1. Production, Composition, Use and Regulations

1.1 Production and trade

1.1.1 *History*

The common tobacco plants of commerce had apparently been used for millenia by the peoples of the Western hemisphere before contact with Europeans began in 1492. The plants were cultivated by native Americans in Central and South America. Tobacco often had religious uses as depicted in Mayan temple carvings (Slade, 1997).

The start of the spread of tobacco from the Americas to the rest of the world invariably seems to date back to 11 October 1492, when Columbus was offered dried tobacco leaves at the House of the Arawaks, and took the plant back with him to Europe (IARC, 1986a). Presumably, the technique of smoking was picked up at the same time. The plant was named 'nicotiana' after the French ambassador to Portugal, who is said to have introduced it to the French court. The tobacco grown in France and Spain was *Nicotiana tabacum*, which came from seed that originated in Brazil and Mexico. The species first grown in Portugal and England was *Nicotiana rustica*, the seed coming from Florida and Virginia, respectively (IARC, 1986a).

Although claims were made that tobacco had been used earlier in China, no convincing documentation for this exists, but it is clear from Table 1.1 (IARC, 1986a) that tobacco was used widely and that a number of early societies discovered the effects of a self-administered dose of nicotine independently of each other, which implies that the plant was widely distributed, at least throughout the Americas.

Tobacco was grown, smoked and chewed by numerous peoples and eventually became ubiquitous; it certainly featured as an important tradeable source of income from the time of its discovery by Columbus until the present day.

The modern history of tobacco really starts with the design of the cigarette machine in the middle of the nineteenth century; a machine was patented in 1880 by James Bonsack (Bonsack, 1881). Another factor that contributed to the rise of cigarette smoking was concern over the spread of tuberculosis by spitting of smokeless tobacco (Glover & Glover, 1992). Since the 1920s, most tobacco has been smoked in cigarettes, with cigars, pipes and chewing tobacco declining to relatively small proportions of the global consumption. This does not mean that these other forms of use are trivial, as fashions have

Table 1.1. Chronicle of early tobacco cultivation and use

Date	Event
1492 (11 October)	Columbus sighted the home of the Arawaks and was offered 'dried' tobacco leaves.
1499	Amerigo Vespucci recorded the use of chewing tobacco on an island off Venezuela.
1545	Iroquois Indians near Montreal, Canada, were found to have smoking habits.
1556	Tobacco was first grown or became known in France.
1558	Tobacco was used in Brazil and Portugal.
1559	Tobacco was used in Spain.
1560	*Nicotiana rustica* was used in Central Africa.
1565	Tobacco was used in England.
1600	Tobacco was introduced to Italy, Germany, Norway, Sweden, Russia, Persia, India, Indochina, Japan, China and the west coast of Africa.
1612	John Rolfe, at Jamestown, Virginia, was the first man known to grow tobacco commercially for export.
1631	Tobacco production extended to Maryland and then gradually to other areas.
1650s	Portuguese took tobacco to South Africa and other countries. Spaniards distributed tobacco to the Philippines, Guatemala and other Central and South American countries and to the West Indies. Tobacco cultivation was begun in Indonesia. Tobacco cultivation was extended in Europe.

From IARC (1986a)

been started for the use of chewing tobacco and cigars as deliberate marketing ploys within the last two decades (Glover & Glover, 1992; Gupta, 1992; Gerlach *et al*., 1998).

1.1.2 *World production and trade*

World tobacco production is currently declining. It peaked in 1997 at 7 975 360 tonnes (US Department of Agriculture, 2001a) and by 2001 had fallen to 5 883 324 (US Department of Agriculture, 2002a; see Table 1.2). It is a little early to interpret the significance of these figures, and certainly too early to conclude that they reflect the beginning of a long-term downward trend.

The pattern of production has shifted significantly in recent decades. Whereas exports from the USA have fallen slightly, those from Brazil, China and Zimbabwe have increased substantially.

Table 1.2. World tobacco production

Crop year	Hectares	Tonnes
1976/77	4 127 740	5 892 000
1980	3 823 340	5 575 000
1985	4 519 600	6 433 300
1990	4 612 420	7 096 730
1996	4 544 060	7 349 480
1997	4 893 810	7 975 360
1998	4 658 040	7 473 000
1999	3 755 130	6 341 430
2000[a]	NA	5 923 797
2001[a]	NA	5 883 324
2002[a]	NA	5 678 753

From US Department of Agriculture (2001b)
[a] From US Department of Agriculture (2002a)
NA, not available

Table 1.3. Tobacco leaf imports and exports in selected countries between 1970 and 1998 (tonnes)

Country	1970		1998	
	Import	Export	Import	Export
Brazil	9	54 468	14 726	300 513
China	10 337	19 055	20 687	106 355
Malawi	3 602	19 801	1 100	81 000
Turkey	–	74 014	42 174	155 058
USA	99 241	234 262	246 763	215 222
Zimbabwe	–	40 000	9 573	194 141

From Corrao *et al.* (2000)

Table 1.3 gives examples of some of the substantial shifts in tobacco production over the past three decades. Complex reasons lie behind the change in pattern. Economic pressures, often following political decisions, dictate who grows what and where. In developed areas, e.g. in the USA and the European Union, where farmers have, and still do, receive subsidies to grow tobacco, specific measures and programmes have also been initiated to pay farmers to stop growing tobacco or to switch to other crops (Council of the European Union, 2002; US Congress, 2002a,b; Womack, 2002). In developing countries, the cigarette manufacturers may provide seed and expertise as well as an assured market for the tobacco type they need (Time Asia, 2000). In other countries, cigarette manu-

facturers are compelled to purchase a proportion of their tobacco locally. Furthermore, consolidation of cigarette manufacturing followed the opening up of central and eastern Europe with the purchase by transnational corporations of antiquated tobacco monopolies (Griffin-Pustay, 1999, 2002). This affected the pattern of leaf production, import and export. The downward trend in tar and nicotine yields of cigarettes sold in developing countries during the 1990s meant that manufacturers' requirements were changed. The move towards tobacco with a low nitrosamine yield in the USA led to the export of substantial amounts of existing leaf.

The trend towards a smaller number of global brands was accompanied by the trend to global advertising. The complex trading situation is aggravated by the fact that a reported one-third (355 billion cigarettes) of annual global exports are smuggled (Joossens & Raw, 1998). Many smuggled cigarettes may be exported and imported several times.

1.1.3 *What is produced*

There is a wide variety of smoking tobacco products on the world market to chose from, including cigarettes, cigars, cigarillos, bidis, chuttas and kreteks (Table 1.4). Cigarettes and cigars use blended tobaccos and the type of tobacco used in these products has

Table 1.4. Smoking tobacco products

Cigarette	Any roll of tobacco wrapped in paper or other non-tobacco material; filter-tipped or untipped; approximately 8 mm in diameter, 70–120 mm in length
Cigar	Any roll of tobacco wrapped in leaf tobacco or in any other substance containing tobacco Types: little cigars, small cigars ('cigarillos'), regular cigars, premium cigars Some little cigars are filter tipped and are shaped like cigarettes. Regular cigars are up to 17 mm in diameter, 110–150 mm in length.
Bidi	Hand-rolled Indian cigarette; sun-dried temburni leaf rolled into a conical shape together with flaked tobacco and secured with a thread
Chutta[a]	Hand-rolled cigarette used for reverse smoking primarily by women in India
Kretek	Small cigar containing tobacco (approximately 60%[b]), cloves and cocoa. The burning blend gives a characteristic flavour and 'honey' taste to the smoke.

From Stratton *et al*. (2001)
[a] From Narayan *et al*. (1996)
[b] From Clark (1989)

a decisive influence on the physicochemical nature of the smoke they produce. The chemical composition of the tobacco leaf is determined by plant genetics, cultivation practices, weather conditions and curing methods (Tso, 1991). The classification of the leaf tobacco commonly used in cigarettes is primarily based on curing methods and tobacco types. For example, a standard system of classification by the US Department of Agriculture designates six major classes of US tobacco (Table 1.5). Each class comprises two or more different types. Individual types of flue-cured tobacco are no longer easily identified, and the type designation usually refers only to a marketing area. Different countries may use different classification terms, but the general principle is the same.

Table 1.5. Classification of US tobacco types

Tobacco type	Class	Characteristics	Main use	Growing regions
Flue-cured	1	Yellow, blond bright	95% in cigarettes	Alabama, Florida, Georgia, North Carolina, South Carolina, Virginia
Fire-cured	2	Light to dark brown; cured over open fires	'Roll-your-own' cigarettes, chewing tobacco, cigars and smoking tobacco	Kentucky, Tennessee, Virginia
Light air-cured	3A	Burley: cured without supplementary heat	> 90% in cigarettes	Indiana, Kentucky, Missouri, North Carolina, Ohio, Tennessee, Virginia, West Virginia
		Maryland	Almost all in cigarettes	Maryland
Dark air-cured	3B	Light to medium brown	For chewing tobacco and snuff	Kentucky, Tennessee, Virginia
Cigar filler	4	–	Tobacco types for use as cigar fillers, binders and wrappers; used for cigars	Indiana, Ohio, Pennsylvania, Puerto Rico
Cigar binder	5	–	Tobacco types for use as cigar fillers, binders and wrappers; used for cigars	Connecticut, Massachusetts, Minnesota, New York, Pennsylvania, Wisconsin
Cigar wrapper	6	–	Tobacco types for use as cigar fillers, binders and wrappers; used for cigars	Connecticut, Florida, Georgia, Massachusetts
Miscella-neous	7	–		Louisiana

From Tso (1991); US Department of Agriculture (2001c)

The major components of American blend cigarettes are flue-cured tobaccos (often called Virginia, blond or bright tobaccos), air-cured (burley) and Maryland tobaccos, sun-cured (Oriental) tobaccos and reconstituted or homogenized sheet tobacco which is made from tobacco dust, fines and particles, and leaf ribs and stems (Beauman *et al*., 1996; Hoffmann & Hoffmann, 1997). The American blend cigarette has been the predominant type in the USA, and the Virginia blend cigarette has been the most predominant type in Australia, Canada, China, Japan and the United Kingdom (Hoffmann & Hoffmann, 2001).

Blending is done to achieve specific pH, taste, burning characteristics and nicotine content and the type of tobacco blend significantly affects the pH, nicotine content and toxicity of the smoke. The pH strongly influences the concentration of free nicotine in tobacco smoke, whereas the nitrate content influences the carcinogenic potential of smoke. There is a choice of 60 *Nicotiana* species and 100 varieties of tobacco that can be blended. However, almost all commercial tobacco products use *Nicotiana tabacum* species and small amount of *N. rustica*. Cured tobacco lines can contain between 0.2 and 4.75% nicotine by weight, depending on plant genetics, growing conditions, degree of ripening, fertilizer treatment and position of leaf on the stalk (Tso, 1991; Stratton *et al*., 2001).

The actual recipes for blending are closely kept trade secrets and the consolidation of the manufacturing industry worldwide seems to be leading towards a relatively homogeneous cigarette with relatively modest differences in tar and nicotine yield, but considerable diversity in nitrosamine yield (Gray *et al*., 2000).

Roll-your-own (RYO) cigarettes are a cheaper substitute for commercially manufactured brands and are gaining in popularity worldwide. In Europe, two of the major markets for RYO are Germany and the Netherlands (Dymond, 1996). In Canada, they became so popular that, by the end of 1989, sales of RYO accounted for approximately 14% of the Canadian cigarette market (Kaiserman & Rickert, 1992a). In the United Kingdom in 1994, more than 20% of male smokers used RYO products as compared with less than 4% of female smokers (Darrall & Figgins, 1998). In the USA, 3.4 billion RYO cigarettes were smoked in 1994 (Maxwell Tobacco Fact Book, 2000).

A cigar is any roll of tobacco wrapped in leaf tobacco or any other substance containing tobacco. There are four main types of cigar: little cigars, small cigars (‘cigarillos’), regular cigars and premium cigars. Little cigars contain air-cured and fermented tobacco and are wrapped either in reconstituted tobacco or in cigarette paper that contains tobacco and/or tobacco extract. Some little cigars have cellulose acetate filter tips and are shaped like cigarettes. Cigarillos are small, narrow cigars with no cigarette paper or acetate filter. Regular and premium cigars are available in various shapes and sizes and are rolled to a tip at one end. The dimensions of regular cigars are from 110 to 150 mm in length and up to 17 mm in diameter. Regular cigars weigh between 5 and 17 g. Premium cigars (hand-made from natural, long filler tobacco) vary in size, ranging from 12 to 23 mm in diameter and 127 to 214 mm in length (Stratton *et al*., 2001). Although the use of cigarettes declined in the USA throughout the 1990s, consumption of large cigars and cigarillos

increased by 64% during the same period (from 2.34 billion to 3.85 billion pieces; US Department of Agriculture, 2002b).

In certain countries, considerable quantities of tobacco are consumed in forms other than cigarette smoking. Kreteks are a type of small cigarette that contain tobacco (approximately 60%), ground clove buds (40%) and cocoa, which gives a characteristic flavour and 'honey' taste to the smoke (Clark, 1989; Stratton *et al.*, 2001). Kreteks are indigenous to Indonesia, but are also available in the USA. In India, about seven times more bidis are consumed than cigarettes. Bidis are used extensively in India and in the rural areas of several south-east Asian countries (Stratton *et al*., 2001). They are also becoming increasingly popular among teenagers in the USA (Malson & Pickworth, 2002). A bidi is made by rolling a rectangular piece of a dried temburni leaf around approximately 0.2–0.3 g of sun-dried, oriental tobacco and securing the roll with a thread. These cigarettes are perceived by some as a better-tasting, cheaper, safer or more natural alternative to conventional cigarettes (Malson *et al*., 2001; Stanfill *et al.*, 2003). Chutta is an Indian home-made cigar, 5–9 cm long, prepared by rolling local tobacco inside a sun-dried tobacco leaf. Reverse smoking of chutta (with the burning end inside the mouth) is prevalent among women in the rural communities of Andhra Pradesh (van der Eb *et al*., 1993). Chutta is also smoked in the usual way. Additionally, about 40% of total tobacco consumption in India is in the form of smokeless or chewing tobacco (WHO, 1997). Two nicotine-delivery devices which mimic the cigarette, but heat the tobacco rather than burn it, have been developed and test-marketed under the names of Eclipse™ (deBethizy *et al*., 1990; Borgerding *et al*., 1998) and Accord™ (Buchhalter & Eissenberg, 2000).

Reliable figures for the proportion of tobacco that is used for pipes, hand-rolled cigarettes, chewing and snuff (including oral snuff) are not readily available for most countries. Nor is there any good record of the types and amounts of tobacco used as smokeless products.

Tobacco that is grown and used locally is not necessarily taxed or included in national statistics.

1.2 Composition

Both tobacco and tobacco smoke are very complex matrices consisting of thousands of compounds. A total of 3044 constituents have been isolated from tobacco and 3996 from the mainstream smoke of cigarettes (Roberts, 1988). Mainstream smoke is the smoke that is released at the mouth end of the cigarette during puffing whereas sidestream smoke is the smoke released from the burning cone and through the cigarette paper, mostly between puffs. Some 4000 mainstream smoke compounds have been identified to date, and account for more than 95% of the weight of mainstream smoke (Green & Rodgman, 1996; Jenkins *et al.*, 2000). A total of 1172 constituents are present both in tobacco and tobacco smoke (Roberts, 1988). 'Tobacco smoke constituents' refers to all substances present in smoke, regardless of their origin, i.e. whether they come from the

tobacco itself, or from the tobacco additives, the paper, the filter or from the air drawn into the cigarette.

The qualitative composition of smoke components is mainly identical in mainstream smoke, sidestream smoke and secondhand tobacco smoke, sometimes referred to as 'environmental' tobacco smoke (an air-diluted mixture of sidestream smoke and exhaled mainstream smoke). The quantitative composition of these different smoke matrices may, however, vary considerably.

Advances in chemical analytical techniques and an increased knowledge of the genotoxic environmental agents brought the number of carcinogens identified in tobacco smoke to 69 by the year 2000. These carcinogens include 10 species of polynuclear aromatic hydrocarbons (PAHs), six heterocyclic hydrocarbons, four volatile hydrocarbons, three nitrohydrocarbons, four aromatic amines, eight *N*-heterocyclic amines, 10 *N*-nitrosamines, two aldehydes, 10 miscellaneous organic compounds, nine inorganic compounds and three phenolic compounds (Hoffmann *et al.*, 2001).

Eleven compounds (2-naphthylamine, 4-aminobiphenyl, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium, cadmium and polonium-210) classified as IARC Group 1 human carcinogens have been reported as present in mainstream smoke (IARC, 1987, 1990, 1993a, 1994; Hoffmann *et al*., 2001; IARC, 2001).

Since the last *IARC Monograph* on tobacco smoking (IARC, 1986a), the focus of research on carcinogens in tobacco and tobacco smoke has predominantly been on benzo[*a*]pyrene (a surrogate for all PAHs), tobacco-specific *N*-nitrosamines (TSNA), especially *N*′-nitrosonornicotine (NNN) and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and aromatic amines, especially 4-aminobiphenyl (4-ABP), because of their established carcinogenic potency (Vineis & Pirastu, 1997; Hecht, 1998, 1999; Castelao *et al*., 2001; Hecht, 2002).

1.2.1 *Cigarette tobacco*

The types of tobacco used in smoking products are listed in Table 1.5. The most common tobacco product in developed countries is the manufactured cigarette. A cigarette is defined as any roll of tobacco wrapped in paper or other non-tobacco material. Cigarettes can be either commercially manufactured or individually made (roll-your-own). Cigarettes are lit, and the burning process produces smoke that is inhaled through the unlit end. Cigarettes are approximately 8 mm in diameter and 70–120 mm in length (Borgerding *et al*., 2000; Stratton *et al*., 2001).

(*a*) *Occurrence of tobacco-specific carcinogens and their precursors in tobacco*

Unlike cigarette smoke, measurements of nicotine content and other constituents of tobacco have not been made or reported as a part of official tests of commercial cigarettes, although the smoke composition is directly dependent (both qualitatively and quantitatively) on the profile of tobacco smoke precursors.

