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The Changing Cigarette: Chemical Studies and Bioassays

Dietrich Hoffmann, Ilse Hoffmann

INTRODUCTION In 1950, the first large-scale epidemiological studies on smoking and lung cancer conducted by Wynder and Graham, in the United States, and Doll and Hill, in the United Kingdom, strongly supported the concept of a dose response between the number of cigarettes smoked and the risk for cancer of the lung (Wynder and Graham, 1950; Doll and Hill, 1950).

In 1953, the first successful induction of cancer in a laboratory animal with a tobacco product was reported with the application of cigarette tar[a] to mouse skin (Wynder *et al.*, 1953). The particulate matter of cigarette smoke generated by an automatic smoking machine was suspended in acetone (1:1) and painted onto the shaven backs of mice three times weekly for up to 24 months. A clear dose response was observed between the amount of tar applied to the skin of the mice and the percentage of skin papilloma- and carcinoma-bearing animals in the test group (Wynder *et al.*, 1957). Since then, mouse skin has been widely used as the primary bioassay method for estimating the carcinogenic potency of tobacco tar and its fractions, as well as of particulate matters of other combustion products (Wynder and Hoffmann, 1962, 1967; NCI, 1977a, 1977b, 1977c, 1980; Hoffmann and Wynder, 1977; IARC, 1986a). Intratracheal instillation in rats of the PAH-containing neutral subfraction of cigarette tar led to squamous cell carcinoma of the trachea and lung (Davis *et al.*, 1975). A cigarette tar suspension in acetone painted onto the inner ear of rabbits led to carcinoma with metastasis in thoracic organs (Graham *et al.*, 1957).

Dontenwill and colleagues (1973) developed a method that involved placing Syrian golden hamsters individually into plastic tubes and exposing them to cigarette smoke diluted with air (1:15) twice daily, 5 days a week, for up to 24 months (Dontenwill *et al.*, 1973). The method led to lesions primarily in the epithelial tissue of the outer larynx. Using an inbred strain of Syrian golden hamsters with increased susceptibility of the respiratory tract to carcinogens, long-term exposure to cigarette smoke produced a high tumor yield in the larynx (Bernfeld *et al.*, 1974). A dose response was recorded between the degree of smoke exposure and the induction of benign and malignant tumors in the larynges of the hamsters.

In general, inhalation studies have not found that tobacco smoke leads to squamous cell carcinoma of the lung (Wynder and Hoffmann, 1967; Mohr and Reznik, 1978; IARC, 1986a & b). Dalbey and associates from the National Laboratory in Oak Ridge, Tennessee, exposed female F344 rats to diluted smoke of up to 7 cigarettes daily, 5 times a week for up to 2.5 years. A high percentage of the smoke-exposed rats developed hyperplasia and

[a] Throughout the article, the term "tar" is only used as descriptive noun.

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metaplasia in the epithelium of the nasal turbinates and in the larynx, and also some hyperplasia in the trachea. The sham-treated rats developed a small number of lesions in nasal and laryngeal epithelia but none in the trachea. Ten tumors of the respiratory system were observed in 7 out of 80 smoke-exposed rats. These were 1 adenocarcinoma, 1 squamous cell carcinoma in the nasal cavity, 5 adenomas of the lung, 2 alveologenic carcinomas, and 1 squamous cell carcinoma of the lung (Dalbey *et al*., 1980). In the control group of 93 sham-smoked rats, 1 developed an alveologenic carcinoma (Dalbey *et al*., 1980). In 1952, Essenberg reported that cigarette smoke induces an excessive number of pulmonary adenomas; whereas, the sham-exposed mice, as well as the untreated mice, developed significantly lower rates of pulmonary tumors (Essenberg, 1952). In the following years, the Leuchtenbergers repeatedly confirmed the findings by Essenberg. They also demonstrated that even the gas phase increased the occurrence of pulmonary tumors in mice (Leuchtenberger *et al*., 1958; Leuchtenberger and Leuchtenberger, 1970). Several additional studies demonstrated the induction of pulmonary tumors in several strains of mice exposed to diluted cigarette smoke (Mühlbock, 1958; Wynder and Hoffmann, 1967; Mohr and Reznik, 1978; IARC, 1986a & b). Otto exposed mice to diluted cigarette smoke for 60 minutes daily for up to 24 months. Of 30 mice, 4 developed lung adenomas and 1 an epidermoid carcinoma of the lung. In the untreated control group, 3 of 60 mice developed lung adenomas (Otto, 1963).

