g	7.11	7.33	10.5	7.77	10.3	6.53	0.7	0.661	0.629	0.782
CO, ppm	20.0	16.8	22.8	18.3	24.7	25.3	6.3	6.0	6.4	7.7
NO_x, ppb	572	412	445	526	472	520	234	226	242	261
3-Ethenylpyridine, $\mu g/m^3$	114	125	136	149	128	185	25	27	34	27
Nicotine, $\mu g/m^3$	168	202	283	290	169	450	51	61	49	56
RSP, $\mu g/m^3$	1810	1520	2920	2280	1280	5770	1440	1330	1170	1960
Solanesol, $\mu g/m^3$	43	26	16	74	21	102	45	44	35	53

[a] No air supply, no air recirculation.
[b] Three cigar smokers smoked the same cigar brands concurrently for 10 minutes.
[c] Six cigarette smokers smoked the same cigarette brands concurrently.
Abbreviations: ETS, environmental tobacco smoke; Nox, nitrogen oxide plus nitrogen dioxide; RST, respirable suspended particulate matter; FF, full flavor cigarette; FFLT, full flavor-low “tar”; ULT, ultra low “tar” cigarette; 100, full flavor-low “tar” 100 mm cigarette.

References: Nelson et al., 1997; Nelson et al., 1996.

This is the case with nicotine. The ratio between smoke components in ETS thus undergoes changes over time.

Tables 11 and 12 list some data for specific constituents of the vapor phase and of the particulate phase of ETS. These tables present only a fraction of the data that are known about ETS composition. (More detailed information is in the following sources: U.S. Department of Health and Human Services, 1986; National Research Council, 1986; Guerin et al., 1992.) The tables do indicate some elevation in the concentration of toxic agents in enclosed environments polluted with ETS compared to outdoor air. Moreover, there are concerns about an apparent ongoing TSNA formation during aging of ETS, yet there are no data in the literature to verify this phenomenon.

Tables 11 and 12 also list trace amounts of those agents in ETS that IARC (1987) regards as either "carcinogenic to humans," or as "probably or possibly carcinogenic to humans." These include the human carcinogens benzene and the aromatic amines 2-naphthylamine and 4-aminobiphenyl, as well as the animal carcinogens 1,3-butadiene, isoprene, acrylonitrile, formaldehyde, acetaldehyde, volatile *N*-nitrosamines, tobacco-specific *N*-nitrosamines, and various polynuclear aromatic hydrocarbons.

TOXICITY AND CARCINOGENICITY OF CIGAR SMOKE

As stated earlier, tobacco smoke contains at least 4,000 compounds (Roberts, 1988). At first glance, it appears to be an insurmountable task to identify all of the individual chemicals and groups of chemicals that are involved in the toxicity or carcinogenicity of the smoke of cigars, cigarettes, or pipes. However, intensive research in the tobacco sciences and advances in our understanding of toxicology and carcinogenesis during the past five decades have enabled scientists to define which agents, or groups of agents, are major contributors to the biologic activities of tobacco smoke (U.S. Department of Health and Human Services, 1989; Hoffmann et al., 1997).

Toxicity

Tables 6 and 7 list several smoke constituents that contribute to the overall toxicity and carcinogenicity of cigar smoke. Carbon monoxide and nicotine are major contributors to the acute toxicity of cigar smoke. Among agents which also add to the acute toxicity of cigar smoke are nitrogen oxides, hydrogen cyanide, ammonia, and volatile aldehydes.

Human hemoglobin has 210 times greater affinity for carbon monoxide than for oxygen. Inhaling tobacco smoke with up to 6 volume percent of CO diminishes the oxygen carrying capacity of the blood. Carboxyhemoglobin (COHb) concentration in the blood of nonsmokers amounts to about 0.5 percent, whereas in smokers it may reach 8 - 9 percent. The relationship between smoking and CO intoxication has received little attention. In 1969, Hamill and O'Neill reported two cases of CO intoxication of cigar smokers. Both were secondary cigar smokers, practicing inhalation of the smoke just as they did with cigarettes. One smoked 40 - 50 cigars, the other up to 15 cigars per day. Both had CO intoxication with polycythemia and decreased arterial oxygen saturation. Their COHb concentrations were 13 - 15 percent and 12 - 13 percent, respectively. In primary cigar smokers, COHb amounts to about