Table 1.6 shows an international comparison of the concentrations of two carcinogenic tobacco-specific *N*-nitrosamines, NNN and NNK, and their putative precursors, nicotine and nitrate in the tobacco from commercial cigarettes. The assays of a large number of cigarette brands from Canada, the United Kingdom, the USA and other countries around the world, have demonstrated that there is a very wide variation in concentrations of nicotine (from 7.2 to 18.3 mg/cigarette) in the tobacco filler, of nitrate (from 0.3 to 20.6 mg/cigarette), NNN (from 45 to 58 000 ng/g tobacco) and NNK (from not detected to 10 745 ng/cigarette; detection limit < 50 ng/cigarette) (Fischer *et al*., 1989a; Nair *et al*., 1989; Djordjevic *et al*., 1990; Fischer *et al*., 1990b,c; Djordjevic *et al*., 1991b; Tricker *et al*., 1991; Atawodi *et al*., 1995; Kozlowski *et al*., 1998; Djordjevic *et al*., 2000b,c). The country of origin plays a profound role in the chemical composition of the product (e.g. cigarettes from India and Italy contained extremely high levels of tobacco-specific carcinogens, namely, up to 58 000 ng/g NNN and 10 745 ng/cigarette NNK).

The higher TSNA concentrations were usually measured in the tobacco from untipped cigarettes, especially those made of dark tobacco. Among the 55 brands sold in Germany in 1987, the lowest amounts of nitrate, NNN and NNK were measured in Oriental-type cigarettes, followed by Virginia and American blend cigarettes (Table 1.7). The highest levels were reported in the dark tobacco cigarettes (Djordjevic *et al*., 1989a; Fischer *et al*., 1989a,b; Tricker *et al*., 1991). Typically, the levels of NNK are lower than those of NNN in cigarettes except in those made from Virginia flue-cured tobacco, in which higher levels of NNK were reported (Fischer *et al*., 1989a,b, 1990b).

Despite the large variation in the amount of the components measured in various cigarettes by Fischer *et al.* (1989a), the correlations between TSNA and nitrate were high to moderate (NNN: $r^2 = 0.61$; NNK: $r^2 = 0.4$). NNN concentrations increased with increased nitrate concentrations and did not depend on the tobacco type. Oriental and Virginia type cigarettes were very low in nitrate and also had the lowest NNN concentrations. The highest NNN concentrations were found in cigarettes made of dark tobaccos, which also had the highest nitrate levels. The correlation between NNK and nitrate was not as strong as for NNN suggesting that other factors such as the tobacco type may have an influence on the formation of NNK. Although both nitrate and nicotine are precursors for NNN and NNK, only nitrate seems to play a predominant role in their formation. Table 1.7 also shows that NNN, NNK and nitrate levels in tobacco from unfiltered and filtered cigarettes in the same blend category were of the same order of magnitude, although somewhat higher values were reported for unfiltered brands (Tricker *et al*., 1991).

Different types of cigarette are manufactured to deliver different smoke yields under machine-smoking conditions. The terms ‘ultra low-’, ‘low-’, ‘medium-’ and ‘high-yield cigarettes’ are not official government-designated terms but are part of the trademarked names of products that provide information on the smoke yields obtained by machine-smoking using standardized protocols. In general, ultra low-yield products deliver less than 6 mg tar per cigarette, low-yield products between 6 and 15 mg tar and regular ‘full-flavoured’ cigarettes deliver more than 15 mg of tar, although different research groups have made their

Table 1.6. International comparison of the concentration ranges for nitrate, nicotine and preformed tobacco-specific *N*-nitrosamines in tobacco from commercial cigarettes

Country	NO_3^- (nitrate) (mg/cigarette)	Nicotine (mg/g)	NNN (ng/cigarette)	NNK (ng/cigarette)	Reference
Austria	4.2–8.0	NA	306–1122	92–310	Fischer *et al*. (1990c)
Belgium	1.8–10.8	NA	504–1939	219–594	Fischer *et al*. (1990c)
Canada	0.3–3.3	8.0–18.3[a]	259–982	447–884	Fischer *et al*. (1990b); Kozlowski *et al*. (1998)
Germany	0.6–20.6	NA	45–5340	ND[b]–1120	Fischer *et al*. (1989a, 1990c); Tricker *et al*. (1991)
France	1.5–19.4	10.7	120–6019	57–990	Fischer *et al*. (1990c); Djordjevic *et al*. (1989a)
India	NA	14–16.2	1300–58 000[c]	40–4800[c]	Nair *et al*. (1989); Pakhale & Maru (1998)
Italy	6.2–13.3	NA	632 –12 454	153–10 745	Fischer *et al*. (1990c)
Japan	3.7–13.1 mg/g	NA	360–1110[c]	190–330[c]	Djordjevic *et al*. (2000c)
Moldova	NA	NA	93–2090[c]	104–484[c]	Stepanov *et al*. (2002)
Netherlands	1.5–8.8	NA	58–1647	105–587	Fischer *et al*. (1990c)
Poland	4.4–12.8	NA	870–2760	140–450	Fischer *et al*. (1990c)
			670–4870[c]	70–660[c]	Djordjevic *et al*. (2000b)
Sweden	2.4–8.6	NA	544–1511	192–569	Fischer *et al*. (1990c)
Switzerland	6.4–7.8	NA	1280–2208	450–554	Fischer *et al*. (1990c)
United Kingdom	1.4–8.0	9.0–17.5[a]	140–1218	92–433	Fischer *et al*. (1990c); Kozlowski *et al*. (1998)
USA	6.2–13.5	7.2–13.4[a]	993–1947	433–733	Fischer *et al*. (1990c); Kozlowski *et al*. (1998)
	7.8–15.9 mg/g	16.9–17.9	1290–3050[c]	420–920[c]	Djordjevic *et al*. (1990, 2000c)
Former USSR	1.7–9.1	NA	60–850	ND–150[b]	Fischer *et al*. (1990c)
	4.2–17.2 mg/g	7.6–9.4	360–850[c]	ND–70[c,d]	Djordjevic *et al*. (1991b)

NA, not available
[a] Total nicotine (mg/cigarette; Kozlowski *et al*., 1998)
[b] ND, not detected (NNK detection limit < 50 ng/cigarette; Fischer *et al*., 1989a, 1990c)
[c] ng/g tobacco
[d] ND, not detected (NNK detection limit < 10 ng/g; Djordjevic *et al*., 1991b)

Table 1.7. Comparison of the ranges for nitrate, nicotine and preformed tobacco-specific-*N*-nitrosamines in tobacco from commercial cigarettes with a wide range of nicotine and 'tar' yields

Country (total no. of cigarette brands in the study)	Tobacco filler	F/NF	NO_3^- (nitrate) (mg/cigarette)	Nicotine (mg/g)	NNN (ng/cigarette)	NNK (ng/cigarette)	Reference
Canada	Ultra-low yield (V)[a]	F	0.3–3.3	11.2–14.4[b]	288–982	447– 785	Fischer *et al*. (1990b); Kozlowski *et al*. (1998)
(*n* = 25)	Low yield (V)	F	0.4–0.6	11.9–16.7[b]	292–527	510–884	
	Moderate yield (V)	F	0.4–0.8	11.9–18.6[b]	337–407	569–705	
	High yield (V)	F	0.3–1.0	8.0–15.4[b]	259–381	495–663	
Germany	Blend	F	2.2–7.8	NA	400–1390	100–410	Tricker *et al*. (1991)
(*n* = 20)	Blend	NF	5.4–12.3	NA	660–2670	270–500	
	Dark	NF	14.2–20.6	NA	4500–5340	800–960	
(*n* = 55)	Oriental	F + NF	0.6–2.7	NA	45–432	ND–177	Fischer *et al*. (1989a,c)
	Virginia	F + NF	0.7–3.3	NA	133–330	170–580	
	American blend	F	1.8–6.3	NA	500–2534	160–696	
	Dark	NF	10.9–14.4	NA	3660–5316	370–1120	
Japan	Low yield	F	5.7–13.1 mg/g	NA	810–1110[c]	190–330[c]	Djordjevic *et al*. (2000c)[d]
(*n* = 6)	Medium yield	F	3.7–7.5 mg/g	NA	360–1040[c]	200–320[c]	
USA	Ultra-low yield (AB)	F	13.6–14.0 mg/g	17.6–17.9	1750–1980[c]	500–580[c]	Djordjevic *et al*. (1990, 2000c)[d]
(*n* = 13)	Low yield (AB)	F	9.0–12.3 mg/g	17.9	1900–3050[c]	490–800[c]	
	Moderate yield (AB)	F	7.8–10.8 mg/g	16.9	1780–2890[c]	420–890[c]	
	High yield (AB)	NF	11.7–15.9 mg/g	17.9	1290–2160[c]	770–920[c]	

F, filter-tipped cigarettes; NF, non-filtered cigarettes; V, Virginia type cigarettes; AB, American blend cigarettes; NA, not available; ND, not detected

[a] Definite data on the composition of three cigarette brands not available

[b] 23 Canadian cigarette brands; total nicotine (mg/cigarette)

[c] ng/g tobacco

[d] Cigarettes were designated into classes according to nicotine concentrations in mainstream smoke as follows: ultra-low, delivering < 0.5 mg FTC (Federal Trade Commission) nicotine/cigarette; low, delivering 0.5–< 0.85 mg FTC nicotine/cigarette; medium, delivering 0.85–1.2 mg FTC nicotine/cigarette; high, delivering > 1.2 mg FTC nicotine/cigarette. [In Djordjevic *et al.* (2000c), the authors only report the mean nicotine concentration in mainstream smoke of the six brands analysed, and do not specify which brand is unfiltered; the Working Group assumed that it corresponded to a high-yield brand.]

own classifications (Stratton *et al.*, 2001). Tobacco from ultra low-, low-, medium- and high-yield cigarettes contain similar amounts of preformed TSNA and their precursors (Table 1.7) within the brand type regardless the country of origin (Djordjevic *et al.*, 1990; Fischer *et al.*, 1990b; Kozlowski *et al.*, 1998; Djordjevic *et al.*, 2000c). The tobacco from Canadian brands had the least preformed NNN (up to 982 ng/cigarette) and brands in the USA the highest amounts (up to 3050 ng/cigarette). NNK content was of the same order of magnitude between countries (up to 884 ng/cigarette in Canadian cigarettes and up to 920 ng/cigarette in cigarettes in the USA). Japanese cigarettes contained the lowest concentrations of preformed NNK in tobacco (up to 330 ng/g tobacco).

The separate analysis of blend ingredients showed that pure Oriental and flue-cured, pure Virginia tobaccos contain the least nitrate (mean, 1.73 mg/g and 1.54 mg/g, respectively) and preformed tobacco-specific *N*-nitrosamines (mean, 34 ng/g tobacco and 216 ng/g tobacco NNK, respectively) (Table 1.8). The highest nitrate and NNK levels were measured in air-cured pure burley tobaccos (mean, 22.5 mg/g nitrate and 477 ng/g tobacco NNK) (Fischer *et al.*, 1989a). Similar data were reported for flue-cured and sun-dried tobaccos from the former USSR (Djordjevic *et al.*, 1991b).

Table 1.8. Nitrate and tobacco-specific *N*-nitrosamine concentrations in different cured tobaccos produced worldwide

Tobacco type	Nitrate (mg/g)	NNN (ng/g)	NNK (ng/g)
Oriental	0.2–6.0	20–460	ND–70
Virginia	< 0.05–16.0	10–600	30–1100
Burley	8.0–41.0	1300–8850	162–1400

From Fischer *et al*. (1989a); Djordjevic *et al*. (1991b)
ND, not detected (NNK < 50 ppb)

An international comparison of nicotine content in blended cigarettes (Kozlowski *et al.*, 1998) showed a similar spread across the whole range of smoke yields (0.1–1.3 mg nicotine and 1–17 mg tar per cigarette). Tobacco from American blended cigarettes ($n = 32$) contained an average of 10.2 mg nicotine/cigarette (range, 7.2–13.4 mg). The tobacco from Canadian Virginia blend cigarettes ($n = 23$) contained an average of 13.5 mg nicotine/cigarette (range, 8.0–18.3 mg), and that from British Virginia blend cigarettes ($n = 37$), 12.5 mg nicotine/cigarette (range, 9.0–17.5 mg).

(*b*) *The significance of the content of preformed TSNA precursors in tobacco*

The TSNA are formed predominantly during the curing process (Bush *et al*., 2001; Peele *et al*., 2001) although small quantities of TSNA have also been found in freshly harvested (green) leaves. The mean concentrations of NNN and NNK in green leaves

harvested from all stalk positions of the NC-95 flue-cured tobacco plant were 260 ppb and 280 ppb, respectively (Djordjevic *et al*., 1989b). These concentrations were six times higher in cured tobacco (1560 ppb and 1810 ppb, respectively). Bhide *et al*. (1987) reported on the presence of TSNA in green leaves of *N. tabacum* and *N. rustica* species grown in India in two different seasons. In one season, at one location, mature green leaves of *N. rustica* contained as much as 46 100 ppb NNN and 2340 ppb NNK. One year later, tobacco harvested at the same location contained 5730 ppb NNN and 352 ppb NNK. These levels were elevated to 15 000 ppb NNN and 25 800 ppb NNK in sun-cured tobacco. The extremely high potential of *N. rustica* to form carcinogenic TSNA is important because this tobacco species is still commercially grown in Russia, and several other former republics of the former USSR, and in Poland, South America and, to a limited extent, in India (Hoffmann & Hoffmann, 1997). The data shown in Table 1.6 suggest that *N. rustica* may have been used as a component of the blend in Indian (Nair *et al.*, 1989), but not in Polish cigarettes or those from the former USSR.

(*c*) *TSNA-reduced tobacco*

In recent years, it has been demonstrated that the use of new curing technologies can considerably reduce the levels of TSNA, especially NNK, or even completely eliminate them (Djordjevic *et al*., 1999; Wahlberg *et al*., 1999; Peele *et al*., 2001). Inhibition of the microbial reduction of nitrate to nitrite that reacts with tobacco alkaloids to form TSNA is one method to reduce the levels of these carcinogens in tobacco. The second method was described by Peele *et al.* (2001). It is common practice to flue-cure Virginia tobacco in bulk barns that have forced air ventilation and temperature control. Nitrogen oxides (NOx) are a combustion by-product of the liquid propane gas commonly used for curing; they react with naturally occurring tobacco alkaloids to form TSNA. The newly developed heat-exchange curing method precludes exposure of the tobacco to combustion gases and by-products, thereby eliminating this significant source of TSNA formation.

The flue-cured lamina that were used to produce test cigarettes for the evaluation of smoke composition contained from undetectable levels of NNK to 22 ng/g tobacco (detection limit for NNK, 0.11 ng/g tobacco; Djordjevic *et al.*, 1999). The concentration of nitrogen in the form of nitrite in 'TSNA-reduced' tobacco was similar, however, to that determined for a commercial American blend cigarette (1.8 versus 1.9 µg/g tobacco). The concentration of nitrogen in the form of nitrate was somewhat lower (1.5 versus 2.0 mg/g tobacco) and the nicotine content was higher (22.2 versus 15.9 mg/g tobacco). The levels of NNK in mainstream smoke as determined using the Federal Trade Commission (FTC) method in the test cigarette made with 'TSNA-reduced' tobacco were 6.5 ng/cigarette compared with 130 ng in a commercial American blend cigarette tested under the same experimental conditions (30% and 25% of the levels measured in tobacco, respectively).

(*d*) *The origin of TSNA in tobacco smoke*

The question of the origin of TSNA in the mainstream smoke has been also the subject of investigation since the previous *IARC Monograph* on tobacco smoking (IARC,

1986a). The studies have reported different results. In one study, the tobacco column was spiked with [carbonyl-^{14}C]NNK to determine the recovery of unchanged NNK in the smoke, and with [methyl-^{14}C]nicotine, to determine the extent of nicotine nitrosation during smoking. The researchers found that most of the NNK in cigarette smoke (63–74%) is pyrosynthesized from nicotine and nitric oxides during combustion and that the NNK yield in the smoke is independent of the nitrate content in the tobacco (Adams *et al*., 1983). Similarly, based on the 11.3% transfer rate of [^{14}C]-labelled NNN, it was concluded that 46% of NNN in the mainstream smoke of US blended cigarettes is due to the transfer from tobacco and that the remainder is synthesized during smoking (Hoffmann *et al*., 1977). More recent studies, however, have demonstrated that the levels of preformed TSNA in tobacco determine yields in smoke. The addition of the nitrosamine precursors nitrate and nicotine to the tobacco before the machine-smoking of cigarettes did not change the levels of NNN and NNK in mainstream smoke (Fischer *et al*., 1990a). The mainstream smoke/tobacco ratios for NNN and NNK for the commercial German cigarettes, even when corrected for the ventilation and cigarette length, remained constant and were dependent neither on the nicotine nor the nitrate content of the tobacco with the exception of NNK in the cigarettes made from nitrate-rich dark tobacco (Fischer *et al*., 1990a). The calculated transfer rates for NNN and NNK from tobacco in the mainstream smoke were 23% and 34%, respectively, for untipped cigarettes and 13% and 23%, respectively, for filter-tipped cigarettes. Based on these results, Fischer *et al*. (1990a) concluded that pyrosynthesis of NNN and NNK is not likely, at least for cigarettes containing Virginia, American blend and Oriental type tobacco.

The addition of increasing amounts of potassium nitrate (0.22%, 0.53%, 1.12% and 1.78% in the tobacco filler) in experimental blend cigarettes (50% Virginia, 15% Oriental, 10% Burley and 25% reconstituted tobacco sheets) resulted in a linear increase in the concentrations of oxides of nitrogen and *N*-nitrosopyrrolidine (NPYR), a volatile *N*-nitrosamine. NNK was not influenced by the nitrate concentrations in the tobacco filler whereas NNN and *N*′-nitrosoanatabine increased slightly with increased nitrate concentrations (Tricker *et al*., 1993a).