IDENTIFICATION OF CARCINOGENS, TUMOR PROMOTERS, AND CARCINOGENS IN TOBACCO SMOKE

Green and Rodgman (1996) estimated that there were about 4,800 compounds in tobacco smoke. In addition, additives out of a list of 599 compounds disclosed by tobacco companies (Doull *et al*., 1994) may be added to cigarette tobacco in the process of manufacturing a cigarette in the United States (Green and Rodgman, 1996; Doull *et al*., 1994). Tables 5-1 and 5-2 list the major constituents of the vapor phase (Table 5-1) and the particulate phase (Table 5-2) and their concentrations in the mainstream smoke (MS) of non-filter cigarettes (Hoffmann and Hecht, 1990; Ishiguro and Sugawara, 1980). The agricultural chemicals and pesticides, as well as their specific thermic degradation products, are omitted from the two tables because of the many variations in the nature and amount of these agents in tobacco from country to country and from year to year (Wittekindt, 1985). Table 5-3 lists the major toxic components in the MS of cigarettes (Hoffmann *et al*., 1995).

Development of highly sensitive analytical methods, as well as reproducible short-term and long-term assays, has led to the identification of 69 carcinogens (Table 5-4). Of these, 11 are known human carcinogens (Group I), 7 are probably carcinogenic in humans (Group 2A), and 49 of the animal carcinogens are possibly also carcinogenic to humans (Group 2B). This classification of the carcinogens is according to the International Agency for Research on Cancer (IARC, 1983, 1984, 1986b, 1987, 1988, 1991, 1992, 1994a–e, 1995a & b, 1996, 1999a & b). Two suspected carcinogens have yet to be evaluated by the IARC.

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Table 5-1
Major Constituents of the Vapor Phase of the Mainstream Smoke of Non-Filter Cigarettes

Compound[a]	Concentration/Cigarette (% of Total Effluent)
Nitrogen	280-320 mg (56-64%)
Oxygen	50-70 mg (11-14%)
Carbon dioxide	45-65 mg (9-13%)
Carbon monoxide	14-23 mg (2.8-4.6%)
Water	7-12 mg (1.4-2.4%)
Argon	5 mg (1.0%)
Hydrogen	0.5-1.0 mg
Ammonia	10-130 µg
Nitrogen oxides (NO_x)	100-600 µg
Hydrogen cyanide	400-500 µg
Hydrogen sulfide	20-90 µg
Methane	1.0-2.0 mg
Other volatile aromatic alkanes (20)	1.0-1.6 mg[b]
Volatile alkenes (16)	0.4-0.5 mg
Isoprene	0.2-0.4 mg
Butadiene	25-40 µg
Acetylene	20-35 µg
Benzene	12-50 µg
Toluene	20-60 µg
Styrene	10 µg
Other volatile hydrocarbons (29)	15-30 µg
Formic acid	200-600 µg
Acetic acid	300-1,700 µg
Propionic acid	100-300 µg
Methyl formate	20-30 µg
Other volatile acids (6)	5-10 µg
Formaldehyde	20-100 µg
Acetaldehyde	400-1400 µg
Acrolein	60-140 µg
Other volatile aldehydes (6)	80-140 µg
Acetone	100-650 µg
Other volatile ketones (3)	50-100 µg
Methanol	80-180 µg
Other volatile alcohols (7)	10-30 µg
Acetonitrile	100-150 µg
Other volatile nitriles (10)	50-80 µg[b]
Furan	20-40 µg
Other volatile furans (4)	45-125 µg[b]
Pyndine	20-200 µg
Pyridine (3)	15-80 µg
3-Vinylpyridine	10-30 µg
Other volatile pyridines (25)	20-50 µg[b]
Pyrrole	0.1-10 µg
Pyrrolidine	10-18 µg
N-Methylpyrrolidine	2.0-3.0 µg
Volatile pyrazines (18)	3.0-8.0 µg
Methylamine	4-10 µg
Other aliphatic amines (32)	3-10 µg

[a]*Numbers in parentheses represent the individual compounds identified in a given group*
[b]*Estimate*

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Table 5-2
Major Constituents of the Particulate Matter of the Mainstream Smoke of Non-Filter Cigarettes