Table 11
Concentrations of ETS-compounds in indoor air - vapor phase*

	Concentration		
Compound	Mean	Range	Reference
Carbon Monoxide, ppm			
25 offices	2.8		Szadkowski et al., 1976
Nonsmoking offices	2.6		Szadkowski et al., 1976
Office: 72m^3-40 cigs/day		< 2.5 - 4.6	Harke, 1974
Office: 78m^3-70 cigs/day		< 2.5 - 9.0	Harke, 1974
Offices - 66, urban area	2.3 ± 2.0	0.1 - 10.5	Guerin et al., 1992
Offices - 57, control-outdoor	2.5 ± 2.3	NR - 10.4	Guerin et al., 1992
Working areas - 221 situations	2.2	0.0 - 31.9	
controls - 450 situations	2.1	0.0 - 21.9	Guerin et al., 1992
Restaurants, 49	3.4 ± 1.2	2.0 - 7.9	Guerin et al., 1992
13 controls	3.0 ± 0.6	2.0 - 4.1	Guerin et al., 1992
Restaurants, 99	4.2 ± 2.7	1.5 - 42.3	Guerin et al., 1992
99 outdoor controls	2.5 ± 2.1	0.3 - 13.7	Guerin et al., 1992
Nitrogen Oxides, ppb			
10 Office Buildings, NO_2	24 ± 7	11 - 32	Guerin et al., 1992
outdoor controls, NO_2	27 ± 11		Guerin et al., 1992
5 Office Buildings, NO_2	16 ± 5	7 - 20	Guerin et al., 1992
outdoor controls	14 ± 6		Guerin et al., 1992
44 workrooms[a], 227 determ., NO	82		Weber and Fischer, 1986
44 workrooms[a], 227 determ., NO_2	64		Weber and Fischer, 1986
44 workrooms[b], 102 determ., NO	66		Weber and Fischer, 1986
44 workrooms[b], 102 determ., NO_2	49		Weber and Fischer, 1986
Aliphatic Hydrocarbons µg/m^3			
Ethane		56 - 100	Löfroth et al., 1989
outdoor air, control		8 - 9	
Propane		30 - 70	Löfroth et al., 1989
outdoor air, control		6 - 7	
1,3-Butadiene[c]		11 - 19	Löfroth et al., 1989
outdoor air, control		< 1 - 1	
(Bar at 3 different days)	3.5	27 - 4.5	Brunnemann et al., 1990
Isoprene[c], 6 taverns		85 - 150	Löfroth et al., 1989
outdoor air, control		< 1 - 1	
4 restaurants	42.6	16.6 - 90	Higgins et al., 1991
1 bar, 3 samplings	97	60 - 106	Brunnemann et al., 1990
Aromatic Hydrocarbons, µg/m^3			
Benzene[a], 6 coffee houses	100	50 - 150	Badré et al., 1978
3 train spaces	68	20 - 100	Badré et al., 1978
cars, ventilation	30	20 - 40	Badré et al., 1978
cars, no ventilation		150	Badré et al., 1978
trains			Löfroth et al., 1989
outdoor air, control		6 -	
bar, 3 samplings	31	31 - 36	Brunnemann et al., 1990

Table 11 *(continued)*

Compound	Concentration Mean	Range	Reference
Toluene, coffee house	448	40 - 1,040	Badré et al., 1978
4 train compartments	1128	180 - 1,870	Badré et al., 1978
car, ventilation		500	Badré et al., 1978
car, no ventilation	30	50 - 70	Badré et al., 1978
bar, 3 days	55	41 - 80	Brunnemann et al., 1990
Formaldehyde[b], (tavern) µg/m^3		89 - 109	Löfroth et al., 1989
Acetaldehyde[c] (tavern) µg/m^3		183 - 204	Löfroth et al., 1989
coffees	460	170 - 630	Badré et al, 1978
trains	546	65 - 1,040	Badré et al, 1978
automobile - ventilation	370	260 - 480	Badré et al, 1978
automobile - no ventilation		1080	Badré et al, 1978
Acetonitrile bowling alley, µg/m^3		75.9	Higgins et al., 1991
residence, smoke		17.3	Higgins et al., 1991
residence, no smoke		3.4	Higgins et al., 1991
4 restaurants	17.5	2.4 - 48.9	Higgins et al., 1991
Acrylonitrile[b] bowling alley, µg/m^3		1.8	Higgins et al., 1991
residence, smoker		0.8	Higgins et al., 1991
residence, nonsmoker		0.6	Higgins et al., 1991
4 restaurants	0.6	0.1 - 1.9	Higgins et al., 1991
Pyridine bowling alley, µg/m^3		38	Higgins et al., 1991
residence, smoker		6.5	Higgins et al., 1991
residence, nonsmoker		0.6	Higgins et al., 1991
4 restaurants	5.0	0.8 - 15.7	Higgins et al., 1991
3-Vinylpyridine bowling alley, µg/m^3		3.6	Higgins et al., 1991
residence, smoker		6.4	
residence, nonsmoker	3.2	ND	
4 restaurants	3.2	0.2 - 6.4	
415 nonsmokers, smoker's home			Jenkins et al., 1996
16 h breathing some samples	14.0		Jenkins et al., 1996
520 nonsmokers, workplace			
8 h breathing some samples	5.52		
Volatile N-Nitrosamines µg/m^3			
N-Nitrosodimethylamine[b]			
train, beverage car		0.11 - 0.13	Brunnemann and Hoffmann, 1978
bar		0.24	Brunnemann and Hoffmann, 1978
discotheque		0.09	Brunnemann and Hoffmann, 1978

The concentrations of individual components in ETS reported before 1985-1988 are, in general, significantly higher than those reported today. This is a consequence of measures to limit indoor smoking or to ban smoking entirely, as in the case of US airlines.

[a,b,c] These compounds are all carcinogenic to animals. According to the International Agency for Research on Cancer (1987), compounds are: [a]carcinogenic to humans; [b]probably carcinogenic to humans; and [c] possibly carcinogenic to humans.