When an American blend unfiltered cigarette was spiked with 10 mg nicotine prior to machine-smoking, no detectable NNN or NNK was formed (Djordjevic *et al*., 1991a). The addition of 1 mg of the secondary tobacco alkaloid nornicotine, however, increased the concentration of NNN in mainstream smoke by 27%. The spiking of a French dark tobacco, untipped cigarette with 10 mg nicotine increased the NNK level in mainstream smoke by 40%. Brunnemann *et al*. (1996) concluded, based on the analysis of a variety of commercial Thai cigarettes, across a wide range of yields in smoke, that the concentration of TSNA in mainstream smoke, as well as the tar and nicotine yields, depend on tobacco composition.

The preformed TSNAs in tobacco appear to be determinants of the TSNA yields in the mainstream smoke of certain types of cigarette, although some formation may also occur under certain conditions during smoking.

However, there are other (qualitative) factors to be considered. Of particular note is the trend, at least in the USA, towards tobaccos higher in nitrate that lead to an increase in carcinogenic TSNAs in smoke and a reduction in carcinogenic PAHs (Hoffmann & Hoffmann, 1997). A major US cigarette manufacturer was awarded a patent in 1978 for developing a process that reduces the nitrate content of the reconstituted tobacco made from ribs and stems by more than 90%. It is unclear to what extent this patented method has been applied to the manufacture of cigarettes (Hoffmann & Hoffmann, 2001).

(*e*) *The occurrence of volatile* N-*nitrosamines and non-volatile* N-*nitrosamino acids and other toxic compounds in tobacco*

In addition to TSNA, the presence of several carcinogenic volatile *N*-nitrosamines, including *N*-nitrosodimethylamine (NDMA), *N*-nitrosoethylmethylamine (NEMA) and NPYR has been reported in cigarette tobacco (Tricker *et al*., 1991). The levels of volatile *N*-nitrosamines in tobaccos from 20 commercial German cigarettes were: NDMA, from 0.4 to 5.0 ng/cigarette; NEMA, from not detected (limit of detection, 0.1 ng/cigarette) to 1.5 ng; and NPYR, from 0.6 to 5.2 ng/cigarette. The levels of NEMA and NPYR were 87% and 53% higher in untipped than in filter-tipped cigarettes of the same blend type. The highest levels were measured in unfiltered brands made of dark tobacco.

The presence of several non-volatile *N*-nitrosamino acids, such as 4-(*N*-nitroso-*N*-methylamino)butyric acid (NMBA), *N*-nitrosopipecolic acid (NPIC), *N*-nitrososarcosine (NSAR), 3-(*N*-nitroso-*N*-methylamino)propionic acid (NMPA), *N*-nitrosoproline (NPRO), *N*-nitrosodiethanolamine (NDELA) and 4-(*N*-nitrosomethylamino)-4-(3-pyridyl)butyric acid (*iso*-NNAC), have also been reported in cigarette tobaccos (Djordjevic *et al*., 1989a, 1990; Tricker *et al*., 1991). Some of them, such as NSAR (IARC, 1978), NMPA and NMBA, are carcinogenic *per se* (Hoffmann *et al*., 1992), whereas others may undergo thermal decarboxylation during the pyrolysis of cigarette tobacco (Brunnemann *et al*., 1991) to yield their corresponding volatile *N*-nitroso analogues; for example, pyrolytic decarboxylation of NPRO gives rise to NPYR, whereas NMPA gives rise to NEMA. The levels of *N*-nitrososarcosine in cigarette tobacco range from 22 to 460 ng per cigarette, NMPA from 110 to 4990 ng/cigarette, and NMBA from not detected (limit of detection, 1.0 ng/cigarette) to 200 ng/cigarette. The upper values were usually found in untipped cigarettes made from dark tobacco (Tricker *et al*., 1991).

In 1989, the nicotine derived *N*-nitroso acid *iso*-NNAC was identified (Djordjevic *et al*., 1989a) and its concentration measured in both French dark tobacco and American blend cigarettes (Djordjevic *et al*., 1989a, 1990, 1991a). The *iso*-NNAC levels in tobacco ranged from not detected to 50 ppb, being higher in French dark tobacco cigarettes. *iso*-NNAC was not detected in the mainstream smoke of American blend cigarettes and was formed in minute amounts when the filler was spiked with the putative precursors cotinine and cotinine acid 4-(methylamino)-4-(3-pyridyl)butyric acid (COTAC) prior to machine smoking (Djordjevic *et al*., 1991a).

The minute amounts of preformed *iso*-NNAC in blended tobacco (other than dark tobacco), its very low transfer rate in mainstream smoke (1.1%), and the possibility that

this compound can also be formed endogenously, could make it a suitable candidate biomarker for the assessment of the levels of endogenously formed tobacco-derived *N*–nitrosamines. However, in one study, *iso*-NNAC was detected in the urine of four of 20 cigarette smokers (at levels of 44, 65, 74 and 163 ng/day) (Tricker *et al*., 1993b). The oral administration of nicotine and cotinine to abstaining smokers did not result in *iso*-NNAC excretion even after supplementation with 150 mg oral nitrate. The authors concluded that the occasional presence of *iso*-NNAC in smokers' urine resulted from exogenous exposure to the preformed compounds in mainstream smoke and not from the endogenous nitrosation of nicotine and its metabolites. It was not clear whether there were any smokers of dark tobacco cigarettes among the 20 volunteers in this study.

Stanfill and Ashley (1999) quantified 12 flavour-related compounds in cigarette tobacco: coumarin, pulegone, piperonal and nine alkenylbenzenes, including *trans*-anethole, safrole, methyleugenol and myristicin. In 62% of 68 brands analysed, one or more of these flavour-related compounds were detected (concentrations ranged from 0.0018 to 43 μg/g tobacco). The toxic properties and in some cases carcinogenic properties (e.g. of coumarin and safrole) (IARC, 1976) of these flavour-related compounds may constitute an additional health risk related to cigarette smoking.

1.2.2 *Mainstream cigarette smoke*

Cigarette mainstream smoke aerosol can be broadly categorized as consisting of CO, other vapour-phase components, particulate matter (tar) and nicotine. These four major components of smoke are simultaneously delivered to the active smoker as a complex and dynamic aerosol containing thousands of chemical constituents composed of several billion electrically-charged semi-liquid particles per cm^3 (aerodynamic diameter, 0.1–0.3 μm; 5×10^9 particles per cm^3) within the mixture of combustion gases (Smith & Fischer, 2001). The chemicals in the mainstream smoke aerosol are distributed between the particulate and vapour phase depending on their physical properties (e.g. volatility and stability) and their chemical properties as well as the characteristics of the environment (Jenkins *et al.*, 2000).

According to Hoffmann and Hoffmann (1997, 2001) and Kozlowski *et al*. (2001), the composition of cigarettes and of cigarette smoke has changed dramatically since the first large-scale epidemiological studies linking smoking and lung cancer were conducted in the 1950s (Doll & Hill, 1950; Wynder & Graham, 1950) and the subsequent reports of the Royal College of Physicians (1962), US Department of Health and Human Services (1964) and IARC (1986a). During that period, numerous carcinogens in tobacco smoke were identified and quantified and their biological activities and relevance to cancer have also been studied. The major focus, though, has been on PAHs such as benzo[*a*]pyrene and TSNAs such as NNK, which are considered to be major lung carcinogens (Hecht, 1998, 1999). 4-ABP and other aromatic amines have also been studied intensively because of their role in bladder carcinogenesis (Castelao *et al*., 2001). The carcinogenic heterocyclic amines such as 2-amino-1-methyl-6-phenylimidazo(4,5-*b*)pyridine (PhIP),

frequently found in cooked foods, and 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-1) and 2-aminodipyridol[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-2), the pyrolysis products of glutamic acid, have also been quantified in the smoke of filtered cigarettes from Japan, the United Kingdom and the USA (Kanai *et al*., 1990; Manabe *et al*., 1991).

(*a*) *Nicotine, tar and CO yields and other components in cigarette smoke*

(i) *Machine-smoking method — ISO/FTC parameters*

In 1998, there were 1294 brands of cigarette on the market in the USA for which the emissions of tar, nicotine and carbon monoxide (CO) had been measured (Federal Trade Commission, 2000). The reported emissions were based on a standardized machine-smoking procedure, introduced in 1936 by Bradford *et al*., and adopted with some modifications by the Federal Trade Commission (Federal Trade Commission, 1967; Pillsbury *et al*., 1969). This method sets up the smoking machine to draw 35-mL puffs of 2 sec duration once per minute until the predetermined butt length of 23 mm for unfiltered cigarettes — or the length of filter over wrapping paper plus 3 mm for filtered cigarettes — has been reached. Ventilation holes (when present) are not blocked during smoking.

The FTC machine-smoking method, which is used in the USA, is very similar to that of the International Organization for Standardization (ISO), which is used widely throughout the rest of the world (Eberhardt & Scherer, 1995). The key parameters of these and of the other machine-smoking protocols referred to in this monograph are summarized in Table 1.9.

Table 1.9. Machine-smoking protocols for measuring smoke yields of tobacco products

Protocol	Puff duration (sec)	Puff interval (sec)	Puff volume (mL)	Butt length (mm)	Filter ventilation holes
Tobacco Research Council	2	60	35	25	NA
Federal Trade Commission	2	60	35	23[a]	Open
International Standards Organization	2	60	35	23[a]	Open
Massachusetts	2	30	45	23[a]	50% blocked
Health Canada 1998–99	2	26	56	23[a]	Fully blocked
Health Canada 2000	2	30	55	23[a]	Fully blocked
International Committee for Cigar Smoke Study	1.5	40	20	33	Open

NA, not applicable

[a] Cigarettes smoked to a 23-mm butt length or, if in excess of 23 mm, to the length of the filter and overwrap plus 3 mm

Tar yields in mainstream smoke are influenced primarily by filtration, ventilation (filter tip ventilation and paper porosity) and the choice of tobacco type and blending recipe. As with any agricultural product, there is natural variation in tobacco composition from year to year. In order to manufacture a consistent product, tobacco blends are made using the crops from previous years. The length of cigarettes and their burning rate also influence smoke yields. A faster rate of burning results in a lower tar yield in mainstream smoke per cigarette, because the burn time determines the number of puffs and the total tar delivery increases with each puff (Kozlowski *et al*., 1980; Darby *et al*., 1984; Kozlowski *et al*., 1998).

The tar and nicotine yields of cigarettes marketed in the USA have been systematically reported by the FTC since 1967, and the carbon monoxide (CO) ratings since 1980. The mainstream smoke of cigarettes currently marketed in the USA yields from < 0.05 mg to 2 mg nicotine, < 0.5 mg to 27 mg tar and < 0.5 mg to 22 mg CO per cigarette. The sales-weighted average yields of nicotine and 'tar' in smoke are now 0.9 mg and 12 mg per cigarette, compared with 1.4 mg and 21.6 mg, respectively, in 1968, a decrease of about 40% (Federal Trade Commission, 2000).

The reduction in tar has been achieved by several methods including reduced tobacco weight, improved filtration, dilution with air through ventilation holes on the filter wrapping paper, the use of reconstituted and expanded tobacco, the use of chemical additives to control the combustion rate and changes in agronomic practices. These modifications have also significantly reduced the yields of constituents associated with the vapour phase (Hoffmann & Hoffmann, 2001; Kozlowski *et al*., 2001). For example, in comparison with an untipped cigarette with a yield of vinyl chloride of 15.3 ng/cigarette, charcoal filtration reduced vinyl chloride in mainstream smoke to 5.1 ng/cigarette. The yield of benzene in mainstream smoke was correlated with the amount of tobacco burned and with the tar level. Agronomic factors such as production practices and soil characteristics, and environmental conditions such as rainfall, reportedly influence the accumulation of metals, including cadmium, beryllium, chromium, nickel and arsenic in the leaf. The use of fertilizers low in nitrates and heavy metals could reduce the yields of specific constituents in mainstream smoke (Smith *et al*., 1997).

In the USA, the FTC-rated yields of tar and nicotine in smoke decreased by at least 60% between 1950 and 1993 due largely to the introduction of filters (Stellman *et al*., 1997). However, smokers responded to low-yield cigarettes by changing their smoking behaviour so that they still obtained the desired amount of nicotine. Nicotine concentration in mainstream smoke is highly correlated with that of tar (r = 0.97 [0.93–0.99]; Kozlowski *et al*., 1998). The subject of changes in lung cancer mortality or incidence subsequent to changes in cigarette composition is discussed in Section 2.1.

In the United Kingdom, sales-weighted average tar yields have declined steadily. For example, in 1999, tar yield was 9.6 mg per cigarette, less than half the level in 1972. Over the same period, nicotine yields have decreased from 1.33 mg to 0.8 mg per cigarette; CO yields have shown smaller declines. At the same time as the absolute yields have declined, there have also been changes in tar to nicotine ratios. Smokers in the United Kingdom in

1999 were exposed to 22% less tar per unit of nicotine than in 1973. In the United Kingdom, cigarettes have been tested according to ISO standards since 1991. Before 1991, the Laboratory of the Government Chemist used a UK-specific definition of butt length, which resulted in slightly higher yields than the ISO method. There were also changes to the way nicotine was measured in 1991 which resulted in a decline of about 5% in values measured, or 0.05 mg/cigarette for a mean yield of 1 mg (Jarvis, 2001). During 1983–90, a series of special studies investigated the yields and range of additional analytes (e.g. hydrogen cyanide, aldehydes, acrolein, nitric oxide (NO), low-molecular weight phenols and PAHs) and their inter-relationship with the routinely monitored components. With the exception of NO, which is strongly dependent on tobacco type, and the delivery of some phenols and PAHs, the routinely monitored tar, nicotine and CO provided an adequate guide to the yields of other analytes in mainstream smoke of cigarettes available in the United Kingdom in the 1980s. Standard machine smoking conditions in terms of the duration (2 sec), volume (35 mL) and interval (58 sec) between puffs were applied (Phillips & Waller, 1991).

(ii) *ISO–FTC machine-smoking method — human smoking parameters*

When standard international smoking conditions (cigarettes were machine-smoked to a fixed butt length of 30 mm or filter-plus-overwrap plus 3 mm, when this length was greater than 27 mm; FTC puff volume, duration and frequency were applied) were compared with 26 different nonstandard conditions (variable puff volume, puff duration and interval between puffs), it was revealed that up to 95% of the variation in tar yield per cigarette could be explained by variation in the total volume of smoke produced per cigarette (Rickert *et al*., 1986).

When the influence of smoking parameters (puff profile including duration, volume and frequency of puffs) on the delivery of TSNAs into mainstream smoke was investigated, the total volume drawn through the cigarette was found to be the main factor responsible for the amount of TSNA delivery in mainstream smoke (Fischer *et al*., 1989c).

To obtain realistic estimates of smokers' exposure to components of cigarette smoke, the puffing characteristics of 133 adult smokers of cigarettes rated by the FTC as having yields of 1.2 mg of nicotine or less (56 smokers of low-yield cigarettes (≤ 0.8 mg nicotine/cigarette) and 77 smokers of medium-yield cigarettes (0.9–1.2 mg nicotine per cigarette)) were assessed by a pressure transducer system. The smoking profiles for a randomly chosen subset of 72 smokers were then programmed into a piston-type machine to generate smoke from each smoker's usual brand of cigarettes for assays of nicotine, tar, carbon monoxide, benzo[*a*]pyrene and NNK. The FTC protocol was used in parallel to assess levels of benzo[*a*]pyrene and NNK in the 11 brands most frequently smoked by study subjects. Comparison with the FTC protocol values showed that smokers of low- and medium-yield brands took statistically significantly larger puffs (48.6-mL and 44.1-mL puffs, respectively) at statistically significantly shorter intervals (21.3 and

18.5 sec, respectively) and they drew larger total smoke volumes than those specified in the FTC parameters. Consequently, smokers of low- and medium-yield brands received 2.5 and 2.2 times more nicotine and 2.6 and 1.9 times more tar, respectively, than FTC-derived amounts, as well as about approximately twice as much benzo[*a*]pyrene and NNK. Smokers of medium-yield cigarettes received higher doses of all components than did smokers of low-yield cigarettes. The major conclusion of this study was that the FTC protocol underestimates doses of nicotine and carcinogens received by smokers and overestimates the proportional benefit of low-yield cigarettes (Djordjevic *et al*., 2000a).

(iii) *Machine-smoking method — Massachusetts parameters*

The most comprehensive data on the profile of the biologically active mainstream and sidestream smoke constituents of contemporary cigarettes, based on standardized machine-smoking methods, were compiled in 'The 1999 Massachusetts Benchmark Study. Final Report' (Borgerding *et al*., 2000). Eighteen leading brands from the USA (26 brand styles with between 0.05 and 9% of market share by brand style), delivering from 1 to 26 mg tar per cigarette (by FTC parameters) were screened. All were American blend cigarettes made by mixing different tobacco types and grades, including reconstituted tobacco sheets, expanded tobacco and additives. Cigarette smoke was generated for the assay of 44 constituents (Table 1.10) both in vapour and particulate phase using both the FTC method and the Massachusetts machine-smoking method (45-mL puffs of 2 sec duration drawn twice a minute until the predetermined butt length of 23 mm for untipped cigarettes (or the length of filter over wrapping paper plus 3 mm) was reached: when applicable, the ventilation holes were 50% blocked) (Borgerding *et al*., 2000). The 'more intense' Massachusetts method was developed in response to the debate on the validity of the FTC method for the assessment of smokers' exposure (Shopland, 2001).