Compound[a]	µg/Cigarette[b]
Nicotine	1.000-3.000
Nornicotine	50-150
Anatabine	5-15
Anabasine	5-12
Other tobacco alkaloids (17)	NA
Bipyridyls (4)	10-30
n-Hentriacontane (*n*-$C_{31}H_{64}$)[c]	100
Total nonvolatile hydrocarbons (45)[c]	300-400[c]
Naphthalene	2-4
Naphthalenes (23)	3-6[c]
Phenanthrenes (7)	0.2-0.4[c]
Anthracenes (5)	0.05-0.1[c]
Fluorenes (7)	0.6-1.0[c]
Pyrenes (6)	0.3-0.5[c]
Fluoranthenes	0.3-0.45[c]
Carcinogenic polynuclear aromatic hydrocarbons (11)[b]	0.1-0.25
Phenol	80-160
Other phenols (45)[c]	60-180[c]
Catechol	200-400
Other catechols (4)	100-200[c]
Other dihydroxybenzenes (10)	200-400[c]
Scopoletin	15-30
Other polyphenols (8)[c]	NA
Cyclotenes (10)[c]	40-70[c]
Quinones (7)	0.50
Solanesol	600-1,000
Neophytadienes (4)	200-350
Limonene	30-60
Other terpenes (200-250)[c]	NA
Palmitic acid	100-150
Stearic acid	50-75
Oleic acid	40-110
Linoleic acid	150-250
Linolenic acid	150-250
Lactic acid	60-80
Indole	10-15
Skatole	12-16
Other indoles (13)	NA
Quinolines (7)	2-4
Other aza-arenes (55)	NA
Benzofurans (4)	200-300
Other *0*-heterocyclic compounds (42)	NA
Stigmasterol	40-70
Sitosterol	30-40
Campesterol	20-30
Cholesterol	10-20
Aniline	0.36
Toluidines	0.23
Other aromatic amines (12)	0.25
Tobacco-specific *N*-nitrosamines (6)	0.34-2.7
Glycerol	120

[a]Numbers in parentheses represent individual compounds identified.
[b]For details, See Table 5-4
[c]Estimate. NA=Not available.

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Table 5-3
Major Toxic Agents in Cigarette Smoke[a]

Agent	Concentration/ Non-Filter Cigarette	Toxicity
Carbon monoxide	10-23 mg	Binds to hemoglobin, inhibits respiration
Ammonia	10-130 µg	Irritation of respiratory tract
Nitrogen oxide (NO_x)	100-600 µg	Inflamation of the lung
Hydrogen cyanide	400-500 µg	Highly ciliatoxic, inhibits lung clearance
Hydrogen sulfide	10-90 µg	Irritation of respiratory tract
Acrolein	60-140 µg	Ciliatoxic, inhibits lung clearance
Methanol	100-250 µg	Toxic upon inhalation and ingestion
Pyridine	16-40 µg	Irritates respiratory tract
Nicotine[b]	1.0-3.0 mg	Induces dependence, affects cardiovascular and endocrine systems
Phenol	80-160 µg	Tumor promoter in laboratory animals
Catechol	200-400 µg	Cocarcinogen in laboratory animals
Aniline	360-655 µg	Forms methemoglobin, and this affects respiration
Maleic hydrazide	1.16 µg	Mutagenic agent

[a]This is an incomplete list.
[b]Toxicity: oral/rat, LD_{50} free nicotine 50 mg/kg, nicotine bitartrate 65 mg/kg.
Source: Hoffmann et al., 1998.

Table 5-4
Carcinogens in Cigarette Smoke

Agent	Conc./Non-filter Cigarette	IARC Evaluation Evidence of Carcinogenicity in Lab Animals	in Humans	Group[a]
PAH				
Benz(*a*)anthracene	20-70 ng	Sufficient		2A
Benzo(*b*)fluoranthene	4-22 ng	Sufficient		2B
Benzo(*j*)fluoranthene	6-21 ng	Sufficient		2B
Benzo(*k*)fluoranthene	6-12 ng	Sufficient		2B
Benzo(*a*)pyrene	20-40 ng	Sufficient	Probable	2A
Dibenz(*a,h*)anthracene	4 ng	Sufficient		2A
Dibenzo(*a,l*)pyrene	1.7-3.2 ng	Sufficient		2B
Dibenzo(*a,e*)pyrene	Present	Sufficient		2B
Indeno(1,2,3-*cd*)pyrene	4-20 ng	Sufficient		2B
5-Methylchrysene	0.6 ng	Sufficient		2B
Heterocyclic Compounds				
Quinoline[b]	1-2 ng			
Dibenz(*a,h*)acridine	0.1 ng	Sufficient		2B
Dibenz(*a,j*)acridine	3-10 ng	Sufficient		2B
Dibenzo(*c,g*)carbazole	0.7 ng	Sufficient		2B
Benzo(*b*)furan	Present	Sufficient		2B
Furan	18-37 ng	Sufficient		2B

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Table 5-4 (continued)