Table 12
Concentrations of ETS-compounds in indoor air - particulate phase*

Compound	Concentration Mean	Range	Reference
Nicotine**, μg/m³			
(residences, 47 houses)	2.2	0.1 - 9.4	Lederer & Hammond, 1991
(residences, 3 houses)	11.1	7.6 - 14.6	Muramatsu et al., 1984
(offices, 44)	1.1	0.0 - 16.0	Weber & Fischer, 1986
(offices, 10)	2.3	0.3 - 6.7	Thompson et al., 1989
(restaurants, 6 coffees)		25 - 52	Badré et al., 1978
(restaurants, 5 coffees)	14.8	7.1 - 27.8	Muramatsu et al., 1984
(cafeterias, 3)	26.4	11.6 - 42.2	Muramatsu et al., 1984
		2.3 - 4.4	Thompson et al., 1989
(bars, 2)	8.4	4.7 - 13.0	Kirk et al., 1968
(bars, 5)	7.4	2.0 - 13.1	Miesner et al., 1989
(pubs, 3)	31		Muramatsu et al., 1987
Automobile (natural ventilation)	65		Badre et al., 1978
(ventilation)	1,010		Badre et al., 1978
Trains (8)	16.4	8.6 - 26.1	Muramatsu et al., 1984
Airplanes, (48 smoking seats)			Oldaker & Conrad, 1987
(20 nonsmoking seats)	5.5	≤0.08 - 40.2	Oldaker & Conrad, 1987
Aromatic Amines, μg/m³			
2-Naphthylamine[a] (offices)		0.27 - 0.34	
4-Aminobiphenyl[a]		0.1	
Carcinogenic PAH, μg/m³			
Benzo(*b*)fluoranthene[c] (rooms)		0.132 - 0.578	Gundel et al., 1990
(outdoor air)		0.007 - 0.098	Gundel et al., 1990
Benzo(*a*)pyrene[b] (common smoking conditions)		0.2 - 10	Guerin et al., 1988
(heavy smoking conditions)		10 - 20	Guerin et al., 1988
Benzo(*a*)pyrene (room air)		3.25	Adlkofer et al., 1989
Tobacco-Specific *N*-Nitrosamines, μg/m³			
*N*¹-Nitrosonornicotine[c] (3 bars)	11.8	4.3 - 22.8	Brunnemann et al., 1992
(2 restaurants)		nd. - 1.8	Brunnemann et al., 1992
(2 train comparts.)		n.d.	Brunnemann et al., 1992
(smoker's home)		n.d.	Brunnemann et al., 1992
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone[c]			
(3 bars)	14.9	9.6 - 23.8	Brunnemann et al., 1992
(2 restaurants)		1.4, 3.3	Brunnemann et al., 1992
(2 train comparts.)		4.9 - 5.2	Brunnemann et al., 1992
(smoker's home)		1.9	Brunnemann et al., 1992

*See footnote of Table 9.
**Although in ETS, generally, 90-95% of the nicotine is in the vapor phase for didactic reasons, nicotine in ETS is listed under "Particulate Phase".
n = not detected.
[a,b,c] The compounds are all carcinogenic to animals. According to the International Agency for Research on Cancer (1987), compounds are: [a]carcinogenic to humans; [b]probably carcinogenic to humans; and [c]possibly carcinogenic to humans.

2 percent; in secondary cigar smokers, the values are usually higher, up to 11 percent (Castleden and Cole, 1973).

Ciliatoxic Agents

Development of squamous epithelium metaplasia is likely to be accentuated by the presence of ciliatoxic compounds that cause mucus stagnation. This knowledge motivated several investigators to identify the ciliatoxic agents in tobacco smoke in *in vitro* and *in vivo* assays (Kensler and Battista, 1963; Wynder et al., 1963; Bernfeld et al., 1964; Dalhamn and Rylander, 1966). Battista (1976) tabulated the existing knowledge about the chemical nature of ciliatoxic agents in tobacco smoke (Table 13). Although the concentrations of ciliatoxic agents per volume of cigar smoke are somewhat higher than those in cigarette smoke, the lungs of primary cigar smokers will only be exposed to a fraction of these toxic agents because these smokers tend to inhale far less of the smoke than cigarette smokers do. However, secondary cigar smokers who are inhaling this smoke into their lungs will have significant exposure to ciliatoxins.

Genotoxicity

During the past two decades, *in vitro* and *in vivo* short-term assays have been employed to establish the genotoxicity of xenobiotic agents in order to gain an indication of their carcinogenic potential. Genotoxic agents have the ability to form DNA adducts and DNA-oxidation products in cellular nuclei, or otherwise change the configuration of DNA. So far, only one short-term test for the genotoxicity of cigar "tar" has been reported. Sato et al. (1977) tested five cigar "tars" for their mutagenic activities on the *Salmonella typhimurium* tester strains TA98 and TA100 and compared these activities with those of eight cigarette "tars." The genotoxic agents in these "tars" were metabolically activated with an S9 liver fraction of untreated rats. The number of revertants induced by 1 mg of cigar "tar" in TA100 was 922 ± 63; those in TA98 were 2,320 ± 305. One mg of cigarette "tar" caused, on average 735 ± 101 revertants in TA 100 and 1,460 ± 317 revertants in TA98. The mutagenicity of cigar "tars" was significantly higher (in TA100, $p = 0.01$; in TA98, $p = 0.004$) when compared to cigarette "tars."