The yields of selected toxic and carcinogenic mainstream smoke constituents obtained by machine-smoking of the 26 brand styles of cigarettes using the Massachusetts method are shown in Table 1.10 (these data were also summarized by Gray & Boyle, 2002). The average nicotine yields of the 26 brands tested ranged from 0.50 mg to 3.32 mg/cigarette. The results are representative of the nature of mainstream smoke, as they illustrate the variety of constituents present and their variations in yield even within a narrow range of products. Relatively few constituents (e.g. tar, nicotine and CO) are delivered in milligram-per-cigarette quantities. Twenty-four of the 44 constituents assayed (including benzene, formaldehyde, 1,3-butadiene and acetaldehyde) are delivered in microgram-per-cigarette quantities and the remainder in nanogram-per-cigarette quantities. For some compounds, the data presented in Table 1.10 compare well with those published earlier by the National Research Council (1986). However the emission of others (e.g. acetone, acrolein and benzene) exceeds the levels reported in 1986. The explanation for these discrepancies is that the NRC values described the range of deliveries measured by the machine-smoking of commercial untipped cigarettes using the FTC method, whereas the data from the Massachusetts Benchmark Study describe the mainstream smoke emissions from filtered cigarettes measured using the more intense smoking method.

Table 1.10. Yields of 44 smoke constituents in the mainstream smoke of cigarettes assayed for the 1999 Massachusetts Benchmark Study

Constituent	Median yield/ cigarette	Range/cigarette	Unit
Tar	25.8	6.1–48.7	mg
Carbon monoxide	22.5	11.0–40.7	mg
Nicotine	1.70	0.50–3.32	mg
Acetaldehyde	1618.1	596.2–2133.4	µg
Isoprene	713.2	288.1–1192.8	µg
Acetone	627.9	258.5–828.9	µg
Nitric oxide	457.3	202.8–607.1	µg
Hydrogen cyanide	380.8	98.7–567.5	µg
Methyl ethyl ketone	170.3	72.5–230.2	µg
Acrolein	162.9	51.2–223.4	µg
Toluene	124.2	48.3–173.7	µg
Propionaldehyde	110.2	46.8–144.7	µg
Hydroquinone	103.9	27.7–203.4	µg
Catechol	92.1	28.1–222.8	µg
Benzene	75.9	28.0–105.9	µg
1,3-Butadiene	75.2	23.6–122.5	µg
Butyraldehyde	70.0	28.8–95.6	µg
Formaldehyde	49.5	12.2–105.8	µg
Crotonaldehyde	44.1	11.6–66.2	µg
Ammonia	36.6	9.8–87.7	µg
Phenol	25.1	7.0–142.2	µg
Acrylonitrile	23.2	7.8–39.1	µg
meta-Cresol + *para*-cresol	19.4	7.3–77.3	µg
Pyridine	14.9	2.8–27.7	µg
Styrene	11.7	4.5–19.3	µg
ortho-Cresol	8.0	ND–33.9	µg
Quinoline	1.0	0.3–2.7	µg
Resorcinol	NQ	NQ	µg
NNN	199.1	99.9–317.3	ng
N-Acetyltransferase	186.3	95.2–298.6	ng
NNK	147.3	53.5–220.7	ng
Cadmium	131.8	31.0–221.8	ng
Lead	52.1	11.0–92.1	ng
1-Aminonaphthalene	30.7	13.4–64.5	ng
N-Nitrosoanabasine	26.2	14.2–45.3	ng
Benzo[*a*]pyrene	22.5	5.6–41.5	ng
2-Aminonaphthalene	15.5	5.7–28.6	ng
Arsenic	10.7	1.6–24.9	ng
Mercury	4.8	2.5–14.2	ng

Table 1.10 (contd)

Constituent	Median yield/ cigarette	Range/cigarette	Unit
4-Aminobiphenyl	4.5	1.8–7.8	ng
3-Aminobiphenyl	2.9	1.3–4.8	ng
Nickel	NQ	ND	ng
Chromium	NQ	ND	ng
Selenium	NQ	ND	ng

From Borgerding *at al*. (2000)
ND, not detected (limit of detection for nickel, 8.4 ng/cigarette; for chromium, 3 ng/ cigarette; for selenium, 11.4 ng/cigarette; and for *ortho*-cresol, 1.3 μg/cigarette); NQ, not quantifiable (limit of quantification for resorcinol, 3 μg/cigarette); NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

The functional relationships established by the Massachusetts Benchmark Study can be used to predict the yields of certain individual mainstream smoke constituents for other brand styles that have not yet been tested, but for which data on nicotine, tar and CO yields measured using the FTC parameters are available. The example brand of cigarette illustrated in Table 1.11 is a full-flavour brand style that delivers 1.1 mg nicotine and 14.5 mg tar according to the FTC method. By using the data on nicotine obtained by the FTC method for the example brand, the yields of mainstream smoke constituents found in the particulate phase can be predicted (these values are shown in the 'mean' column). Similarly, the CO yield for the example brand provides the basis for predicting mainstream smoke vapour-phase constituents. The highlighted constituents in Table 1.11 are predicted based on the CO yield. In addition to the mean values interpolated from the mainstream smoke functional relationships, lower and upper prediction interval values are provided. For nicotine, the predicted upper yield for the example brand was 2.4 mg per cigarette and that for tar 34 mg per cigarette. Therefore, the established functional relationships provide both tentative predictions of the yields of some individual constituents, given standard nicotine and CO yields, and the expected range of yields of some constituents.

The drawback of this approach is that cigarettes with different tar and nicotine yields as measured by the FTC method are designed in ways that lead smokers to smoke them differently. Therefore, no single set of machine-smoking parameters will adequately reflect individual smoking behaviours and the resulting exposure to smoke carcinogens. Moreover, a very large inter-individual variation in smoking topography[1] for each brand needs to be taken into consideration during the exposure assessment. To demonstrate this,

[1]Smoking topography is a method of assessing exposure, e.g. how much smoke enters the lung as estimated by measuring puff volume, the number of puffs per cigarette, puff duration, total inhalation time, flow rate and interval between puffs.

Table 1.11. Application of mainstream functional relationships to estimate yield values for a hypothetical brand style: Massachusetts smoke constituent form

Brand name…….	Example brand
Sub brand……	Full flavour
FTC Nicotine yield (mg/cigarette)…….	1.10
FTC Carbon monoxide yield (mg/cigarette)…..	14.5

Constituents	Units	Massachusetts yields predicted from 1999 Benchmark Study		
		Mainstream smoke		
		Mean	Lower[a]	Upper[a]
Nicotine	mg/cigarette	2.2	1.9	2.4
'Tar'	mg/cigarette	31	28	34
CO	mg/cigarette	27	19	34
Ammonia	µg/cigarette	50	32	67
2-Aminonaphthalene	ng/cigarette	18	13	23
1-Aminonaphthalene	ng/cigarette	37	29	44
4-Aminobiphenyl	ng/cigarette	5	4	6
Benzo[*a*]pyrene	ng/cigarette	27	24	31
Formaldehyde	µg/cigarette	69	43	95
Acetaldehyde	µg/cigarette	1796	1488	2104
Acetone	µg/cigarette	696	566	825
Acrolein	µg/cigarette	184	150	218
Propionaldehyde	µg/cigarette	125	100	150
Crotonaldehyde	µg/cigarette	55	42	67
Methyl ethyl ketone	µg/cigarette	196	154	238
Butyraldehyde	µg/cigarette	81	64	98
Hydrogen cyanide	µg/cigarette	436	373	500
Mercury	ng/cigarette	6	2	10
Nickel	ng/cigarette	< 12	NA	NA
Lead	ng/cigarette	63	44	82
Cadmium	ng/cigarette	151	110	192
Chromium	ng/cigarette	< 12	NA	NA
Arsenic	ng/cigarette	14	< 12	19
Selenium	ng/cigarette	< 12	NA	NA
Nitric oxide	µg/cigarette	514	409	618
N′-Nitrosonornicotine	ng/cigarette	250	158	342
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone	ng/cigarette	176	140	213
N-Nitrosoanatabine	ng/cigarette	231	154	308
N-Nitrosoanabasine	ng/cigarette	33	21	46
Pyridine	µg/cigarette	19	13	24

Table 1.11 (contd)

Constituents	Units	Massachusetts yields predicted from 1999 Benchmark Study		
		Mainstream smoke		
		Mean	Lower[a]	Upper[a]
Quinoline	µgcigarette	1	1	2
Hydroquinone	µg/cigarette	125	89	160
Resorcinol	µg/cigarette	< 3	NA	NA
Catechol	µgcigarette	121	80	161
Phenol	µg/cigarette	37	10	64
meta + *para*-Cresol	µg/cigarette	26	12	41
ortho-Cresol	µg/cigarette	9	< 5	19
1,3-Butadiene	µg/cigarette	89	60	119
Isoprene	µg/cigarette	846	594	1099
Acrylonitrile	µg/cigarette	30	16	43
Benzene	µg/cigarette	87	62	113
Toluene	µg/cigarette	143	102	184
Styrene	µg/cigarette	14	9	19

From Borgerding *et al*. (2000)
[a] 'Lower' and 'upper' values calculated from 95% prediction intervals
NA, not applicable

the smoke yields measured by the Massachusetts method for the two leading full flavour regular and mentholated cigarettes in the USA were compared with the values obtained by mimicking the puffing patterns of two individuals who smoked those particular cigarettes (Table 1.12). The smoker of the mentholated brand drew in 5.6 mg nicotine per cigarette and the smoker of the non-mentholated brand drew in 4.1 mg nicotine. These amounts were twice those estimated by the Massachusetts method. Moreover, the smoker of non-mentholated brand took in four times more carcinogenic TSNAs (Djordjevic *et al*., 2000a) than determined by the 'intense' Massachusetts method or by the FTC method.

When hand-rolled Thai cigarettes made with local-brand tobacco were machine-smoked at a rate of two puffs per minute, an average of 5.8 mg nicotine per cigarette was measured in the mainstream smoke by the FTC method (Mitacek *et al*., 1990). Indian cigarettes delivered up to 34 mg total particulate matter and up to 2.6 mg nicotine per cigarette when machine-smoked under the same conditions (Pakhale & Maru, 1998).

The delivered doses of some gaseous carcinogens could be higher than those shown in Table 1.10 if smokers completely blocked the filter air vents during puffing. Brunnemann *et al*. (1990) found that the levels of 1,3-butadiene, acrolein, isoprene, benzene and toluene were 3.3–8.8 times higher than the levels obtained by not blocking the ventilation holes. Stanfill and Ashley (2000) also reported that complete blocking of

Table 1.12. The yields of four components in the mainstream smoke of the two leading full-flavour filter-tipped cigarettes from the USA smoked by two individuals

	Full-flavour, non-mentholated				Full-flavour, mentholated			
	FTC[a]	Mass.[b]	HSC[c]	HSC/ Mass.	FTC	Mass.	HSC[d]	HSC/ Mass.
Nicotine (mg/cigarette)	1.1	2.1	4.1	2.0	1.2	2.6	5.6	2.2
B*a*P (ng/cigarette)	12.5	27.8	34.6	1.2	15.4	31.2	34.3	1.1
NNN (ng/cigarette)	270	202.0	794.0	3.9	302	243.1	537.0	2.2
NNK (ng/cigarette)	156	184.0	714.0	3.9	164	198.4	239.0	1.2

From Borgerding *et al*. (2000); Djordjevic *et al*. (2000a)

[a] Federal Trade Commission machine-smoking parameters: a 35-mL, 2-sec puff once per minute

[b] Massachusetts machine-smoking parameters: a 45-mL, 2-sec puff every 30 sec, 50% of the ventilation holes blocked

[c] Human Smoking Conditions: smoking machine programmed to imitate the puffing behaviour of a smoker of full-flavour, non-mentholated cigarettes

[d] Human Smoking Conditions: smoking machine programmed to imitate the puffing behaviour of a smoker of full-flavour, mentholated cigarettes

B*a*P, benzo[*a*]pyrene; NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

ventilation holes in a cigarette's filter increased the percentage transfer of flavour-related alkenylbenzenes (eugenol, isoeugenol, methyleugenol, myristicin and elemicin) from tobacco to the particulate fraction of mainstream smoke by twofold to sevenfold.

(iv) *Machine-smoking method — Health Canada parameters*

The Tobacco Sales Act (1998) of British Columbia, Canada, mandates a machine-smoking method for cigarette testing that utilizes even more intense settings (puff volume, 55 mL; puff interval, 30 sec; puff duration, 2 sec; and 100% of the ventilation holes must be blocked during smoking). (For the reporting years 1998 and 1999, puff volume was 56 mL, puff interval 26 sec and the other parameters were the same as those currently in use).

The British Columbia Ministry of Health web site provides information on both in mainstream and sidestream smoke deliveries of 44 constituents in commercial leading Canadian cigarettes (the top 22 brands in British Columbia account for 70–80% of the market) under both standard (FTC/ISO methods) and modified, more intense smoking conditions, known as Health Canada smoking parameters (http://www.healthplanning.gov.bc.ca/ttdr/index.html). In 1999, 'regular', 'light', 'extra light' and 'ultra light' varieties of a leading Canadian cigarette brand sold in British Columbia were reported to deliver into mainstream smoke an average of 0.8–1.1 mg nicotine as measured by ISO smoking parameters and 2.5–2.9 mg nicotine per cigarette when measured by Health Canada

Table 1.13. Yields of IARC carcinogens in the mainstream smoke of Canadian regular size cigarettes — Comparison of ISO and Health Canada machine-smoking parameters

Compound	ISO smoking parameters[a]						
	Regular	Light	Extra light	Ultra light	Regular/ light	Regular/ extra light	Regular/ ultra light
Tar (mg/cig)	13.4	11.1	8.6	5.7	1.2	1.6	2.3
Nicotine (mg/cig)	1.1	1.1	1.1	0.8	1.0	1.0	1.3
IARC Group 1							
Benzene (µg/cig)	56.3	51.8	40.6	27.2	1.1	1.4	2.1
Cadmium (ng/cig)	114.0	108.0	80.2	32.4	1.1	1.4	3.5
2-Aminonapththalene (ng/cig)	11.8	7.5	9.5	6.7	1.6	1.2	1.8
Nickel (ng/cig)	4.0	5.1	3.8	3.9	0.8	1.1	1.0
Chromium (ng/cig)	5.0	2.1	3.3	2.8	2.4	1.5	1.8
Arsenic (ng/cig)	BDL	NQ	BDL	BDL			
4-Aminobiphenyl (ng/cig)	1.4	1.2	1.4	1.1	1.2	1.0	1.3
IARC Group 2A							
Formaldehyde (µg/cig)	60.8	25.8	20.5	9.7	2.4	3.0	6.3
1,3-Butadiene (µg/cig)	46.6	26.4	26.9	15.3	1.8	1.7	3.0
Benzo[*a*]pyrene (ng/cig)	11.3	10.6	8.7	6.2	1.1	1.3	1.8
IARC Group 2B							
Acetaldehyde (µg/cig)	703.0	565.0	439.0	260.0	1.2	1.6	2.7
Isoprene (µg/cig)	222.0	173.0	131.0	78.8	1.3	1.7	2.8
Catechol (µg/cig)	74.5	74.7	69.0	50.9	1.0	1.1	1.5
Acrylonitrile (µg/cig)	11.9	11.3	7.2	4.4	1.1	1.6	2.7
Styrene (µg/cig)	10.9	5.7	3.5	2.9	1.9	3.1	3.8
NNK (ng/cig)	84.4	58.0	73.1	56.9	1.5	1.2	1.5
NNN (ng/cig)	42.0	23.3	35.2	26.4	1.8	1.2	1.6
Lead (ng/cig)	15.2	13.4	8.7	5.2	1.1	1.7	2.9

BDL, below detection level; NQ, not quantifiable; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NNN, *N*′-nitrosonornicotine

[a] International Standards Organization/United States Federal Trade Commssion test conditions: puff volume, 35 mL; puff interval, 60 sec; puff duration, 2 sec; ventilation holes not blocked

[b] Modified ISO test conditions: puff volume, 56 mL; puff interval, 26 sec; puff duration, 2 sec; ventilation holes full blocked

smoking parameters. The tar deliveries into mainstream smoke were 5.7–13.4 mg per cigarette under ISO, and 28.2–36.1 mg per cigarette, under the Health Canada smoking conditions (Table 1.13).

The yields of six IARC Group 1 carcinogens (benzene, cadmium, 2-aminonaphthalene, nickel, chromium and 4-aminobiphenyl) in the mainstream smoke from the above-mentioned Canadian cigarettes were an average of 2–4 times higher when measured by Health Canada than when measured by ISO smoking parameters. For example, using the ISO parameters, the mean yields of benzene were 27–56 µg/cigarette and using Health Canada parameters, 82–121 µg/cigarette. Similar 2–4-fold differences were seen in mainstream smoke

Table 1.13 (contd)

Health Canada (HC) smoking parameters[b]							HC/ ISO Regular	HC/ ISO Light	HC/ ISO Extra light	HC/ ISO Ultra light
Regular	Light	Extra light	Ultra light	Regular/ light	Regular/ extra light	Regular/ ultra light				
36.1	34.2	28.3	28.2	1.1	1.3	1.3	2.7	3.1	3.3	4.9
2.5	2.9	2.6	2.6	0.9	1.0	1.0	2.4	2.7	2.3	3.3
81.9	121.0	97.0	92.0	0.7	0.8	0.9	1.5	2.3	2.4	3.4
258.0	216.0	263.0	244.0	1.2	1.0	1.1	2.3	2.0	3.3	7.5
18.1	6.2	18.3	16.8	2.9	1.0	1.1	1.5	0.8	1.9	2.5
7.2	23.5	9.4	11.5	0.3	0.8	0.6	1.8	4.6	2.5	2.9
11.8	13.1	15.1	15.5	0.9	0.8	0.8	2.4	6.4	4.6	5.5
NQ	NQ	NQ	NQ							
3.0	1.3	3.2	3.0	2.3	0.9	1.0	2.2	1.1	2.3	2.8
140.0	81.6	79.9	100.0	1.7	1.8	1.4	2.3	3.2	3.9	10.3
76.3	71.9	66.2	66.2	1.1	1.2	1.2	1.6	2.7	2.5	4.3
29.3	21.6	26.8	24.7	1.4	1.1	1.2	2.6	2.0	3.1	4.0
1372.0	1354.0	1133.0	1098.0	1.0	1.2	1.2	2.0	2.4	2.6	4.2
357.0	428.0	356.0	344.0	0.8	1.0	1.0	1.6	2.5	2.7	4.4
144.0	144.0	163.0	168.0	1.0	0.9	0.9	1.9	1.9	2.4	3.3
21.2	34.0	23.5	22.0	0.6	0.9	1.0	1.8	3.0	3.2	5.0
26.5	29.5	26.0	25.4	0.9	1.0	1.0	2.4	5.2	7.4	8.8
174.0	115.0	184.0	166.0	1.5	0.9	1.0	2.1	2.0	2.5	2.9
82.3	52.5	90.6	76.5	1.6	0.9	1.1	2.0	2.3	2.6	2.9
32.1	27.5	25.2	27.0	1.2	1.3	1.2	2.1	2.1	2.9	5.2

yields of 11 IARC Group 2 carcinogens (formaldehyde, 1,3-butadiene, benzo[*a*]pyrene, acetaldehyde, isoprene, catechol, acrylonitrile, styrene, NNN, NNK and lead) between the results obtained using the ISO and Health Canada methods. Whereas the yields of most of the 17 IARC carcinogens measured in mainstream smoke are significantly lower in the 'ultra light' cigarette than in the 'regular' cigarette, there was practically no difference in yields for most IARC carcinogens between the 'ultra light' cigarette and the 'regular' cigarette when measured by the Health Canada method. For example, in the 'regular' and 'ultra light' cigarettes, benzene yields were 56 and 27 µg/cigarette using ISO parameters compared with 82 and 92 µg/cigarette using the Health Canada parameters (Table 1.13).