Agent	Conc./Non-filter Cigarette	IARC Evaluation Evidence of Carcinogenicity in Lab Animals	in Humans	Group[a]
***N* -Nitrosamines**				
N -Nitrosodimethylamine	2-180 ng	Sufficient		2A
N -Nitrosoethylmethylamine	3-13 ng	Sufficient		2B
N -Nitrosodiethylamine	ND-2.8 ng	Sufficient		2A
N -Nitrosodi-*n*-propylamine	ND-1.0 ng	Sufficient		2B
N -Nitroso-di-*n*-butylamine	ND-30 ng	Sufficient		2B
N -Nitrosopyrrolidine	3-110 ng	Sufficient		2B
N -Nitrosopiperidine	ND-9 ng	Sufficient		2B
N -Nitrosodiethanolamine	ND-68 ng	Sufficient		2B
N -Nitrosonornicotine	120-3,700 ng	Sufficient		2B
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	80-770 ng	Sufficient		2B
Aromatic Amines				
2-Toluidine	30-337 ng	Sufficient		2B
2,6-Dimethylaniline	4-50 µg	Sufficient		2B
2-Naphthylamine	1-334 ng	Sufficient	Sufficient	1
4-Aminobiphenyl	2-5.6 ng	Sufficient	Sufficient	1
***N* -Heterocyclic Amines**				
AaC	25-260 ng	Sufficient		2B
IQ	0.3 ng	Sufficient		2B
Trp-P-1	0.3-0.5 ng	Sufficient		2B
Trp-P-2	0.8-1.1 ng	Sufficient		2B
Glu-P-1	0.37-0.89 ng	Sufficient		2B
Glu-P-2	0.25-0.88 ng	Sufficient		2B
PhIP	11-23 ng	Sufficient	Possible	2A
Aldehydes				
Formaldehyde	70-100 µg	Sufficient	Limited	2A
Acetaldehyde	500-1,400 µg	Sufficient	Insufficient	2B
Volatile Hydrocarbons				
1,3-Butadiene	20-75 µg	Sufficient	Insufficient	2B
Isoprene	450-1,000 µg	Sufficient		2B
Benzene	20-70 µg	Sufficient	Sufficient	1
Styrene	10 µg	Limited		2B
Misc. Organic Compounds[c]				
Acetamide	38-56 µg	Sufficient		2B
Acrylamide	Present	Sufficient		2B
Acrylonitrile	3-15 µg	Sufficient	Limited	2A
Vinyl chloride	11-15 ng	Sufficient	Sufficient	1
DDT	800-1,200 µg	Sufficient	Probable	2B
DDE	200-370 µg	Sufficient		2B
Catechol	100-360 µg	Sufficient		2B
Caffeic acid	< 3 µg	Sufficient		2B
1,1-Dimethylhydrazine	Present	Sufficient		2B
Nitromethane	0.3-0.6 µg	Sufficient		2B

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Table 5-4 (continued)

Agent	Conc./Non-filter Cigarette	IARC Evaluation Evidence of Carcinogenicity in Lab Animals	in Humans	Group[a]
2-Nitropropane	0.7-1.2 µg	Sufficient		2B
Nitrobenzene	25 µg	Sufficient		2B
Ethyl carbamate	20-38 µg	Sufficient		2B
Ethylene oxide	7 µg	Sufficient	Sufficient	1
Propylene oxide	12-100 ng	Sufficient		2B
Methyleugenol	20 ng			
Inorganic Compounds				
Hydrazine	24-43 ng	Sufficient	Inadequate	2B
Arsenic	40-120 µg	Inadequate	Sufficient	1
Beryllium	0.5 ng	Sufficient	Sufficient	1
Nickel	ND-600 ng	Sufficient	Sufficient	1
Chromium (only hexavalent)	4-70 ng	Sufficient	Sufficient	1
Cadmium	7-350 ng	Sufficient	Sufficient	1
Cobalt	0.13-0.2 ng	Sufficient	Inadequate	2B
Lead	34-85 ng	Sufficient	Inadequate	2B
Polonium-210	0.03-1.0 pCi	Sufficient	Sufficient	1

*Abbreviations: ND, not detected; PAH, polynuclar aromatic hydrocarbons; AaC, 2-amino-9*H*-pyrido[2,3-*b*]indole; IQ, 2-amino-3-methylimidazo[4,5-*b*]quinoline; Trp-P-1, 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole; Trp-2, 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole; Glue-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.*

[a]IARC Monographs on the Evaluation of Carcinogenic Risks. *Volume 1 and Supplements 1-8, 1972-1999. (1) Human carcinogens; (2A) Probably carcinogenic in humans; (2B) Possibly carcinogenic to humans; (3) Not classifiable as to their carcinogenicity to humans.*

[b]*Unassigned carcinogenicity status by IARC at this time*

[c]*In 1982, the IARC assigned di(2-ethylhexyl)phthalate as sufficient to Group 2B. However, in 2000, re-evaluation of the carcinogenicity was classified as not carcinogenic (IARC 1982, 2000). We cited di(2-ethylhexyl)phthalate as a 2B carcinogen (Hoffmann and Hoffmann, 1997) and in this article, it is deleted from Table 5-4, "Carcinogenicity in Cigarette Smoke."*

Sources: International Agency for Research on Cancer, 1982, 2000.