Carcinogenicity and Carcinogenic Agents

The first report on the carcinogenicity of the "tar" from cigars was conducted with denicotinized "tar" by Croninger et al., 1958 (Table 14). Subsequently, three additional bioassays with cigar "tar" were reported in the literature (Table 14). Several of these studies, especially the study by Davies and Day (1969) reported a significantly higher tumorigenic activity with cigar "tar" in mouse skin than with cigarette "tar," as reflected in the induction of both papilloma and carcinoma in the skin. This result was expected since cigar "tar" contains higher concentrations of carcinogenic PAH.

Table 15 lists those agents in cigarette and cigar smoke that, according to the International Agency for Research on Cancer (1987, 1990, 1991, 1993a, 1993b, 1994, 1996), are animal carcinogens; ten of these are also carcinogenic in humans. Because data for cigar smoke are lacking, the yields of carcinogens in the smoke of cigarettes made exclusively from bright and blended tobacco are compared with those in the smoke of cigarettes made exclusively from burley tobacco (Table 16). Because cigars are primarily

Table 13
Vapor phase constituents with high ciliatoxic potency - *in vitro*

Compound	Potency	Amount in Smoke (μg/puff) Typical (Range)
Hydrogen Cyanide	+++	38 (16-63)
Formaldehyde	+++	5 (2.5-11)
Acrolein	+++	10 (5.6-10.4)
Sulfur Dioxide	+++	<1
Crotonaldehyde	++	1.6
2,3-Butanedione	++	12
Ammonia	++	1
Nitrogen Dioxide	++	<10
Methacrolein	+	1
Vinyl Acetate	+	0.5
Nitric Oxide	+	60 (12-75)

Score	ED_{50} (8 puffs) (μg/puff)
+++	High = ≤50
++	Moderate = 50-100
+	Low = 100-500

Vapor phase constituents with low ciliatoxic potency - in vitro

Aliphatic Hydorcarbons
- Cyclopentane
- Cyclopentene
- *Cis*-1,3-Pentadiene
- *Trans*-1,3-Pentadiene
- 2-Methyl-1,3-Butadiene
- Limonene

Aromatic Hydrocarbons
- Benzene
- Toluene

Aldehydes
- Acetaldehyde
- Propionaldehyde
- Butyraldehyde
- Valeraldehyde
- Isovaleraldehyde
- Pivaldehyde
- 2-Methylvaleraldehyde

Ketones
- Acetone
- 2-Butanone
- 2-Pentanone
- 3-Pentanone

Ethers
- Furan
- 2-Methylfuran
- 2,5-Dimethylfuran

Esters
- Methyl Formate
- Methyl Acetate
- Ethyl Acetate

Nitriles
- Acetonitrile
- Propionitrile
- Acrylonitrile
- Isobutyronitrile
- Methacrylonitrile

Sulfur Compounds
- Hydrogen Sulfide

Other Nitrogenous Compounds
- Nitrous Oxide

Miscellaneous
- Carbon Dioxide
- Carbon Monoxide
- Phenol Vapor

+≥ 500 μg/puff needed to achieve activity comparable to cigarette smoke. None of the above are present in cigarette smoke at levels ≥ 20 % of the amount needed for biological activity.

Source: Battista, 1976

Table 14
Comparison of the induction of papilloma and carcinoma in the skin of mice with "tars" from cigars and cigarettes

Mouse Strain	Sex	% "Tar" Suspension	"Tar" dose per application, mg	Applications each week	# mice	Cigar "Tar" % papilloma	% cancer	"Tar" from # mice	Control % papilloma	Cigarettes % cancer	Reference
Swiss	F	33	25	3	100	33	18				Croninger et al., 1958
CAF_1	F	33	25	3	100	50	10				Croninger et al., 1958
Swiss	F	50 - NF	40	3	100	65*	41	100	47	37	Croninger et al., 1958
Swiss	M,F	50		3		42	40		40	24	Kensler, 1962
Swiss	M,F	50		3		42	40		34	34	Kensler, 1962
CAF_1	M	50	21	3	87	27.5	15	86	27	15	Homburger et al., 1963
CAF_1	F	50	21	3	82	37.5*	19	96	15	23	Homburger et al., 1963
ICI - Albino	F	25	75	2	144	44.4**	27.1**	144	27.8	13.2	Davies & Day, 1969
ICI - Albino	F	12.5	37.5	2	144	20.8*	11.1**	144	7.6	0.7	Davies & Day, 1969
ICI - Albino	F	6.25	18.7	2	144	6.3	2.1				Davies & Day, 1969

Abbreviations: NF, nicotine free "tar."
Cigar "tar" induces significantly more papilloma or carcinoma than the cigarette control "tar."
$*p \leq 0.05$; $** p \leq 0.01$.