(*b*) *The emissions of nicotine and carcinogens in mainstream smoke: international comparison*

Regardless of the designation of the cigarettes as low-yield and high-yield, the presence of a large pool of nicotine in tobacco enables the smoker, driven by a physiological need, to titrate his or her own dose by engaging in compensatory (more intense) smoking behaviours (i.e. more and longer puffs) (Henningfield *et al.*, 1994; Kozlowski *et al.*, 1998; Djordjevic *et al.*, 2000a). As a consequence, the more intense smoking will not only drive up the nicotine yield in smoke, but carcinogen yields as well. Therefore, both the qualitative and quantitative composition of a cigarette blend need to be considered when evaluating the addictive and carcinogenic potential of a specific product.

Table 1.14 lists the tobacco smoke carcinogens that have been evaluated previously in the *IARC Monographs* series and for which there is at least sufficient evidence of carcinogenicity in laboratory animals. Among these, there are 11 human carcinogens. The compounds listed here are those primarily responsible for the cancer-causing effects of tobacco smoke. There are also other compounds in tobacco smoke that may be carcinogenic, but have not been evaluated by IARC. Tobacco smoke also contains tumour promoters (phenolics), co-carcinogens (catechol and related compounds), toxic agents (acrolein and other aldehydes) and free radical species (nitric oxide and others). Most of the compounds listed in Table 1.14 are thought to exert their carcinogenic effects through classical genotoxic mechanisms, e.g. the formation and persistence of DNA adducts with consequent miscoding. Non-genotoxic (epigenetic) mechanisms such as cytotoxicity through means other than DNA damage, changes in gene expression via hypermethylation and genomic instability are other mechanisms of carcinogenesis that could operate after exposure to compounds in tobacco smoke.

Data on the carcinogenicity of the specific compounds in animals and humans in Table 1.14 are not discussed in this monograph, which focuses on the effects of tobacco smoke as a mixture. All the data on the carcinogenicity of these compounds are given in the appropriate *IARC Monographs*. The carcinogenic properties of some of these compounds are described briefly below.

PAHs are a diverse group of carcinogens formed during the incomplete combustion of organic material such as tobacco. They are found in tobacco smoke, broiled foods and polluted environments. Workers in iron and steel foundries and aluminium production plants are exposed to PAHs and these exposures are thought to be the cause of excess cancers in these settings (IARC, 1983a, 1984). Benzo[*a*]pyrene is the best known member of this class of compounds. PAHs are potent locally acting carcinogens in laboratory animals. They induce tumours of the upper respiratory tract and lung when administered by inhalation, instillation in the trachea or implantation in the lung (IARC, 1973, 1983a).

N-Nitrosamines are a large group of carcinogens that induce tumours in a wide variety of animal species and tissues. There is no reason to assume that humans might be resistant to the effects of these carcinogens. They are present in small amounts in foods and can be formed endogenously, but tobacco products are the most widespread and largest source of

Table 1.14. Carcinogens in cigarette smoke

Agent	Amount in mainstream cigarette smoke	*IARC Monographs* evaluation of carcinogenicity			Monograph volume, year
		In animals	In humans	IARC Group	
Polynuclear aromatic hydrocarbons					
Benz[*a*]anthracene	20–70 ng	Sufficient		2A	*32*, 1983a; *S7*, 1987
Benzo[*b*]fluoranthene	4–22 ng	Sufficient		2B	*32*, 1983a; *S7,* 1987
Benzo[*j*]fluoranthene	6–21 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*k*]fluoranthene	6–12 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*a*]pyrene	8.5–11.6 ng[a]	Sufficient		2A	*32*, 1983a; *S7*, 1987
Dibenz[*a,h*]anthracene	4 ng	Sufficient		2A	*32*, 1983a; *S7*, 1987
Dibenzo[*a,i*]pyrene	1.7–3.2 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenzo[*a,e*]pyrene	Present	Sufficient		2B	*32*, 1983a; *S7*, 1987
Indeno[*1,2,3-cd*]pyrene	4–20 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
5-Methylchrysene	ND–0.6 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Heterocyclic hydrocarbons					
Furan	20–40 μg[b]	Sufficient		2B	*63*, 1995b
Dibenz(*a,h*)acridine	ND– 0.1 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenz(*a,j*)acridine	ND–10 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenzo(*c,g*)carbazole	ND– 0.7 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo(*b*)furan	present	Sufficient		2B	*63*, 1995b
***N*-Nitrosamines**					
N-Nitrosodimethylamine	0.1–180 ng[b]	Sufficient		2A	*17*, 1978; *S7*, 1987
N-Nitrosoethylmethylamine	ND–13 ng	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosodiethylamine	ND–25 ng[b]	Sufficient		2A	*17*, 1978; *S7*, 1987
N-Nitrosopyrrolidine	1.5–110 ng[b]	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosopiperidine	ND–9 ng	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosodiethanolamine	ND–36 ng[b]	Sufficient		2B	*17*, 1978; *77*, 2000
N′-Nitrosonornicotine	154–196 ng[a]	Sufficient		2B[c]	*37*, 1985b; *S7*, 1987
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	110–133 ng[a]	Sufficient		2B[c]	*37*, 1985b; *S7*, 1987
Aromatic amines					
2-Toluidine	30–200 ng[b]	Sufficient	Limited	2A	*S7*, 1987; *77*, 2000
2,6-Dimethylaniline	4–50 ng	Sufficient		2B	*57*, 1993
2-Naphthylamine	1–22 ng[b]	Sufficient	Sufficient	1	*4*, 1974; *S7*, 1987
4-Aminobiphenyl	2–5 ng[b]	Sufficient	Sufficient	1	*1*, 1972; *S7*, 1987
***N*-Heterocyclic amines**					
A-α-C	25–260 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
MeA-α-C	2–37 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
IQ	0.3 ng	Sufficient		2A	*S7*, 1987; *56*, 1993

Table 1.14 (contd)

Agent	Amount in mainstream cigarette smoke	*IARC Monographs* evaluation of carcinogenicity			Monograph volume, year
		In animals	In humans	IARC Group	
Trp-P-1	0.3–0.5 ng	Sufficient		2B	*31*, 1983b; *S7*, 1987
Trp-P-2	0.8–1.1 ng	Sufficient		2B	*31*, 1983b; *S7*, 1987
Glu-P-1	0.37–0.89 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
Glu-P-2	0.25–0.88 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
PhIP	11–23 ng	Sufficient		2B	*56*, 1993b
Aldehydes					
Formaldehyde	10.3–25 µg[a]	Sufficient	Limited	2A	*S7*, 1987; *62*, 1995a
Acetaldehyde	770–864 µg[a]	Sufficient		2B	*S7*, 1987; *71*, 1999
Phenolic compounds					
Catechol	59–81 µg[a]	Sufficient		2B	*S7*, 1987; *71*, 1999
Caffeic acid	< 3 µg	Sufficient		2B	*56*, 1993b
Volatile hydrocarbons					
1,3-Butadiene	20–40 µg[b]	Sufficient	Limited	2A	*S7*, 1987; *71*, 1999
Isoprene	450–1000 µg	Sufficient		2B	*60*, 1994; *71*, 1999
Benzene	12–50 µg[b]	Sufficient	Sufficient	1	*29*, 1982; *S7*, 1987
Nitrohydrocarbons					
Nitromethane	0.5–0.6 µg	Sufficient		2B	*77*, 2000
2-Nitropropane	0.7–1.2 ng[c]	Sufficient		2B	*S7*, 1987; *71*, 1999
Nitrobenzene	25 µg	Sufficient		2B	*65*, 1996
Miscellaneous organic compounds					
Acetamide	38–56 µg	Sufficient		2B	*S7*, 1987; *71*, 1999
Acrylamide	present	Sufficient		2A	*S7*, 1987; *60*, 1994
Acrylonitrile	3–15 µg	Sufficient		2B	*S7*, 1987; *71*, 1999
Vinyl chloride	11–15 ng	Sufficient	Sufficient	1	*19*, 1979; *S7*, 1987
1,1-Dimethylhydrazine	present	Sufficient		2B	*4*, 1974; *71*, 1999
Ethylene oxide	7 µg	Sufficient	Limited	1	*60*, 1994; *S7*, 1987
Propylene oxide	0–100 ng	Sufficient		2B	*60*, 1994; *S7*, 1987
Hydrazine	24–43 ng	Sufficient		2B	*S7*, 1987; *71*, 1999
Urethane	20–38 ng[b]	Sufficient		2B	*7*, 1974; *S7*, 1987
Metals and metal compounds					
Arsenic	40–120 ng[b]	Sufficient	Sufficient	1	*84*, 2004a
Beryllium	0.5 ng	Sufficient	Sufficient	1	*S7*, 1987; *58*, 1993a
Nickel	ND–600 ng	Sufficient	Sufficient	1	*S7*, 1987; *49*, 1990
Chromium (hexavalent)	4–70 ng	Sufficient	Sufficient	1	*S7*, 1987; *49*, 1990
Cadmium	41–62 ng[b]	Sufficient	Sufficient	1	*S7*, 1987; *58*, 1993a
Cobalt	0.13–0.20 ng	Sufficient		2B	*52*, 1991

Table 1.14 (contd)

Agent	Amount in mainstream cigarette smoke	*IARC Monographs* evaluation of carcinogenicity			Monograph volume, year
		In animals	In humans	IARC Group	
Lead (inorganic)	34–85 ng	Sufficient	Limited	2A	*23*, 1980; *S7*, 1987; *87*, 2004b
Radio-isotope Polonium-210	0.03–1.0 pCi	Sufficient		1	*78*, 2001

This table (modified from Hoffmann *et al*., 2001) shows components of unfiltered mainstream cigarette smoke, with amounts given per cigarette. Virtually all these compounds are known carcinogens in experimental animals. In combination with data on cancer in humans and – in some cases – other relevant data (see *Preamble*), IARC Monographs classifications for these agents have been established as Group 2B (possibly carcinogenic to humans), Group 2A (probably carcinogenic to humans) or Group 1 (carcinogenic to humans). When IARC evaluations were made more than twice, only the two most recent Monographs are listed, with volume number and year of publication. No entry in the column 'humans' indicates inadequate evidence or no data.

Abbreviations: *S7*, Supplement 7 of the *IARC Monographs*; ND, not detected; A-α-C, 2-amino-9*H*-pyrido[2,3-*b*]indole; MeA-α-C, 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole; IQ, 2-amino-3-methylimidazo-[4,5-*b*]quinoline; Trp-P-1,3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole; Trp-P-2, 3-amino-1-methyl-5*H*-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; pCi, picoCurie.

[a] Data from Swauger *et al*. (2002) (for 'full-flavour' cigarettes)

[b] Data from US Department of Health and Human Services (1989)

[c] Corrected value (see Fowler & Bates, 2000)

exposure to these carcinogens. Tobacco smoke contains volatile *N*-nitrosamines such as NDMA and NPYR as well as TSNAs such as NNN and NNK. TSNAs are chemically related to nicotine and other tobacco alkaloids and are therefore found only in tobacco products or related materials. Many *N*-nitrosamines are powerful carcinogens in laboratory animals, displaying striking organospecificity. For example, NNN causes tumours of the oesophagus and nasal cavity in rats, whereas the principal target of NNK in rodents is the lung. NNK is the only tobacco smoke carcinogen that induces lung tumours systemically in all three commonly used rodent models (i.e. rat, mouse and hamster) (IARC, 1978; Hecht, 1998).

Aromatic amines were first identified as carcinogens as a result of the exposure of workers in the dye industry. Of these, 4-aminobiphenyl and 2-naphthylamine are well-established human bladder carcinogens (IARC, 1972, 1974). Aromatic amines cause tumours at a variety of sites in laboratory animals. Some members of this class such as *ortho*-toluidine are only weakly carcinogenic. Heterocyclic aromatic amines are protein pyrolysate products found in broiled foods as well as in tobacco smoke. They are mode-

rately carcinogenic in various tissues including breast and colon (IARC, 1983b, 1986b, 1987, 1993b).

Formaldehyde and acetaldehyde induce respiratory tract tumours in rodents when administered by inhalation (IARC, 1987, 1995, 1999). They are weaker carcinogens than PAHs, *N*-nitrosamines and aromatic amines, but their concentrations in tobacco smoke are thousands of times higher. Butadiene and benzene are volatile hydrocarbons that also occur in considerable quantities in tobacco smoke. Butadiene is a multi-organ carcinogen, with particular potency in mice, whereas benzene causes leukaemia in humans (IARC, 1982, 1987, 1999). Metals such as nickel, chromium and cadmium are human carcinogens that are also present in tobacco smoke (IARC, 1987, 1990, 1993a).

Of the carcinogens discussed here, only NNK and NNN are specific to tobacco products. This is important when considering biomarkers of human carcinogen uptake. Carcinogen uptake in humans exposed to tobacco smoke can thus be specifically monitored by measurement of NNK metabolites (Hecht, 2003).

The total yields of carcinogens per cigarette are often several times higher than their yields in mainstream smoke. For example, total yields (mainstream smoke + sidestream smoke) of four popular Canadian cigarette brands including 'regular', 'light', 'extra light' and 'ultra light' cigarettes measured in nanograms per cigarette were: benzene, 278 000–548 000; cadmium, 115–592; arsenic, below detection level; nickel, 38–631; chromium, 64–78; 2-naphthylamine, 155–193; and 4-aminobiphenyl, 21–24 (Government of British Columbia, 2002).

The data presented in Table 1.15 on the composition of mainstream smoke generated by machine-smoking according to the FTC standard of cigarettes sold globally point to a wide range of emissions of nicotine, 'tar' and TSNA. The highest concentrations of TSNA were measured in unfiltered cigarettes sold in France and Italy (up to 1353 ng NNN and up to 1749 ng NNK per cigarette). The same brands contained the highest amounts of preformed TSNA (Fischer *et al*., 1990c). The lowest emissions were measured in blended cigarettes sold in Canada, Japan, the Netherlands, Sweden and the United Kingdom, with upper values of 66–103 ng NNK. Surprisingly, the NNN and NNK levels in the mainstream smoke of two cigarette brands from India were very low given the extremely high levels of preformed TSNA in the tobacco (Nair *et al*., 1989). The concentrations of benzo[*a*]pyrene in mainstream smoke ranged from 2.2 ng/cigarette to 28.4 ng/cigarette, except in Indian brands, in which the concentrations were 85–114 ng/cigarette (Table 1.15).

The comparative assessment of the composition of mainstream smoke of three popular brands of filter-tipped cigarette from the USA purchased on the open market in 29 countries worldwide showed little remarkable variation in the amounts of tar and nicotine, but substantial differences in the yields of NNN and NNK within each brand (Table 1.16). While the maximal variation in 'tar' levels in mainstream smoke ranged from 1.5- to twofold, the yields of NNK varied from three- to ninefold. NNK and NNN yields were highly correlated ($r = 0.88$; Gray *et al*., 2000).