SMOKING CONDITIONS

In 1936, the American Tobacco Company began using standard machine smoking conditions, which, to some extent, reflected the smoking habits of cigarette smokers at that time. The estimated sales-weighted average nicotine yields of the cigarettes smoked at that time were around 2.8 mg (Bradford *et al.*, 1936). In agreement with the U.S. tobacco industry, the Federal Trade Commission (FTC) adapted the 1936 standard method in 1969 with only slight modifications. Since then, machine-smoking conditions are one puff/minute with a volume of 35 ml drawn during 2 seconds, leaving a butt length of 23 mm for a non-filter (plain) cigarette, and length of the filter and overwrap plus 3 mm for a filter cigarette (Pillsbury *et al.*, 1969). In Canada and the United Kingdom, the standard smoking conditions of the International Standards Organization (ISO) have been accepted since 1991 (ISO, 1991). In other European countries, the standard smoking conditions for cigarettes are those developed by CORESTA (Centre De Cooperation Pour Les Recherches Scientifiques Relative Au Tabac), which are similar to the FTC standard smoking conditions (CORESTA, 1991). In Japan, the FTC standard smoking conditions are employed for the machine smoking of cigarettes (Pillsbury *et al.*, 1969). The FTC method defines tar as smoke particulates minus water and nicotine, whereas CORESTA defines tar as total particulates minus water (Pillsbury *et al.*, 1969; ISO, 1991; CORESTA, 1991). The standard conditions for machine

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smoking of tobacco products used by the different testing protocols are presented in Table 5-5. Using the FTC method, the sales-weighted average tar and nicotine yields of U. S. cigarettes decreased from about 37 mg and 2.7 mg in 1954 to 12 mg and 0.85 mg in 1993 (Figure 5-1).

More than 20 years ago, M.A.H. Russell in the United Kingdom and N.L. Benowitz in the United States reported that long-term smokers of cigarettes with lower nicotine yields took more than one puff per minute, drew puff volumes exceeding 35 ml, and inhaled the smoke more deeply than smokers of higher yield cigarettes (Russell, 1976, 1980; Benowitz *et al.*, 1983).

Table 5-6 presents the smoking characteristics of 56 volunteer smokers who regularly consumed low-yield cigarettes (≤ 0.8 mg nicotine/cigarette according to the FTC smoking machine method) and of 77 volunteer smokers regularly consuming medium-nicotine cigarettes (FTC, 0.9–1.2 mg/cigarette). These two ranges of nicotine yield constituted more than 73.4 percent of all cigarettes smoked in the U.S. in 1993 (FTC, 1995). The results of this study clearly indicated that the majority of U.S. smokers smoked their cigarettes much more intensely to satisfy their acquired need for nicotine. Comparing the yields of the same cigarettes smoked under FTC standard machine smoking conditions with the smoke inhaled by the consumers of cigarettes with low- and medium-nicotine content revealed that smokers inhaled 2.5 and 2.2 times more nicotine/cigarette, 2.6 and 1.9 times more tar, 1.8 and 1.5 times more carbon monoxide, 1.8 and 1.6 times more BaP, and 1.7 and 1.7 times more NNK than is generated by the FTC machine-smoking method (Table 5-6; Djordjevic *et al.,* 2000).

The discrepancy in exposure assessment between recent measurements and former interpretations of machine-smoking data has led to criticism of the FTC standard machine smoking method for consumer guidance. The suggestion that there is a meaningful quantitative relationship between the FTC-measured yields and actual intake (by the cigarette smoker) is misleading (Benowitz, 1996). In view of these concerns, it appears "that the time has come for meaningful information on the yields of cigarettes" (Wilkenfeld *et al.*, 2000a & b). The FTC agrees, in principle, that a better and more comprehensive test program for cigarettes is needed (Peeler and Butters, 2000).