Table 15
Carcinogens in tobacco and tobacco smoke

Compound	In processed tobacco[b] (per gram)	In mainstream smoke[b] (per cigarette)	IARC evaluation evidence of carcinogenicity[a]	
			In laboratory animals	In humans
PAHs[c]				
Benz(a)anthracene		20-70 ng	Sufficient	
Benzo(b)fluoranthene		4-22 ng	Sufficient	
Benzo(j)fluoranthene		6-21 ng	Sufficient	
Benzo(k)fluoranthene		6-12 ng	Sufficient	
Benzo(a)pyrene	0.1-90 ng	20-40 ng	Sufficient	Probable
Dibenz(a,h)anthracene		4 ng	Sufficient	
Dibenzo(a,l)pyrene		1.7-3.2 ng	Sufficient	
Dibenzo(a,l)pyrene		present	Sufficient	
Indeno(1,2,3-cd)pyrene		4-20 ng	Sufficient	
5-Methylchrysene		0.6 ng	Sufficient	
Aza-arenes				
Quinoline		1-2 µg	Sufficient	
Dibenz(a,h)acridine		0.1 ng	Sufficient	
Dibenz(a,j)acridine		3-10 ng	Sufficient	
7-H-Dibenzo(c,g)-carbazole		0.7 ng	Sufficient	
N-Nitrosamines				
N-Nitrosodimethylamine	ND-215 ng	0.1-180 ng	Sufficient	
N-Nitrosoethylmethylamine		3-13 ng	Sufficient	
N-Nitrosodiethylamine		ND-2.8 ng	Sufficient	
N-Nitrosopyrrolidine	5-50 ng	3-60 ng	Sufficient	
N-Nitrosodiethanolamine	50-3000 ng	ND-68 ng	Sufficient	
N-Nitrososarcosine	20-120 ng		Sufficient	
N-Nitrosonornicotine	0.3-89 µg	0.12-3.7 µg	Sufficient	
4-(Methylnitrosamino)-3-(pyridyl)-1-butanone	0.2-7 µg	0.08-0.77 µg	Sufficient	
N'-Nitrosoanabasine	0.01-1.9 µg	0.14-4.6 µg	Limited	
N-Nitrosomorpholine	ND-690 ng		Sufficient	
Aromatic amines				
2-Toluidine		30-200 ng	Sufficient	Inadequate
2-Napththylamine		1-22 ng	Sufficient	Sufficient
4-Aminobiphenyl		2-5 ng	Sufficient	Sufficient
N-Heterocyclic amines				
AaC		25-260 ng	Sufficient	
MeAaC		2-37 ng	Sufficient	
IQ		0.26 ng	Sufficient	Probable
Trp-P-1		0.29-0.48 ng	Sufficient	
Trp-P-2		0.82-1.1 ng	Sufficient	
Glu-P-1		0.37-0.89 ng	Sufficient	
Glu-P-2		0.25-0.88 ng	Sufficient	
PhIP		11-23 ng	Sufficient	Possible
Aldehydes				

Table 15 *(continued)*

Compound	In processed tobacco[b] (per gram)	In mainstream smoke[b] (per cigarette)	IARC evaluation evidence of carcinogenicity[a] In laboratory animals	In humans
Formaldehyde	1.64-7.4 µg	70-100 µg[d]	Sufficient	Limited
Acetaldehyde	1.4-7.4 µg	18-1400 µg[d]	Sufficient	Inadequate
Miscellaneous organic compounds				
1,3-Butadiene		20-75 µg	Sufficient	Probable
Isoprene		450-1000 µg	Sufficient	Possible
Benzene		12-70 µg	Sufficient	Sufficient
Styrene		10 µg	Limited	Possible
Vinyl chloride		1-16 µg	Sufficient	Sufficient
DDT[e]	20-13,400 ng	800-1200 ng	Sufficient	Possible
DDE[e]	7-960 ng	200-370 ng	Sufficient	
Acrylonitrile		3.2-15 µg	Sufficient	Limited
Acrylamide		Present	Sufficient	Probable
1,1-Dimethylhydrazine	60-147 µg		Sufficient	
2-Nitropropane		0.73-1.21 µg	Sufficient	
Nitrobenzene		25.3 ng	Sufficient	Possible
Ethyl carbamate	310-375 ng	20-38 ng	Sufficient	
Ethylene oxide		7 µg	Sufficient	Sufficient
Di(2-ethylhexyl)phthalate	Present	20 µg	Sufficient	
Furan		18-30 µg	Sufficient	Inadequate
Benzo(b)furan		Present	Sufficient	Inadequate
Inorganic compounds				
Hydrazine	14-51 ng	24-43 ng	Sufficient	Inadequate
Arsenic	500-900 ng	40-120 ng	Inadequate	Sufficient
Beryllium	15-75 mg	0.5 mg	Sufficient	Sufficient
Cobalt	90-1,400 mg	0.13-0.2 mg	Sufficient	Inadequate
Nickel	2000-6000 ng	0-600 ng	Sufficient	Limited
Chromium	1000-2000 ng	4-70 ng	Sufficient	Sufficient
Cadmium	1300-1600 ng	41-62 ng	Sufficient	Sufficient
Lead	8-10 µg	35-85 ng	Sufficient	Inadequate
Polonium-210	0.2-1.2 pCi	0.03-1.0 pCi	Sufficient	Sufficient

[a] No designation indicates that IARC has not evaluated the compound.
[b] ND, not detected.
[c] PAH, polynuclear aromatic hydrocarbons: AaC, 2-amino-9H-pyrido[2,3-b]indole; MeAaC, 2-amino-3-methyl-9H-pyrido[2,3-b]indole; IQ, 2-amino-3-methylimidazo[4,5-b]quinoline; Trp-P-1, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole; Trp-2, 3-amino-1-methyl-5H-pyrido[4,3-b]indole; Glu-P-1, 2-amino-6-methyl[1,2-a:3',2"-d]imidazole; Glu-P-2, 2-aminodipyrido[1,2-a:3',2'-d]imidazole; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.
[d] The 4th report of the Independent Scientific Committee on Smoking and Health (1988) published values for the 14 leading British cigarettes in 1986 (51.4% of the market) of 20-1050 µg/cigarette (mean 910 µg) for acetaldehyde.
[e] During the last decade, DDT and DDE levels have been drastically reduced in U.S. cigarette tobacco ((60 ng and (13 ng).