To determine what governs the nitric oxide yields of cigarettes, 17 British, 14 American, eight French and one Turkish brand with a mean tar yield of 14.4 mg/cigarette in

Table 1.15. International comparison of the ranges of mainstream smoke yields of selected constituents of commercial cigarettes[a]

Country	Tar (mg/cig)	Nicotine (mg/cig)	Carbon monoxide (mg/cig)	Benzo[*a*]-pyrene (ng/cig)	NNN (ng/cig)	NNK (ng/cig)	Reference
Austria	9–15[b]	0.7–0.9[b]	NA	NA	42–172	12–100	Fischer *et al*. (1990c)
Belgium	13–16[b]	1.0–1.3[b]	NA	NA	38–203	29–150	Fischer *et al*. (1990c)
Canada	0.7–19[b]	0.1–1.4[b]	1–21[b]	3.4–28.4	4–37	6–97	Rickert *et al*. (1985); Fischer *et al*. (1990b); Kaiserman & Rickert (1992a); Kozlowski *et al*. (1998)
Germany	1–28[b]	0.1–2.0[b]	NA	NA	5–855	ND–470	Fischer *et al*. (1989c, 1990c); Tricker *et al*. (1991)
France	6–44[b]	0.3–2.7[b]	NA	NA	11–1000	19–498	Djordjevic *et al*. (1989a); Fischer *et al*. (1990c)
India	18.3–28.3[c]	0.94–1.79	NA	85–114	6–401	ND–34.4	Pakhale *et al*. (1988); Nair *et al*. (1989); Pakhale *et al*. (1989, 1990); Pakhale & Maru (1998)
Italy	NA	NA	NA	NA	21–1353	8–1749	Fischer *et al*. (1990c)
Japan	6–16	0.6–1.6	6–19	5.1–13.3	36–129	37–66	Djordjevic *et al*. (1996)
Netherlands	1–18[b]	0.2–1.5[b]	NA	NA	9–163	5–102	Fischer *et al*. (1990c)
Poland	19[b]	1.4[b]	NA	NA	68–347	36–105	Fischer *et al*. (1990c); Djordjevic *et al*. (2000b)
Sweden	9–23[b]	0.8–1.8[b]	NA	NA	44–141	27–84	Fischer *et al*. (1990c)
Switzerland	12–15[b]	0.9–1.2[b]	NA	NA	121–226	69–124	Fischer *et al*. (1990c)

Table 1.15 (contd)

Country	Tar (mg/cig)	Nicotine (mg/cig)	Carbon monoxide (mg/cig)	Benzo[*a*]-pyrene (ng/cig)	NNN (ng/cig)	NNK (ng/cig)	Reference
Thailand	5–28	0.2–2.4	15–19	NA	28–730	16–369	Mitacek *et al*. (1990); Brunnemann *et al*. (1996)
United Kingdom	1–24	0.2–2.4	0.5–17.5	NA	17–123	18–103	Borland & Higenbottam (1987); Fischer *et al*. (1990c); Kozlowski *et al*. (1998)
USA	< 0.5–27	0.04–2.0	< 0.5–22	2.2–26.2	14–1007	6–425	Adams *et al*. (1987); Fischer *et al*. (1990c); Djordjevic *et al*. (1990, 1996); Brunnemann *et al*. (1994); Kozlowski *et al*. (1998); Federal Trade Commission (2000)
Former USSR	21.6–29.2	0.9–1.4	NA	16.1–27.3	23–389	4–55	Fischer *et al*. (1990c); Djordjevic *et al*. (1991b)

[a] Obtained by FTC method
[b] From cigarette package declaration
[c] Total particulate matter
NA, not available; ND, not detected, limit < 4 ng/cigarette; NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

Table 1.16. The chemical composition of the three cigarette brands sold in 29 countries worldwide

	Brand I (Camel)	Brand II (Lucky Strike)	Brand III (Marlboro)
Tar (mg/cig)	10.6–15.7	11.8–20.4	8.4–15.9
Nicotine (mg/cig)	0.85–1.3	0.85–1.3	0.68–1.25
NNK (ng/cig)	40–150	50–240	35–325

From Gray *et al*. (2000)
NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

mainstream smoke were analysed under standard machine-smoking conditions (Borland & Higenbottam, 1987). The country of origin appeared to be the major factor affecting NO yield. The mean values for American and French brands exceeded those for British brands by three- to fivefold. The NO yields in the mainstream smoke of British cigarettes ranged from 10 to 222 μg/cigarette, those in American cigarettes from 230 to 384 μg and those in French cigarettes from 320 to 409 μg/cigarette. These international differences in NO yields reflect differences in the nitrate content of tobaccos traditionally used in the manufacture of cigarettes in those countries. In 1996, the yields of tar and NO in the mainstream smoke of 33 cigarette brands from the British market were determined to ascertain if the formulations that reduced FTC tar yields when compared with those measured in the 1980s had an effect on NO yields. The mean tar yield was 10.8 mg/cigarette and the mean NO yield 141.4 μg/cigarette (range, 22–279 μg/cigarette). For the 11 cigarette brands for which samples manufactured in the 1980s were available for comparison, the median NO yields in 1996 were higher: 145 versus 110 μg/cigarette, with corresponding ranges of 70–279 and 40–450 μg/cigarette (Laboratory of the Government Chemist, 1998).

The yields of volatile *N*-nitrosamines in mainstream smoke are one or two orders of magnitude lower than those of TSNA. In Germany and the USA, NDMA yields ranged from 4.1 ng to 15.2 ng/cigarette in filter-tipped cigarettes and from 9.4 ng to 76 ng in untipped cigarettes. NPYR levels ranged from 3.9 to 32.7 and from 6.9 to 64.5 ng/cigarette for filter-tipped and untipped cigarettes, respectively (Adams *et al*., 1987; Tricker *et al*., 1991; Brunnemann *et al*., 1994). In Thai cigarettes, NDMA yields ranged from 8.5 to 31.9 ng/cigarette and NPYR from 8.8 to 49.6 ng/cigarette (Mitacek *et al.*, 1999).

The concentrations of benzene and associated volatile compounds were determined in the mainstream smoke of 26 cigarette brands on the British market by the ISO smoking parameters. The average benzene yield was 40 μg/cigarette (range from 3.2 to 61.7 μg per cigarette) in British brands, in comparison with an average yield of 55 μg/cigarette in the USA (Darrall *et al*., 1998).

In the six major brands of Thai filter-tipped and untipped cigarettes with tar yields of 4.98–34.8 mg, the levels of benzene were 25.5–40 μg/cigarette and the levels of 1,3-buta-

diene were 44.6–78.7 μg/cigarette. The amount of acrolein ranged from 79.9 to 181 μg/cigarette and that of isoprene from 313 to 694 μg/cigarette. The yields of these substances showed no correlation with tar deliveries in mainstream smoke (Mitacek *et al*., 2002).

Smoking fewer cigarettes may erroneously be expected to reduce exposure to toxins even if the smoker smokes more intensely to compensate for the reduced number of cigarettes. In a controlled experiment in which the average number of cigarettes smoked was reduced from an average of 37 to 5 cigarettes per day, the resulting urinary mutagenic activity per cigarette increased roughly threefold and daily exposure to nicotine and CO declined by only 60 and 50%, respectively (Benowitz *et al*., 1986). The reduction of the number of cigarettes smoked from 40 per day to 20 per day was not followed by a consistent reduction in the concentration of biomarkers of exposure to tobacco carcinogens (Hurt *et al*., 2000).

(*c*) *Other constituents of cigarette smoke*

Polychlorodibenzodioxins (PCDDs) and polychlorodibenzofurans (PCDFs) have been quantified in the 10 best-selling brands of German cigarettes. None of the cigarettes were found to contain 2,3,7,8-tetrachlorodibenzodioxin (TCDD). The total delivery of tetra-octachlorodibenzodioxins in mainstream smoke expressed as TCDD equivalents ranged from 0.05 to 0.17 pg/cigarette. The total PCDD deliveries were 4.4–10.3 pg/cigarette, and PCDF deliveries were 1.4–5.2 pg/cigarette (Ball *et al.*, 1990). 2,3,7,8-TCDD concentrations were also below the limit of detection (0.5 pg/g) in cigarettes and cigarette smoke analysed in Japan, but the toxic equivalent value for total PCDDs in smoke was 1.81 ng/m^3. Daily intake of PCDDs by smoking 20 cigarettes was estimated to be approximately 4.3 pg/kg bw per day (Muto & Takizawa, 1989).

The levels of organochlorinated pesticides were assessed in cigarettes from Japan, the USA and the former USSR. The major organochlorinated pesticides identified in tobacco and in the mainstream smoke of commercial cigarette brands in the USA that were manufactured between 1961 and 1979 were: *p*,*p*′-isomers of DDD (1540–20 220 ng/g tobacco), DDT (720–13 390 ng/g tobacco) and DDE (58–730 ng/tobacco). Since 1970, the concentrations of individual organochlorinated pesticides in tobacco have gradually decreased by over 98%. The transfer rates from tobacco into mainstream smoke were 22% for DDD, 19% for DDT and 27% for DDE. In 1995, the concentrations of organochlorinated pesticides in tobacco from the USA were below the maximum permissible limits set by the US Environmental Protection Agency. Until 1970, the organochlorinated pesticides in tobacco and mainstream tobacco smoke contributed significantly to the bioaccumulation of these pesticides in smokers. Currently, tobacco and mainstream cigarette smoke are minor sources of human exposure to organochlorinated pesticides (Djordjevic *et al.*, 1995).

During the smoking of cigarettes with charcoal filters, toxin-coated charcoal granules and other components of the filter are released in the mainstream smoke and inhaled or ingested by the smoker. An average of 3.3 charcoal granules per cigarette were observed on the filter tips of 80% of the 400 cigarettes examined. An increased health risk may

result from the inhalation of tar-coated particles (cellulose acetate fibres, paper and tobacco fibres, glass fibres and charcoal granules) released from the filter (Pauly *et al*., 1995, 1997, 1998).

The free radical and hydrophobicity-related toxicity of 203 of the 253 different substituted phenols present in cigarette smoke was considered. Of these, 162 that have electron-releasing groups may form potentially toxic phenoxyl-free radicals. In contrast, 41 substituted phenols with electron-withdrawing groups do not form phenoxyl-free radicals, but exert their toxic action primarily through lipophilicity. According to quantitative studies of the structure–activity relationship and evaluations of in-vitro cytotoxicity, the most toxic phenols in mainstream smoke included in descending order of toxicity: 2-(dimethylamino)-phenol, 2-ethyl-6-methyl-1,4-benzenediol, 2-methoxy-1,4-benzenediol and 4-ethyl-2-methoxy-6-methylphenol (Smith *et al.*, 2002).

1.2.3 *Roll-your-own cigarettes*

In a study by Darrall and Figgins (1998), 57% of cigarettes rolled by smokers for their own consumption produced higher levels of tar than the 15 mg/cigarette that was the maximum allowed for manufactured cigarettes in the United Kingdom until 1998. Seventy-seven per cent of smokers of roll-your-own (RYO) cigarettes made cigarettes with smoke nicotine yields greater than 1.1 mg/cigarette. Dutch consumers make RYO cigarettes that deliver, on average, 13.2 mg tar and 1.2 mg nicotine per cigarette (Dymond, 1996). These findings are comparable with the smoke yields for 31 brands of RYO tobaccos tested in Canada (15.5 mg tar and 1.1 mg nicotine per cigarette; Kaiserman & Rickert, 1992b). In another study, the same authors (1992a) reported even higher levels of tar and nicotine (19.4 mg and 1.6 mg per cigarette, respectively). Similar smoke yields were reported by Rickert *et al*. (1985) for fine-cut tobacco (21 mg tar and 1.3 mg nicotine per cigarette). Five of six brands handmade from fine-cut tobacco delivered significantly more tar, nicotine and CO both per cigarette and per litre of smoke than did the identically named manufactured brand. According to Kaiserman and Rickert (1992b), in addition to tobacco, it is the combination of the tube and filter that determines the delivery of toxic constituents to smokers. The mainstream smoke of three brands of hand-rolled cigarettes from Thailand was reported to yield 28.5–40.8 mg tar and 1.1–5.5 mg nicotine per cigarette (Mitacek *et al*., 1991).

The amount of benzo[*a*]pyrene in RYO cigarettes was reported to be 22.9–25.93 ng/cigarette in the particulate matter of the mainstream smoke of Canadian cigarettes (Kaiserman & Rickert, 1992a) and 48 ng/g tobacco for RYO cigarettes in the USA (Appel *et al*., 1990). Benzene and associated volatile components (toluene, ethylbenzene, xylene, styrene, isoprene and acrylonitrile) were measured in the vapour phase of the mainstream smoke of commercial and RYO cigarettes in the United Kingdom. The mean quantities of the above-mentioned compounds in the mainstream smoke of RYO cigarettes that had been made using 0.5 g of tobacco per cigarette were of the same order of magnitude or up to 2.6 times higher than the mean values reported for 26 commercial brands of

cigarette sold in the United Kingdom (Darrall *et al*., 1998). Based on a representative sample of 110 cigarette brands available on the United Kingdom market in 1999, the average weight of tobacco in a single cigarette was reported to be 0.76 g (Laboratory of the Government Chemist, 2001). The highest concentrations of benzene (an average of 68 μg/g tobacco) in the mainstream smoke of RYO cigarettes were reported by Appel *et al*. (1990). Appel *et al*. (1990) also tried to measure the lead content in the mainstream smoke of RYO cigarettes, but the concentrations were below the limit of reliable quantitation. No data are presently available on the levels of other carcinogens in the smoke of RYO cigarettes or on smoking topography and the true deliveries of smoke constituents as the result of specific smoking behaviours.

1.2.4 *De-nicotinized cigarettes*

Tobacco-based de-nicotinized cigarettes have been used in smoking research to distinguish the effects of smoking related to the delivery of nicotine or other components of tobacco smoke, from those related to the sensory process of smoking (Robinson *et al.*, 1992, 2000). For research purposes, four types of cigarettes were developed with FTC mainstream smoke yields ranging from 10 to 17.3 mg tar and from 0.07 mg to 1.0 mg nicotine per cigarette (Pickworth *et al*., 1999). The commercial de-nicotinized brand that was briefly test-marketed in the 1990s had similar mainstream smoke nicotine and tar yields as measured by the FTC criteria (0.04 and 10.2 mg, respectively) and detectable quantities of nicotine in tobacco (0.4 mg/g). However, despite being de-nicotinized, the commercial brand still contained amounts of preformed carcinogenic NNK in the tobacco comparable to five other commercial cigarettes (650 ng/g versus 500–890 ng/g tobacco; Djordjevic *et al*., 1990). This observation is very significant because it indicates that manipulation of tobacco composition, such as removing a single compound or group of compounds from tobacco, would not necessarily result in a reduction in the overall toxicity of the product.

1.2.5 *Cigars*

Concentrations of benzene, benzo[*a*]pyrene and lead were measured in the mainstream smoke of six brands of cigar following the Tobacco Research Council (TRC) recommended machine-smoking parameters (puff duration, 2 sec; puff volume, 35 mL; butt length, 25 mm), with the puff frequency altered to two per minute. The mean yields per gram of tobacco burned were 156 μg (range, 92–246 μg) for benzene and 42 ng (range, 35–49 ng) for benzo[*a*]pyrene. The quantities of lead were below the limit of reliable quantification (0.2 μg/cigar) (Appel *et al.*, 1990).

In 1997 in the USA, the leading brands of little, large and premium cigars (ranging in length from 7.3 to 17.6 cm and in weight from 1.24 to 8.1 g) were analysed and the levels of nicotine and selected carcinogens (e.g. benzo[*a*]pyrene, NNN and NNK) measured in the mainstream smoke (Table 1.17; Djordjevic *et al*., 1997). The results were obtained by

Table 1.17. Smoke yields of leading cigarette brands and little, large and premium cigars in the USA

	Medium-yield cigarettes (0.9–1.2 mg FTC nicotine)[a,b]	Cigars[c,d]		
		Little[e]	Large	Premium
Nicotine (mg/unit)	1.11	1.5	1.4	3.4
Tar (mg/unit)	15.4	24	37	44
Carbon monoxide (mg/unit)	14.6	38	98	133
Benzo[*a*]pyrene (ng/unit)	14.0	26.2	96	97.4
NNK (ng/unit)	146.2	290	805	2490

[a] From Djordjevic *et al*. (2000a)
[b] The cigarettes were smoked under FTC conditions: 1 puff/min, 35-mL volume, 2-sec puff duration, butt length; length of filter overwrap plus 3 mm (Pillsbury *et al*., 1969).
[c] From Djordjevic *et al*. (1997)
[d] The cigars were smoked under the ICCSS (International Committee for Cigar Smoke Study, 1974) conditions: 1 puff/40 sec, 20-mL volume, 1.5-sec puff duration, butt length 33 mm.
[e] Little cigars had filter tips
FTC, Federal Trade Commission; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

machine-smoking the cigars under standard smoking conditions as defined by the International Committee for Cigar Smoke Study (ICCSS 1974; i.e. 20-mL puffs of 1.5 sec duration drawn once every 40 sec to the predetermined butt length of 33 mm). The delivered dosages of nicotine, tar and CO were higher in premium cigars than in cigarettes. The levels of nicotine, benzo[*a*]pyrene and NNK were higher by three, seven and 17 times, respectively, in the mainstream smoke of premium cigars. The NNN levels were reported to be 22.4 times higher in cigar smoke (Rickert & Kaiserman, 1999). Another study compared mainstream smoke yields of tar, nicotine, CO and PAHs from 30 cigarette brands with those of 10 small cigar brands, using the ISO/FTC machine-smoking parameters. It was expected that the mainstream smoke yields of those cigars that were heavier than cigarettes would be significantly higher than the yields from cigarettes. However the yields from cigarette-size cigars (length, 74–99 mm; weight, 0.65–1.14 g) are also well above the corresponding cigarette yields: mean tar yield, 10.6 mg/cigarette versus 29 mg/cigar and mean benzo[*a*]pyrene yield, 11 ng/cigarette versus 21 ng/cigar. This is undoubtedly because cigars do not have the physical characteristics that are used to modify yields in cigarettes, such as filter retention, ventilation and paper porosity. It is evident, therefore, that yields of cigars are approximately proportional to the weight of tobacco burnt (Laboratory of the Government Chemist, 2002).

When little filter-tipped cigars were machine-smoked in a way that stimulated the puffing characteristics of smokers (larger puff volume, more frequent puffs), the emissions of total TSNA were twice as high (Djordjevic *et al*., 1997) as those determined using the standard ICCSS method. A similar 2.2-fold difference in the level of all smoke constituents due to more 'intense smoking' was reported by Rickert and Kaiserman (1999).

Under standard ISO conditions, the yields of certain mainstream smoke constituents generated from three brands of cigarette and one brand of cigar were substantially different (ammonia, 12.7 versus 327 μg/unit; nitric oxide, 48 μg versus 1.08 mg/unit; NNN, 41.5 versus 931 ng/unit) (Rickert & Kaiserman, 1999).

To control for variations in the total volumes of smoke delivered from cigarettes and cigars, standardized comparisons in milligrams of toxic substance per litre of smoke were made by Rickert *et al*. (1985). The mean deliveries of tar, nicotine and CO per litre of smoke were highest for small cigars, followed by hand-rolled and manufactured cigarettes. Large cigars had the lowest deliveries.

Henningfield *et al*. (1999) analysed 17 brands of cigar ranging in weight from 0.53 to 21.5 g. There was considerable variation in the total nicotine content of the tobacco, which ranged from 5.9 to 335.2 mg per cigar, as well as in the aqueous pH of the tobacco from the cigars (range, 5.7–7.8). The smoke pH values of the smallest cigars were generally acidic, changed little across the puffs and more closely resembled the profiles previously reported for typical cigarettes. The smoke pH of smaller cigars and cigarillos only became acidic after the first third of the rod had been smoked and remained acidic thereafter. The smoke pH of larger cigars was acidic during the smoking of the first third of the rod and became quite alkaline during the smoking of the last third. This phenomenon needs to be taken into consideration when the bio-availability and addictive potential of cigars is being evaluated.