CHANGES IN CIGARETTE SMOKE COMPOSITION WITH VARIOUS DESIGN CHANGES

Filter Tips

In 1959, Haag *et al*. reported the selective reduction of volatile smoke constituents by filtration through charcoal filter tips (Haag *et al.*, 1959). Several of the compounds that are selectively removed from mainstream smoke (MS) in this fashion are major ciliatoxic agents, such as hydrogen cyanide, formaldehyde, acrolein, and acetaldehyde. Charcoal filters reduce the MS levels of these agents by up to 66 percent (Kensler and Battista, 1966; Tiggelbeck, 1976; Battista, 1976). However, for tar reduction, charcoal filters are less efficient than cellulose acetate filters. Several types of combination filters are in use. The early charcoal-activated dual and triple filter tips were cellulose acetate filters with embedded charcoal powder or granulated char-

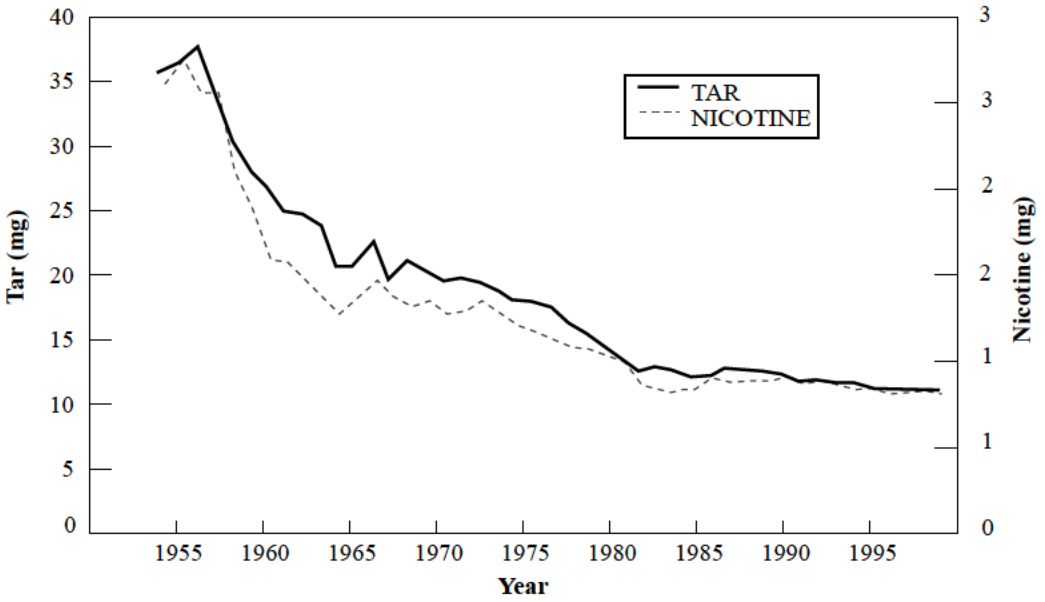
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Table 5-5
Standard Conditions for Machine Smoking of Tobacco Product

Parameters	Cigarettes		Bidis	Little Cigars	Small Cigars	Cigars	Premium	Pipes
	FTC	CORESTA		FTC	CORESTA	CORESTA	CORESTA	CORESTA
Weight (g)	0.8-1.1	0.8-1.1	0.55-0.80	0.9-1.3	1.3-2.5	5-17	6-20	*
Puff								
Frequency (sec)	60.0	60.0	30.0	60.0	40.0	40.0	40.0	20.0
Duration (sec)	2.0	2.0	2.0	2.0	1.5	1.5	1.5	2.0
Volume (ml)	35.0	35.0	35.0	35.0	40.0	40.0	40.0	50.0
Butt length (mm)								
Non-filter	23.0	23.0	23.0	23.0	33.0	33.0	33.0	
Filter	F&OW+3	F+8	F&OW+3					

Abbreviations: FTC = Federal Trade Commission method; CORESTA = Centre de Cooperation Pour Les Reherches Scientifiques Relative au Tabac Method; F = filter tip; OW = overwrap.
**One gram of pipe tobacco smoked.*
Sources: Hoffmann et al., 1974; International Committee for Cigar Smoking, 1974; Miller, 1963.