Source: Hoffmann and Hoffmann, 1997

Table 16
Known carcinogens (ng/cigarette) in the smoke of bright or blond and burley and black tobacco

Carcinogens		Bright or blended tobacco	Burley or black tobacco
I. Volatile nitrosamines			
NDMA	NF	6.8-13.8	29
	F	1.8-5.7	4.3
NEMA	NF	(0.1-1.8	2.7
	F	0.4-1.0	0.5
NPYR	NF	11.0-30.3	25
	F	3.1-8.7	10.5
NDMA	NF	9.4-48.4	38.8-76.4
NEMA	NF	(0.1-7.1	2.1-6.3
NPYR	NF	6.9-41.2	22.7-36.1
II. NDELA	NF (Exp. Cigarettes)	30-51	290
III. TSNA			
NNN	NF (Exp. Cigarettes)	620	3700
NNK	NF (Exp. Cigarettes)	420	320
NAT[b]	NF (Exp. Cigarettes)	410	4600
NNN	NF	85-255	512-625
NNK	NF	70-156	108-432
NAT[b]	NF	81-225	266-353
NNN	NF	29	203
NNK	NF	40-136	
NAT[b]	NF	45	108
NNN	NF	79-885	550-800
NNK	NF	62-185	84-470
NAT[b]	NF	75-380	225-520
NNN	F	213	117-389
NNK	F	32	13-55
NAT[b]	F	92	74-196
IV. Aromatic amines			
2-Toluidine	NF	32.2	162
	F	41.0	66.8
2-Naphthylamine	NF	1.0	1.7
	F	2.1	1.8
4-Aminobiphenyl	NF	2.4	4.6
	F	0.3-0.2	23
V. 2-Nitropropane	NF	220-1190	1430-2180

Table 16 *(continued)*

Carcinogens		Bright or blended tobacco	Burley or black tobacco
VI. PAH			
BaA	NF (Exp. Cigarettes)	21.0-25.9	10.7-16.7
BaP	NF (Exp. Cigarettes)	38-53	24
	NF (Exp. Cigarettes)	7.5-9.6	25
	NF (Exp. Cigarettes)	35.4	19.7
VII. Volatile Aldehydes			
Formaldehyde	NF (Exp. Cigarettes)	26,800-36,300	16,100-25,100
Acetaldehyde	NF (Exp. Cigarettes)	797,000-906,000	726,000-966,000
IX. Benzene		27,000	12,000
X. Quinoline	F	620	1200

Note. Abbreviations: NDMA, nitrosodimethylamine; NEMA, nitrosoethylamine; NPYR, nitrosopyrrolidine; NDELA, nitrosodiethanolamine; TSNA, tobacco-specific *N*-nitrosamines; NNN, *N'*-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, *N'*-nitrosoanatabine; BaA, benz[a]anthracene; BaP, benzo[a]pyrene; NF, nonfilter; F, filter. The pH of the smoke of blond type cigarettes varies between 6.15 (1st puff) and 5.7 (last puff); the pH of the French black cigarette with filter tip measures from 6.8 to 7.4 and without filter tip from 6.6 to 6.95 cm. With pH above 6, the toxicity of the smoke increases.

[a] Black cigarettes = French type black cigarettes made exclusively from Burley tobacco; Blond cigarettes = Virginia type cigarettes and U.S. Blended cigarettes.

[b] NAT contains some N'-nitrosoanabasine (NAB).

Hoffmann and Hoffmann, 1997

made with burley tobacco, this table also indicates those carcinogens that would be expected to be more prevalent in cigar smoke than in cigarette smoke (Hoffmann and Hoffmann, 1997).

BIOMARKERS FOR THE UPTAKE OF TOBACCO SMOKE

Estimates of the smoker's exposure to toxic and carcinogenic smoke constituents are based on the measurements of certain biomarkers. In general, these are determined in saliva, blood, urine, and/or exhaled air.

Nicotine

Upon inhaling alkaline cigar smoke, nicotine is absobed through the mucous membranes in the oral cavity as well as across the alveolar surface of the lung. The nicotine concentration in the blood of a cigar smoker rises gradually (Russell et al., 1980). In blood with a pH of 7.4, about 31 percent of the nicotine is present in unprotonated form. Nicotine transfers from the bloodstream across cell membranes, including those of the central nervous system. In the case of those secondary cigar smokers and of cigarette smokers who inhale tobacco smoke, the aerosol reaches the small airways and alveoli of the lung from which nicotine is quickly absorbed. Within minutes, the blood concentration of nicotine rises to a maximum (U.S. Department of Health and Human Services, 1988). Using nicotine-^{14}C and measuring the radioisotope in exhaled air, Armitage et al., (1975) found that cigarette smokers absorb 82 - 92 percent of the inhaled nicotine; those who do not inhale the smoke absorbed about 29 percent of inhaled nicotine.