Using the FTC smoking conditions, but with the puff frequency altered to two per minute, the average benzene and benzo[*a*]pyrene levels in the mainstream smoke of six brands of cigar sold on the US market reported by Appel *et al.* (1990) were 156 μg/g tobacco and 42 ng/g, respectively.

When tested in a similar manner, Thai cigars delivered 7.95–11.4 mg nicotine per cigar, 91–201 mg tar and 111–819 mg CO in mainstream smoke (Mitacek *et al*., 1991). The tobacco from an Indian cigar brand contained 25 000 ng preformed NNN and 8900 ng NNK per g tobacco (Nair *et al*., 1989).

It has been suggested that switching from smoking cigarettes to cigars, or smoking both products intermittently, may increase the exposure of smokers to toxic and carcinogenic compounds. In contrast with 'only cigar smokers' who relatively seldom inhale smoke into the lung, former cigarette smokers and concurrent cigar and cigarette smokers have a tendency to maintain their cigarette smoke inhalation pattern when they smoke cigars (Fant & Henningfield, 1998).

1.2.6 *Pipe tobacco*

Five brands of pipe tobacco were evaluated by machine-smoking in a pre-conditioned wooden pipe (bowl dimensions: 20 mm internal diameter, depth at centre 39 mm, stem length 60 mm from centre of bowl). The pipe required 3–4 g of tobacco for filling as follows: the pipe was filled loosely with tobacco to the top of the bowl, the tobacco was compressed by half, the bowl refilled and the tobacco compressed to fill about three-quarters of the bowl. The amount of tobacco consumed was approximated from the difference in weight of the pipe plus tobacco before and after smoking (Appel *et al*., 1990). The mean yield of benzene in mainstream smoke from smoking the pipe was 344 μg/g tobacco (range, 253–473 μg/g tobacco). (The FTC machine-smoking guidelines for puff duration and puff volume were applied, but puff frequency was increased to 12/min to keep the tobacco burning.)

1.2.7 *Other products*

Bidis: American versions of bidis were shown to have a lower percentage of tobacco by weight than US and Indian untipped commercial cigarettes (42.4% versus 94%, respectively) (Malson *et al.*, 2001).

The concentration of nicotine in the tobacco of bidi cigarettes (21.2 mg/g) is greater than that in the tobacco from commercial filter-tipped (mean: 16 mg/g; Malson *et al*., 2001; mean: 17.6 mg/g; Djordjevic *et al*., 1990; mean: 10.2 mg/g; Kozlowski *et al*., 1998) and untipped American and Indian commercial brands of cigarette (13.5 mg/g; Malson *et al*., 2001).

The levels of preformed NNN and NNK in bidi tobacco range from 6200 to 12 000 ng/g and from 400 to 1400 ng/g tobacco, respectively (Nair *et al*., 1989). When the concentrations of flavour-related compounds — nine alkenylbenzenes, coumarin, piperonal and pulegone — in Indian bidi cigarette tobacco sold in the USA were measured, two alkenylbenzene compounds, *trans*-anethole and eugenol, were found in more than 90% of the 23 brands analysed. Methyleugenol, pulegone and estragole were each detected in 30% or more of the brands, whereas safrole and elemicin were not detected in any of the brands. The flavour-related compounds with the highest concentrations in tobacco were eugenol (12 000 μg/g tobacco) and *trans*-anethole (2200 μg/g tobacco) — that is about 70 000 and 7500 times more, respectively, than the highest levels previously found in US cigarette brands (Stanfill *et al*., 2003).

Ten volunteers smoked longer and took more puffs to consume bidis (354–452 sec, 14 puffs) than to smoke their usual cigarette brand (297 sec, 10 puffs) (Malson *et al.*, 2002). In smokers who switched to Irie bidi (strawberry-flavoured) cigarettes, plasma nicotine levels increased above the levels recorded when they smoked regular filter-tipped cigarettes (26 ng/mL versus 18.5 ng/mL) (Malson *et al*., 2002).

The amount of nicotine in Indian bidi tobacco was higher than that in Indian filter-tipped cigarettes (38 mg/g versus 14 mg/g). The mainstream smoke of Indian bidis delivered less nicotine than Indian cigarettes (1.86 mg versus 2.58 mg/cigarette). The NNN

levels in the mainstream smoke of bidis ranged from 11.6 ng to 250 ng per cigarette and the NNK levels from not detected to 40 ng per cigarette. These concentrations were comparable with those measured in the mainstream smoke of Indian cigarettes (Pakhale & Maru, 1998).

In conclusion, because of their higher content of nicotine than in cigarette tobacco, and their similar or higher nicotine and TSNA deliveries in the mainstream smoke, bidis cannot be considered less harmful to health than regular cigarettes.

Kreteks: Eugenol, a natural compound found in high concentrations in clove buds, is the active ingredient that distinguishes kreteks from conventional cigarettes (Guidotti, 1989). In addition to eugenol, other constituents of clove and clove cigarette smoke include eugenol acetate, β-caryophyllene and α-humulene (LaVoie *et al*., 1986).

Chuttas: The nicotine content of chutta tobacco is comparable with that of bidi tobacco — 35 mg/g versus 38 mg/g. However, the nicotine level in mainstream smoke from chutta is higher (7 mg/product) than that from bidis (1.9 mg/product) (Pakhale & Maru, 1998). The quantities of NNN and NNK in chutta tobacco were reported to be extremely high (from 21 100 ng to 296 000 ng and from 12 600 ng to 210 000 ng/g, respectively). The reverse smoker inhales both the mainstream and sidestream smoke. The NNN and NNK levels in the mainstream smoke of chutta ranged from 289 ng to 1260 ng per chutta and from 150 ng to 2651 ng per chutta, respectively (Nair *et al*., 1989).

1.2.8 *Novel potentially reduced-exposure products*

There are currently two categories of potentially reduced-exposure smoking tobacco products that are being test-marketed worldwide:

- cigarettes made with modified tobacco containing reduced levels of carcinogens such as tobacco-specific nitrosamines (particularly NNK), or using technologies that reduce PAHs (particularly benzo[*a*]pyrene) and genetically modified tobacco containing no nicotine; and
- cigarette-like nicotine delivery devices (e.g. Eclipse™ and Accord™) engineered to reduce exposure to tobacco toxins using advanced technologies (Fisher, 2001; Stratton *et al*., 2001; Womack, 2002).

The cigarette test-marketed as a reduced-nitrosamine product is, according to the FTC ranking, a low-yield American blend cigarette. The chemical composition of the mainstream smoke as assessed by both the FTC and Massachusetts machine-smoking methods does not differ greatly from that of a normal cigarette except that there is a significant reduction in the amount of NNN and NNK in the smoke (Stratton *et al*., 2001).

No epidemiological data are available for these products and they are therefore not considered further in this monograph.

1.3 Use of tobacco

The forms of tobacco use are as diverse as the cultures and countries in which it is used and the people who use it. It is therefore difficult to compare different populations, as behaviours vary greatly. Although differences in smoking behaviour between one person and another within countries abound, there is some uniformity within national practices, e.g. almost all Japanese smokers use cigarettes. Figures for total consumption provide only a rough, albeit useful, measure of global dose and trends need to be observed over a reasonable period of time before acceptance of their significance (Table 1.18).

With regard to dose, using cigarettes as an example, the indices bearing on it are:

— numbers of cigarettes smoked;
— amount of carcinogen delivered per cigarette (discussed in detail in Section 1.2);
— duration of the behaviour and inhalation practice.

The components of dose are different and less measurable for other practices such as tobacco chewing and pipe smoking.

At present, exposure to tobacco components in most countries is almost entirely through smoke. The products used are mainly cigarettes, although pipes and cigars accounted for proportionally more of the exposure in earlier population cohorts. Several measures bear on the ways in which some populations are exposed to tobacco. These include estimates of national tobacco consumption and surveys of smoking behaviours (which are not always available in developing countries). This section mainly describes global patterns in adult cigarette smoking. Per-capita cigarette consumption appears to have risen in developing countries from 1970 to 2000 (Figure 1.1). The effects of tobacco on health are directly related to the dose consumed and the duration of use. In this context the trends in production and consumption might be expected to give an approximate indication of the trends in risk likely to be seen in the future.

Information on trends in per-capita consumption for most countries is collected by the World Health Organization and, in a general way, reflects actual consumption patterns, with the caveat that they are subject to many of the same economic factors that affect production estimates. The available world data on total cigarette consumption are shown in Table 1.18 (Mackay & Eriksen, 2002).

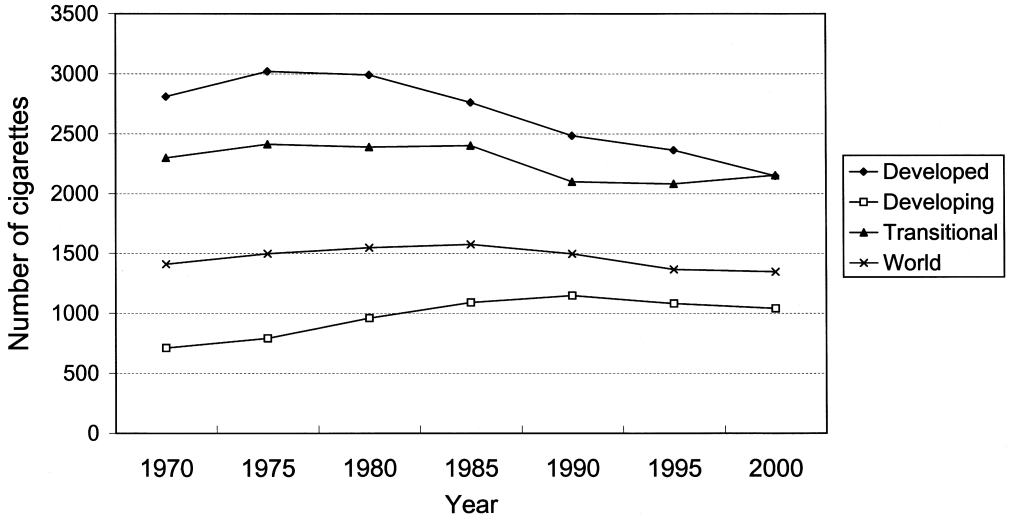
Selected comparative data from Australia, China, Japan, the United Kingdom and the USA (Corrao *et al*., 2000) offer a picture of the trend in cigarette consumption in those countries (Figure 1.2). The data from Australia show a persistent decline since 1980, those

Table 1.18. Global consumption of cigarettes (in thousand millions)

Year	1950	1960	1070	1980	1990	2000
Cigarettes consumed	1686	2150	3112	4388	5419	5500

From Mackay & Eriksen (2002)

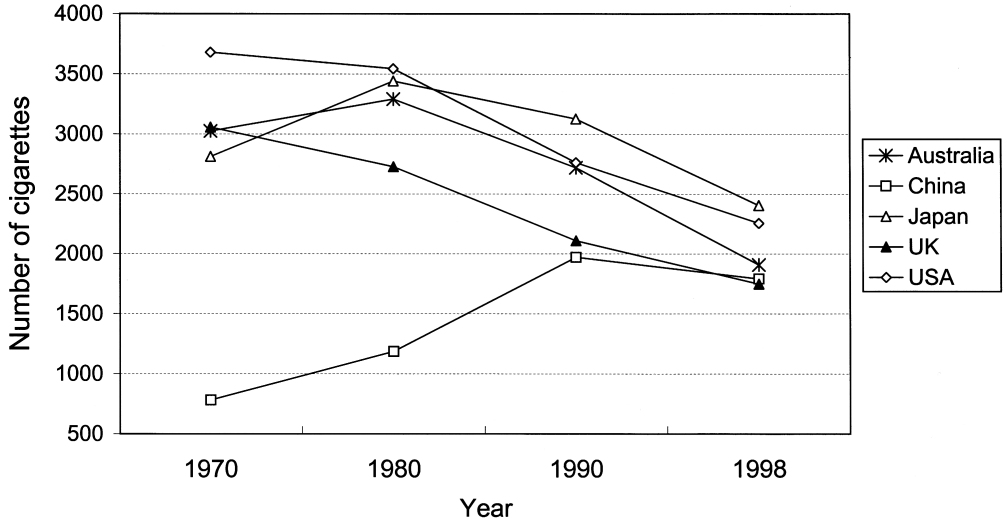
Figure 1.1. Trends in per-capita cigarette consumption by level of development of countries[a]



From Guindon & Boisclair (2003)

[a] Australia, Canada, Japan, New Zealand, USA and western Europe are considered 'developed countries'. Countries in transition from centrally planned to marked economies are labelled 'transitional'. All other countries fall into the 'developing category'.

Figure 1.2. Trends in per-capita cigarette consumption in selected countries



From Corrao *et al.* (2000)

from Japan show a less steep decline also since 1980 and in China, there has been a substantial increase up to the 1990s from a low base in the 1970s.

(*a*) *Surveys of smoking behaviour*

The only means by which it can be ascertained who is smoking, what is smoked, how much, for how long and (sometimes) in what way is through surveys. Regular surveys provide useful public health information, as they may identify populations at risk and some of the reasons they are at risk. Reliable random-sample surveys (using both telephone and in-person interviews) are carried out routinely in most developed countries and, if similar definitions are used, allow useful international comparisons. Table 1.19 shows smoking prevalence rates among adults in the WHO Regions. Since the methods used to collect information vary across these studies, small differences should be interpreted with caution. Nonetheless, smoking rates vary widely across regions. There is about a 1.5-fold difference in total smoking rates between the African or Eastern Mediterranean Regions and the Western Pacific Region. Similarly, smoking rates for women in the Western Pacific Region (5.8%) are much lower than in the European Region (23.4%). A nearly twofold difference in smoking rates is seen in men across the WHO Regions, with the lowest levels in the Eastern Mediterranean Region (34.2%) and the

Table 1.19. Prevalence of tobacco use and number of smokers by WHO Region and level of development in 2000

	Prevalence (% of the population ≥ 15 years of age)			No. of tobacco users (≥ 15 years) (millions)		
	Men	Women	Total	Men	Women	Total
WHO Region						
African Region	29.4	7.4	18.4	51.967	13.420	65.387
Region of the Americas	32.0	20.9	26.3	94.035	64.072	158.107
Eastern Mediterranean Region	35.3	6.1	21.0	52.543	8.670	61.213
European Region	44.9	18.7	31.2	150.628	68.545	219.173
South-East Asian Region	48.1	5.3	27.3	251.699	26.484	278.183
Western Pacific Region	61.2	5.7	33.8	390.632	35.784	426.416
Levels of development						
Developed	33.9	21.2	27.4	114.783	75.891	190.674
Developing	49.8	7.2	28.9	809.725	114.718	924.443
Transitional	54.1	13.9	32.7	82.837	24.153	106.990
World	57.4	10.3	28.9	1005.927	217.755	1223.682

From Guindon & Boisclair (2003)

highest in the Western Pacific Region (62.3%). Based on these weighted prevalence estimates, there are estimated to be over 1.2 billion smokers across the six WHO Regions.

Table 1.20 illustrates the variation in smoking prevalence rates by country (Corrao *et al.*, 2000). Even with the limitations in these data, some striking differences are evident. Women in China, Egypt, India, Republic of Korea, Singapore, Thailand and the United Arab Emirates smoke infrequently, whereas up to one-third of women smoke in other countries, such as Brazil, Denmark, Germany, Kenya, Norway and the United Kingdom.

Table 1.20. Smoking prevalence rates for men and women in selected countries[a]

Country	Year	Age group (years)	Men (%)	Women (%)
Argentina	1999	16–64	46.8	34
Australia	1995	≥ 16	27.1	23.2
Brazil	1995	≥ 15	38.2	29.3
Canada	1999	≥ 15	27	23
China	1996	15–69	63	3.8
Denmark	1998	≥ 14	32	30
Egypt	1997	≥ 18	43.6	4.8
Finland	1999	15–64	27	20
France	1997	≥ 18	39	27
Germany	1997	18–59	43.2	30
Hungary	1998–99	≥ 18	44	27
India	1985–86	25–64	45	7
Israel	1999	≥ 18	33	25
Italy	1998	≥ 14	32.2	17.3
Japan	1998	≥ 15	52.8	13.4
Kenya	1995	≥ 20	66.8	31.9
Mexico	1998	18–65	51.2	18.4
Norway	1998	16–74	33.7	32.3
Peru	1998	12–50	41.5	15.7
Poland	1998	–	39	19
Republic of Korea	1996	≥ 18	64.8	5.5
Russian Federation	1996	≥ 18	63	14
Singapore	1998	18–64	26.9	3.1
South Africa	1998	≥ 15	42	11
Spain	1997	≥ 16	42.1	24.7
Sweden	1998	16–84	17.1	22.3
Thailand	1999	≥ 11	38.9	2.4
United Arab Emirates	1995	≥ 15	24	1
United Kingdom	1996	≥ 16	29	28
USA	1997	≥ 18	27.6	22.1

From Corrao *et al*. (2000)

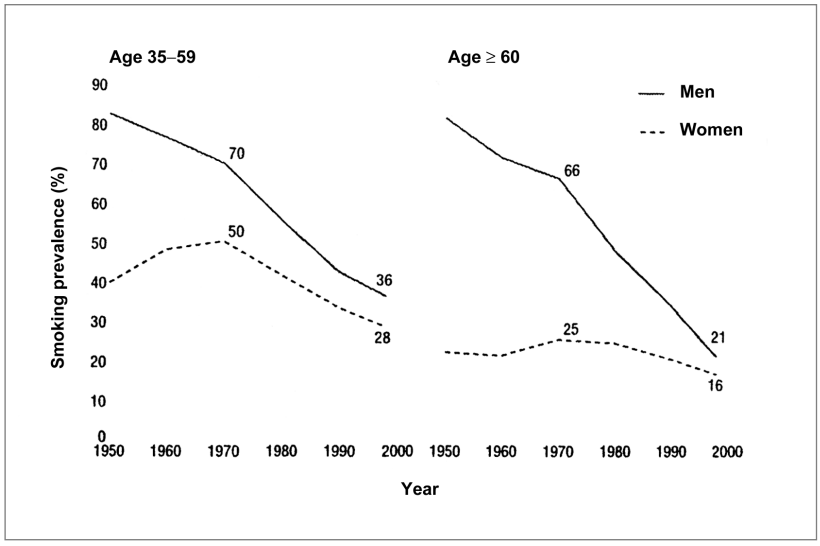
[a] These data are not age-adjusted or weighted.