Figure 5-1
Sales-Weighted Tar and Nicotine Values for U.S. Cigarettes as Measured by Machine Using the FTC Method, 1954*-1998



**Values before 1968 are estimated from available data.*

coal sandwiched between cellulose acetate segments. These filters have been improved by innovative filter designs, incorporating cellulose acetate, charcoal, and cigarette filter paper (Shepherd, 1994). In the United States, however, cigarettes with charcoal filters have accounted for only about 1 percent of all cigarette sales over the past 15 years. In most developed coun-

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Table 5-6
A Comparison of Smoke Data for Two Low-Yield U.S. Filter Cigarettes Smoked According to the FTC-Method and by Smokers

Parameters	FTC Machine Smoking	Cigarette Smokers FTC 0.6-0.8 Nicotine	Cigarette Smokers FTC 0.9-1.2 Nicotine
Puff			
Volume (ml)	35.0	48.6 (45.2-52.3)[a]	44.1 (40.8-46.8)[b]
Interval (sec)	58.0	21.3 (19.0-23.8)[a]	18.5 (16.5-20.6)[b]
Duration (sec)	2.0	1.5 (1.4-1.7)[a]	1.5 (1.4-1.6)[b]
Nicotine (mg/cig)	0.7 (0.6-0.8)	1.74 (1.54-1.98)[c]	
	0.1 (1.09-1.13)		2.39 (2.20-2.60)[d]
Tar (mg/cig)	8.5 (7.7-9.5)	22.3 (18.8-26.5)[e]	
	15.4 (14.2-14.9)		29.0 (25.8-32.5)[f]
CO (mg/cig)	9.7 (9.0-10.4)	17.3 (15.0-20.1)[g]	
	14.6 (14.2-14.9)		22.5 (20.3-25.0)[h]
Ba P (ng/cig)	10 (8.2-12.3)	17.9 (15.3-20.9)[i]	
	14 (10.1-19.4)		21.4 (19.2-23.7)[j]
NNK (ng/cig)	112.9 (96.6-113.0)	186.5 (158.3-219.7)[i]	
	146.2 (132.5-165.5)		250.9 (222.7-282.7)[j]

Test Groups: [a]56 smokers; [b]71 smokers; [c]30 smokers; [d]42 smokers; [e]18 smokers; [f]19 smokers; [g]15 smokers; [h]16 smokers; [i]6 smokers; [j]3 smokers.
Source: Djordjevic et al.*, 2000.*

tries, charcoal filter cigarettes have accounted for, at most, a small percentage of the open cigarette market, exceptions are Japan, South Korea, Venezuela and Hungary, where at least 90 percent of the cigarettes have charcoal filter tips (John, 1996; Fisher, 2000).

Cellulose acetate filter cigarettes first became popular in Switzerland, during the early 1950s, and soon thereafter in Germany. Their popularity spread to the U.S., the UK and Japan, and finally to France. In 1956, the market share of filter cigarettes in Switzerland was 57.2 percent, in Germany 16.7 percent, and in the USA 29.6 percent, with only a few percent in Japan, England, and France. By 1965, the filter cigarette market share in these countries had risen to about 82 percent, 80 percent, 63 percent, 50 percent , 52 percent , and 21 percent, respectively. At this time, cellulose acetate filter cigarettes accounted for at least 95 percent of the cigarette markets in all of the developed countries, except France, where filter cigarettes remained at 85 percent of all cigarette sales (Wynder and Hoffmann, 1994; Waltz and Häusermann, 1963; Hoffmann and Hoffmann, 1997).

In the early 1960s, investigators found that cellulose acetate filter tips retained up to 80 percent of the volatile phenols from the smoke. Reduction of the emissions of volatile phenols from cigarettes was desirable because their tumor promoting activity had been demonstrated in carcinogenesis assays (Roe *et al*., 1959; Wynder and Hoffmann, 1961; Hoffmann and Wynder, 1971). When tested on a gram-to-gram basis, the tar from cellulose acetate-filtered smoke is somewhat more toxic, but less carcinogenic, than tars obtained from charcoal-filtered smoke or from the smoke of non-

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filter cigarettes (Hoffmann and Wynder, 1963; Spears, 1963; Wynder and Mann, 1957; Bock *et al.*, 1962; NCI, 1977c). Cellulose acetate filter tips also selectively remove up to 75 percent of the carcinogenic volatile *N*-nitrosamines (VNA), whereas charcoal-filter tips are much less effective in removing VNA (Brunnemann *et al.*, 1977). Exposure of Syrian golden hamsters twice daily, 5 days per week, for over 60 weeks to the diluted smoke from two different cellulose acetate filter cigarettes elicited a significantly lower incidence of carcinoma of the larynx than exposure to the diluted smoke from the non-filter cigarette ($p<0.01$). In contrast, the incidence rate of carcinoma of the larynx of hamsters exposed to diluted smoke from charcoal-filter cigarettes did not differ significantly from that of larynx carcinoma in hamsters exposed to diluted smoke from the non-filter cigarette (Dontenwill *et al.*, 1973).