After smoking one piece of the respective product, the nicotine level in the plasma of cigarette smokers rose from 25 to between 35 and 40 ng/ml; that of secondary cigar smokers rose from 12.8 to 45.6 ng; and that of primary cigar smokers changed from 3.4 to 5.2 ng/ml as average measurements in five smokers per group (Turner et al., 1977). These data show clearly that the primary cigar smokers takes up far less nicotine because he does not inhale the smoke deep into the lungs as in the case with cigarette smokers and secondary cigar smokers.

Carbon Monoxide The determination of carboxyhemoglobin (COHb) is regarded as the most reliable assay for the uptake of carbon monoxide by smokers. In nonsmokers who have no significant exposure to CO in their occupational or home environment, the COHb level is below 1.7 percent; even levels as low as 0.2 percent COHb have been reported in nonsmokers. Turner et al. (1977) reported the mean concentration of COHb in 1,933 cigarette smokers to be 4.78 percent, with 94.7 percent of the measurements indicating COHb to be (1.7 percent. The mean COHb concentration for 39 primary cigar smokers was 1.36 percent and none showed COHb levels above 1.7 percent. One hundred and fifty-four secondary cigar smokers had a mean COHb concentration of 6.8 percent; 97.4 percent of these had concentrations above 1.7 percent. These data were confirmed by several additional reports, all of which clearly show that the primary cigar smoker tends to inhale not at all or only very shallowly, while the secondary cigar smoker inhales the smoke at least as deeply as the cigarette smoker does.

The determination of CO in exhaled breath is not as reproducible as the COHb determination that measures uptake of CO. However, the method can be readily executed in an office or at any site by just asking the subject to exhale into a CO meter. Ockene et al. (1987) conducted a large-scale study and measured 1.8 - 2.1 CO in the exhaled breath of primary cigar smokers and 3.3 - 11.0 in the breath of secondary cigar smokers. Similar findings were reported by others (Cowie et al., 1973; Goldman, 1976, Wald et al., 1981).

Hydrogen Cyanide The smoke of 1 g tobacco from a cigar contains 1,000 µg of hydrogen cyanide (HCN), and that from a little cigar contains up to 780 µg. The smoke of 1 g cigarette tobacco contains up to 600 µg of HCN (Table 6). The release of HCN into the sidestream smoke per gram of tobacco burned in a little cigar amounts to 114 µg and that in cigarettes reaches 134 - 167 µg (Table 9). Although HCN is liberated from certain food items (cyanogens; *e.g.* cabbage, broccoli, conifers, vegetables, and certain nuts), the quantities produced in this manner are significantly lower than the amounts of HCN inhaled as a tobacco smoke constituent (Galanti, 1997). Therefore, they usually do not interfere with the assay of thiocyanate, the most important metabolite of HCN, in physiological fluids of smokers. Thiocyanate concentration is determined by a colorimetric method in an autoanalyzer (Butts et al., 1974). In one study, the mean concentration of thiocyanate in the saliva of 30 nonsmokers on a cyanogen-containing diet was 101 ± 51 µg/ml; in 15 nonsmokers on a diet free of cyanogens, thiocyanate levels were 92 ± 90µg/ml, and in the saliva of 20 smokers it was 413 ± 172 µg/ml ($p < 0.01$ *vs*. both nonsmokers' groups) (Galanti, 1977).

Pechacek et al. (1985) reported serum thiocyanate levels in never smokers at 2.52 ± 1.60 µg/ml, in primary cigar and pipe smokers at 4.22 ± 2.56 µg/ml, in secondary cigar and pipe smokers at 5.63 ± 3.55 µg/ml, and in cigarette smokers at 8.34 ± 3.03 µg/ml.

Benzene

Benzene, a leukomogenic agent, is a ubiquitous contaminant of the respiratory environment. The American Conference of Governmental Industrial Hygienists has set the upper permissible limit of a time-weighted concentration of benzene for an 8-hour work day and a 40-hour work week (TWA) at 10 ppm (32 µg/L) (American Conference of Governmental Industrial Hygienists, 1996). Benzene in the smoke of 1 g tobacco burned as a cigar, amounts to between 90 and 250 µg per gram tobacco (est. 80-200 µg/L); from 1 g tobacco smoked as a cigarette, one obtains between 8 and 60 µg benzene (est. 25-180 µg/L).

Polynuclear Aromatic Hydrocarbons (PAH)

Tobacco smoke contains at least ten carcinogenic PAH (Hoffmann and Hoffmann, 1997). Benzo(*a*)pyrene (B*a*P) concentration in environmental samples and food items serves as a surrogate measure of PAH-related carcinogenic potential. Per gram tobacco B*a*P yields in the mainstream smoke (MS) of cigars range from 30 to 51 ng; in MS of little cigars, 26 ng; and in MS of a cigarette without a filter tip, 26 - 59 ng (Table 7). Up to 90 percent of the PAH in cigarette smoke is retained upon inhalation in the respiratory tract of a long-term smoker; however, only a small percentage of the PAH is absorbed from food as found in the digestive tract (Bresnick et al., 1983; Grimmer, 1983; Rahman et al., 1986).