The highest prevalences of male smokers are found in Japan, Kenya, Republic of Korea and Russia. In general, more men tend to smoke than women, except in Sweden. The differences between the numbers of men and women smokers are also near zero in other countries such as Denmark, Norway and the United Kingdom.

The data in Tables 1.19 and 1.20 represent only a snapshot of current smoking at one point in time. A more comprehensive set of behavioural endpoints (e.g. time trends in current and former smoking rates) is needed to give a robust explanation of the causes of present and future morbidity and mortality attributable to smoking. As an example, Figure 1.3 illustrates current and former smoking rates since 1950 in the United Kingdom (Peto *et al.*, 2000). Between 1948 and 1952, the prevalence of smoking in men aged 25–34 years was 80% and for women of the same age, 53%. In 1998, however, the prevalence was 39% for men and 33% for women.

The prevalence of smoking in adolescents, although of considerable public health importance as an indication of future cancer trends and patterns, is extremely difficult to measure accurately and, consequently, to compare with other countries. It is usual for smoking habits to become established during adolescence, and smoking rates of young people in their late teens may approximate those of adults.

Figure 1.3. Trends in prevalence of smoking at ages 35–59 (left) and ≥ 60 (right) in men and women in the United Kingdom, 1950–98



From Peto *et al.* (2000)

(*b*) *Other indices of dose in developing countries and future surveillance needs*

Although the relationship between tobacco smoke and lung cancer in developed countries may be the most researched subject in epidemiological history, there remains a paucity of precise information concerning smoking behaviours in developing countries.

It is already clear that there is a worldwide trend towards the sale of machine-made cigarettes. On one hand, the manufacture of bidis and the various other home-grown, home-made products cannot be quantified readily because it is based on village cultivation or small industry. These products are generally cheap, vary widely in size and composition from district to district, and may or may not be subject to taxation. Conversely, cigarettes are mass produced or imported, easy to count and are almost invariably taxed before sale. For this reason, increases in sales can be measured, and taxation figures can be used to monitor sales trends. What cannot be seen is the effect of the market expansion of manufactured cigarettes on the use of other tobacco products. In addition, cigarette smuggling is a significant problem in several regions, e.g. southern Europe, North America and South America (Pagano *et al*., 1996; Galbraith & Kaiserman, 1997; Square, 1998; Yurekli & Zhang, 2000; Shafey *et al*., 2002) and a high rate of smuggling will make taxation figures inaccurate. Almost a third of global cigarette exports are estimated to go to the contraband market (Joossens & Raw, 1998).

In some areas (e.g. South-east Asia and India), it is not clear how far the behaviour of cigarette smoking is becoming a substitute for bidi smoking or for chewing, or whether cigarette smoking is becoming an additional behaviour. Mixed tobacco habits are also common. There is no way of estimating precisely the lifetime exposure to smoking products such as bidis or chuttas.

The detailed patterns and trends in national smoking behaviours can be identified only by regular measures of smoking rates operating within surveillance systems. There are considerable limitations to the current measures of prevalence. Data are expensive to collect and are incomplete or non-existent in many regions. In many cases, prevalence rates are underestimated because of the limitations in surveillance systems (e.g. fewer members of the lower income groups who tend to smoke more have telephones). Data on smoking by young people are incomplete and inaccurate for most countries. To address these issues, information is needed on initiation, prevalence and cessation. Routine surveillance data are needed to track smoking behaviours over time. In the future, much better methods for systematic reporting of smoking rates need to be applied worldwide.

1.4 Regulations

This section reviews the scope and potential impacts of tobacco control regulations. Because the focus of this monograph is on the risks of tobacco smoking, the preventive implications of regulation are covered only briefly with references to the literature for key studies and reviews of regulatory effects and effectiveness. Increasing the cost of ciga-

rettes through taxation and restrictions on smoking in the workplace are two public policy changes for which substantial bodies of information exist to define their effectiveness (Burns, 2000).

In recent years, researchers have increasingly recognized the role of regulation in influencing the use of tobacco. Policy or regulatory measures alter or control the legal, social, economic and physical environment (Brownson *et al*., 1995). Policies are 'those laws, regulations, formal, and informal rules and understandings that are adopted on a collective basis to guide individual and collective behaviour' (Schmid *et al*., 1995). Smokers frequently respond to environmental cues, such as a work break or entering a restaurant, when deciding whether or not to smoke. Regulatory interventions are based on the knowledge that individuals are strongly influenced by the sociopolitical and cultural environment in which they act (US Department of Health and Human Services, 2000).

Roemer (1988) clearly listed a set of purposes for tobacco regulation:

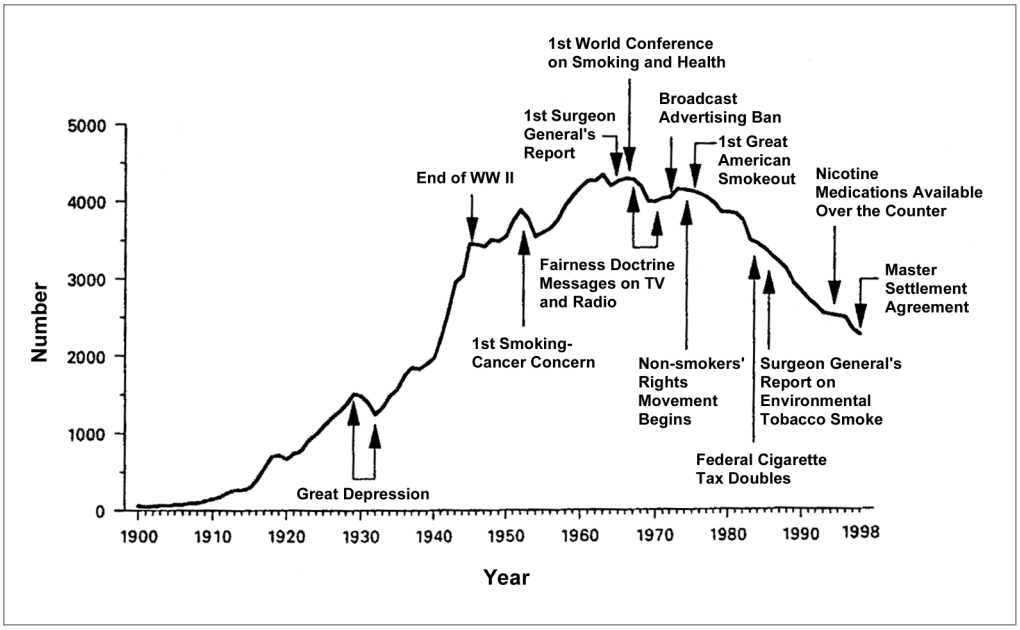
- to set forth governmental policy on the production, promotion and use of tobacco, and to protect the right of nonsmokers to breathe clean air;
- to reduce to some extent the harmful substances in cigarettes;
- to contribute to the development of a social climate in which smoking is unacceptable;
- to provide the basis of allocating resources to support effective programmes to combat smoking; and
- to encourage smokers to stop smoking and to dissuade potential smokers, particularly young persons, from starting to smoke.

The place of legislation in tobacco control was very clearly defined by a World Health Organization Expert Committee in 1983. It stated: 'It may be tempting to try to introduce smoking control programmes without a legislative component, in the hope that relatively inoffensive activity of this nature will placate those concerned with public health, while generating no real opposition from cigarette manufacturers. This approach, however, is not likely to succeed. A genuine broadly defined education programme, aimed at reducing smoking must be complemented by legislation and restrictive measures' (WHO, 1983).

In 2003, the 192 Member States of the World Health Organization unanimously adopted the Global Framework Convention on Tobacco Control (FCTC, 2003), the world's first international tobacco control treaty [added in print after the meeting]. The FCTC was prepared over four years by participants from a wide range of sectors and included representatives of WHO Member States representing 95% of the world's population. The FCTC is intended to provide a comprehensive regulatory structure, which when ratified and enacted as proposed, will lay the legal foundations for the regulation of tobacco and tobacco smoking in a range of situations (e.g. protecting children from tobacco use and exposure, promoting smoke-free environments and promoting healthy tobacco-free lifestyles).

As one example from a developed country, Figure 1.4 shows the correlation between per capita consumption of cigarettes in the USA and historical events since 1900. These events, such as the first US Surgeon General's report, the ban on tobacco advertising in

Figure 1.4. Annual adult per-capita consumption of cigarettes and major smoking and health events, USA, 1900–1998



From US Department of Agriculture; US Department of Health and Human Services (1986)
WWII, Second World War

the broadcast media and increases in the federal cigarette tax were followed by a decrease in tobacco consumption. Similar tracking of regulatory events, such as restrictions on tobacco advertising, may be used by any country wishing to monitor changes in tobacco consumption.

Although most of the regulatory interventions discussed below focus on the passage of a law or ordinance, many others can be implemented through an executive order or regulatory action. An example of an executive order is a ban on tobacco advertising on all city-owned buses. An example of a regulatory action is the adoption of an accrediting standard prohibiting smoking in hospital buildings (Longo *et al*., 1995).

Regulations regarding clean indoor air are described in detail in the monograph on involuntary smoking (Section 1.3). There has been a dramatic increase in the fraction of the working population protected by total bans on smoking in the workplace, which increased from 3% in 1986 to 64% in 1996. The implementation of these restrictions has had two effects on smokers: they have increased the rate at which smokers attempt to quit, and have reduced the number of cigarettes smoked per day (Burns *et al.*, 2000). To estimate the impact of smoking bans on cigarette use, Chapman *et al*. (1999) estimated the contributions of smoke-free workplaces to the recent declines in cigarette consumption noted in Australia and the USA. In Australia, smoke-free workplaces are considered to be

responsible for 22.3% of the 2.7 thousand million decrease in the number of cigarettes smoked between 1988 and 1995. Similarly in the USA, it was estimated that workplace bans are responsible for 12.7% of the 76.5 thousand million decrease in the number of cigarettes smoked between 1988 and 1994.

(*a*) *Price/excise taxes*

A substantial increase in tobacco excise taxes may be the single most effective measure at the national, state and local level for decreasing tobacco consumption (Sweanor *et al.*, 1992; Jha & Chaloupka, 2000). Youths and young adults may be more sensitive to increases in tobacco price than adults (Chaloupka & Warner, 2000). Excise taxes on tobacco products vary widely between the developed countries and in many cases the increases in taxes have been much smaller than the price increases imposed by cigarette manufacturers. The 'earmarking' (allocation of a portion) of tobacco price increases for prevention efforts has proved to be an effective strategy in California, USA (Elder *et al*., 1996; Fichtenberg & Glantz, 2000), Victoria, Australia (Chapman & Wakefield, 2001) and other places.

Numerous studies have quantified the effects of increases in excise tax on smoking rates. A recent systematic review that looked at the median estimates from a number of studies found that a 10% increase in the price of tobacco products resulted in a 3.7% decrease in the number of adolescents and young adults who used tobacco and 4.1% decrease in the amount of tobacco used by the general population (Hopkins *et al*., 2001).

One of the main arguments raised against increases in tobacco tax involves the regressivity of such taxes — that is, a tax where the proportion of an individual's income consumed by the tax is inversely related to income. Health advocates argue that the concern over regressivity is outweighed by the lives saved from unnecessary cancer and heart disease due to the reduced prevalence of smoking (Jacobs, 2001). Smoking and mortality rates from these diseases are disproportionately higher among individuals in lower income groups. Therefore, greater decreases in smoking-related disease and death rates in these groups would be expected to follow a tax increase.

(*b*) *Restricting tobacco advertising and promotion*

Cigarettes are possibly the most heavily advertised and promoted consumer product in the world (Mackay & Eriksen, 2002). In 2000, the six major US tobacco companies spent US$ 9.57 thousand million on cigarette advertising and promotion in the USA — more than US$ 26 million each day (Federal Trade Commission, 2002). The advertising and promotion of tobacco products leads to increased use of tobacco products, particularly by youths (Pierce *et al*., 1991). Advertising and promotion affect cigarette consumption by conveying to children and young adults that smoking has social benefits and that it is far more common than it really is; by creating attitudes and images that reinforce the desirability of smoking, and by suppressing full disclosure by the media of the health hazards of smoking. Numerous institutions involved in cultural events, minority causes and sports are financed by contributions from the tobacco industry. This

situation undermines an institution's ability to enact policies and practices to reduce tobacco use (Kaufman & Nichter, 2001).

Numerous governments have enacted laws banning tobacco advertising by cinemas, posters, press, radio, television and at points of sale. Giving samples and sponsorship are also banned in some countries (European Union, 2000). Governmental entities have banned advertising on public transport, in sports stadiums or on property owned by local government. These actions are based upon the conclusion reached by many localities that national laws do not preempt them from restricting advertising on their own property or within their jurisdiction.

Governments also can support legislative, regulatory and non-legislative policies to reduce tax deductions for tobacco advertising, to restrict tobacco promotions like the Marlboro Adventure Team incentives, to prohibit the exhibition of a cigarette brand name, to restrict product placement and ultimately to eliminate tobacco advertising. Recent evidence has also demonstrated that most of the current warning labels on cigarette packets are neither effective in transferring knowledge regarding the health hazards associated with tobacco use, nor likely to have a positive impact on the health behaviour of people using these products. The experiences in countries such as Canada and Poland where the warning labels and package inserts are larger, more visible and simpler should be examined in detail to determine their effects on public health (Canada ASH; Health Promotion Foundation, 2002). Despite mixed findings on the effectiveness of these warning labels, they are viewed as a cost-effecive anti-smoking measure by their mere presence and are considered to be an important part of larger anti-smoking efforts (Guttman & Peleg, 2003).

(*c*) *Restricting the uptake of tobacco use by young people*

In most countries, adult smokers began their smoking behaviour as young teenagers (National Cancer Institute, 2001). In several developed countries, there has been virtually no decline in smoking rates among all teenagers over the past decade. Because smoking begins at a young age, the most important potential actions for affecting the overall rates of tobacco use should emphasize prevention of tobacco use in youth. As yet, the effects of many of the regulatory actions intended to prevent smoking by young people have not been established by research studies.

For example, in most parts of the world, there are laws prohibiting the sale of cigarettes to persons under 18 years of age. Many researchers and public health practitioners have concluded that the only way to limit minors' access to cigarettes is to ban vending machines, raise tobacco prices and excise taxes and enforce laws governing the access of young people to tobacco. Yet the enforcement of comprehensive laws on the access of minors to tobacco has been the subject of considerable debate and the existing literature on the effectiveness of specific types of enforcement efforts is limited and inconsistent (Forster & Wolfson, 1998; Stead & Lancaster, 2000).

Other approaches that may be used to protect young people from becoming smokers include educational programmes, which in some countries have been made compulsory

by law, and specific prohibitions against smoking in places where young people congregate, such as schools and recreational facilities.

(*d*) *Regulation and litigation*

Litigation efforts include four main categories: individual cases, class actions, public interest lawsuits and health care cost recovery actions. Within the final category, several cases have been brought by several states of the USA to attempt to recover the costs of medical care attributable to cigarette smoking as product liability suits. In general, these actions are based on the fact that taxpayers pay for medical care for smoking-related illnesses through Medicaid and other state-supported systems. The states had no choice as to whether the taxpayers should pay for damages caused by a dangerous product; therefore, the suits claim a need for the recovery of costs on behalf of all state taxpayers. As data on state-specific costs became available, specific damages were calculated that permitted substantial cost recovery from the tobacco companies. As an example, state attorneys general in the USA agreed to a US$ 206 thousand million settlement with the tobacco industry in November 1998, the so-called 'Master Settlement Agreement' (National Association of Attorneys General, 1998). Results to date from this settlement have been less successful than anticipated because much of the funding from the Master Settlement that was originally intended for smoking prevention activities is being diverted to other governmental programmes. Of particular relevance to this monograph, is that one important outcome of the recent tobacco litigation has been the public release of numerous tobacco industry documents (CDC, 2002) (close to 40 million pages) showing what the industry knew about the carcinogenic potential of tobacco and when they knew it.

(*e*) *Regulation of tobacco smoke constituents*

Worldwide, only minimal regulation applies to the constituents of cigarettes and tobacco smoke, as for example in Europe. The maximum tar yield of cigarettes marketed in the European Union was set at 15 mg/cigarette in 1992, 12 mg/cigarette in 1997 (European Commission, 1999) and 10 mg/cigarette in 2001. In addition to tar, the new Directive lays down the maximum permitted nicotine and CO yields for cigarettes released for free circulation, marketed or manufactured in the Member States, i.e. 1 mg/cigarette for nicotine and 10 mg/cigarette for CO. In 2003, it was prohibited to describe one product as less harmful than another (by using names, symbols). Moreover, manufacturers and importers are now required to submit to the Member States, on a yearly basis since 2002, a list of all ingredients used in the manufacture of tobacco products and their quantities, together with toxicological data on their effects on health and any addictive effects. This list must be accompanied by a statement setting out the reasons for the inclusion of the ingredients. It must also be made public and be submitted to the Commission (European Parliament, 2001). For example, currently over 600 additives to tobacco products are permitted in the United Kingdom (Department of Health, 2000).

In the future, it is likely that upper limits for carcinogens and toxins will be set for cigarette smoke as they have already been for car exhausts and other ambient pollutants. This is dependent on the acquisition of appropriate legal powers by regulatory agencies.

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