Carcinogenic PAH are primarily contact carcinogens. They are metabolically activated by P450 isozymes to their ultimate carcinogenic forms, the dihydrodihydroxy epoxides (Dipple et al., 1984). They form intracellular adducts with macromolecules, including DNA (Dipple et al., 1984). The prevailing DNA adduct formed through B*a*P metabolism is (+)*trans-anti*-7,8-dihydro-9-hydroxy-10-N^2-guanosine (Geacintov et al., 1997).

Among biomakers of uptake and metabolic activation of smoke constituents in cigarette smokers, hemoglobin adducts of 4-aminobiphenyl, BaP, and other PAH have been measured, and urinary metabolites and/or detoxification products of NNK and/or benzene have been quantified. As an indicator of endogenous N-nitrosation, leading to N-nitrosamine formation, N-nitrosoproline has been determined in the urine of cigarette smokers. Similar biomarker studies for cigar smokers are lacking.

SUMMARY AND RESEARCH NEEDS

Today, several types of cigars are marketed in the United States: little cigars, (each weighing less than 1.36 g), regular cigars, small cigars, cigarillos, and premium cigars.

Primary cigar smokers tend not to inhale the cigar smoke, whereas primary cigarette smokers do tend to inhale the cigarette smoke. The principal reason for this difference is the pH of cigar smoke which is initially 6.2 for early puffs and rises to 8.0 for later puffs. At alkaline pH conditions, part of the nicotine is present in unprotonated form in the vapor phase. Unprotonated, volatile nicotine is absorbed through the mucous membrane of the oral cavity and is quickly transported via the bloodstream to the various sites, including the central nervous system, where it exerts the pharmacological effects that seem to "satisfy" the smoker. The elevated pH of the smoke of cigars is caused by the relatively high nitrate content of the air-cured and fermented cigar tobacco (1.4 - 2.1 percent) compared to the nitrate content of the U.S. blended cigarette tobacco (0.5 - 1.7 percent).

In the burning cigar, part of the nitrate is reduced to ammonia and part of it yields NO_x. Nitrogen dioxide in the smoke contributes to the *N*-nitrosation of secondary and tertiary amines. The most abundant amines in tobacco smoke, nicotine and the minor *Nicotiana* alkaloids, are thereby nitrosated and become TSNA. Some TSNA are formed by pyrosynthesis and some TSNA transfer from the tobacco into the smoke. TSNA are present in significantly higher amounts in cigar smoke than in cigarette smoke.

Tobacco smoke contains more than 4,000 individual compounds with about 500 of these in the gas phase. One gram of tobacco burned in a cigar delivers between 39 and 65 mg carbon monoxide and 160 - 300 µg nitrogen oxides compared to maxima of 19 mg carbon monoxide and up to 160 µg of nitrogen oxides for the same amount of tobacco burned in a cigarette. These high concentrations of CO and NO_x in cigar smoke are due to the very low porosity of the cigar binder and wrapper which contrasts with the high porosity of cigarette paper.

Many toxic agents and 62 known carcinogens have been identified among the 4000 compounds in cigarette smoke. Fewer of these have been identified in cigar smoke. However, it is highly likely that most of the toxic and carcinogenic constituents found in cigarette smoke are also present in cigar smoke, albeit at different concentrations. Disregarding studies on the effects of additives to cigar tobacco, there is only a limited need to specifically identify toxic and carcinogenic compounds in cigar smoke.

There exists a need to investigate two particular areas with regard to health effects of cigar smoking. One is the study of the smoking patterns of primary and secondary cigar smokers and of the uptake of toxic and carcinogenic smoke constituents by both types of cigar smokers, as well as the study of metabolism of critical constituents by the cigar smoker. It is especially important to verify the possibility of endogenous formation of carcinogenic *N*-nitrosamines in cigar smokers. Except for a few isolated investigations on nicotine uptake by cigar smokers, these aspects remain unexplored.

The second area of needed investigation relates to the reduction of toxic and carcinogenic agents in cigar smoke, including nicotine. Can the porosity of the cigar wrapper be changed? Is it possible, by addressing this aspect and others, to reduce the high yields of carbon monoxide and "tar" in cigar smoke? Are there ways to reduce the high nitrate content of cigar tobacco? In view of the increasing consumption of cigars in the United States, our knowledge regarding the uptake and metabolic fate of the toxic and carcinogenic agents in cigar smoke, and means for their reduction in the smoke should be intensified. Such efforts need to parallel public health measures toward informing the consumers about the ill effects of cigar smoke on human health.

CONCLUSIONS

1. Cigar smoke contains the same toxic and carcinogenic compounds identified in cigarette smoke.
2. When examined in animal studies, cigar smoke tar appears to be at least as carcinogenic as cigarette smoke tar.
3. The differences in risk between cigarette smoking and cigar smoking appear to be related to the differences in patterns of use of those two tobacco products, principally non-daily use and less inhalation among cigar smokers, rather than a difference in the composition of the smoke.
4. The amount of nicotine available as free, unprotonated nicotine is generally higher in cigars than in cigarettes due to the higher pH of cigar smoke. This free nicotine is readily absorbed across the oral mucosa, and may explain why cigar smokers are less likely to inhale than cigarette smokers.

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