Filter perforation allows air dilution of smoke during puff drawing. The velocity of airflow through the burning cone of cigarettes with perforated filters is slowed down because the negative pressure generated by drawing a puff is reduced by drawing air through the filter perforations, and the pressure drop across the tobacco rod is reduced, thus slowing the flow of smoke through the rod. This results in more complete combustion of the tobacco and a higher retention of particulate matter by cellulose acetate in the filter tip (Hoffmann and Hoffmann, 1997; Norman *et al.*, 1984; Durocher, 1984; Baker, 1984). Presently, more than 50 percent of all cigarettes have perforated filter tips. Table 5-7 compares smoke yields of cigarettes without filter tips, cigarettes with cellulose acetate filter tips, and cigarettes with cellulose acetate filter tips that are perforated. The filling tobaccos of these experimental cigarettes were made of an identical blend. The conventional filter tip of cellulose acetate retains more tar, nicotine, and phenol, but releases more CO and ciliatoxic agents, hydrogen cyanide, acetaldehyde, and acrolein than does the cigarette with the perforated filter tip (NCI, 1977c). In mouse skin assays, the tars from both types of filter cigarettes have comparable tumorigenic activity. However, one needs to bear in mind that (a) these comparative data are generated with tars obtained by the standardized machine smoking method, with a 35-ml puff, taken once a minute over 2 seconds; (b) more than 60 percent of today's smokers in the United States and in many developed countries smoke cigarettes with nicotine yields of only 1.2 mg or less (according to FTC standards of smoking); and (c) most of these smokers compensate for the low nicotine delivery.

Compensation and greater smoke intake is governed by the smoker's acquired need for nicotine and, in essence, negates the intended benefits of reducing smoke yields by technical means (Russell, 1976, 1980; Benowitz *et al.*, 1983; Benowitz and Henningfield, 1994; Schultz and Seehofer, 1978; Moody, 1980; Herning *et al.*, 1981; Gritz *et al.*, 1983; Nil *et al.*, 1986; Djordjevic *et al.*, 1995, 2000; see Chapter 2).

Paper Porosity Since about 1960, higher cigarette paper porosity and treatment of paper with citrate have significantly contributed to the reduction of smoke yields of several smoke components. During and in between puff drawing, porous paper enhances the outward diffusion through the paper of hydrogen, NO, CO, CO_2, methane, ethane, and ethylene. On the other hand, it

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Table 5-7
Comparison of Experimental Cigarettes (Yield/Cigarette)[a,b]

Smoke Components	Unit of Measurement	Non-Filter Cigarette	Cellulose Acetate Filter Cigarette	Cellulose Acetate Filter w/Perforation	Cellulose Acetate Filter w/Perforation & Highly Porous Paper
Carbon monoxide	ml	16.2	19.2	8.62	6.66
Hydrogen cyanide	µg	368	296	201	109
Nitrogen oxides-NOx	µg	406	438	364	224
Formaldehyde	µg	36.0	20.9	31.7	21.4
Acetaldehyde	µg	1,040	1,290	608	550
Acrolein	µg	105	104	58.6	48.6
Tar	mg	27.0	14.7	19.2	19.5
Nicotine	mg	1.8	0.94	1.31	1.5
Phenol	µg	161	61.7	122	129
Benz(a)anthracene	µg	40.6 [1.40]	35.3 [2.25]	38.5 [1.88]	40.1 [1.91]
Benzo(a)pyrene	ng	29.9 [1.09]	19.6 [1.25]	29.2 [1.13]	23.9 [1.14]

[a]*The composition of the cigarette tobacco is identical in all four experimentsal cigarettes*
[b]*Numbers in square brackets = µg/dry tar*
Source: National Cancer Institute, 1977c.

accelerates the diffusion of O_2 and N_2 into the tobacco column; this, in turn, causes more rapid smoldering during puff intervals (Hoffmann and Hoffmann, 1997; Owens, 1998). Porous cigarette paper causes a significant decrease of CO, hydrogen cyanide, nitrogen oxides, volatile aldehydes; yet, it hardly changes the yields of tar, nicotine, benz(*a*)anthracene (BaA), and BaP. Importantly, the significant reduction of nitrogen oxides in the smoke of these cigarettes reduces the formation and, thus, significantly lowers the yields of volatile and tobacco-specific *N*-nitrosamines (TSNA) (Owens, 1998; Brunnemann *et al.*, 1994).

Cigarette Construction Smoke yields of cigarettes are also dependent on physical parameters, such as length and circumference of the cigarette, and the width of the cut (number of cuts per inch) of the tobacco filler. Extending the cigarette length from 50 mm to 130 mm produces an increase in the level of oxygen in the mainstream smoke, while the absolute levels of hydrogen, carbon monoxide, methane, ethane, and ethylene decrease. The major reason for this lies in the diffusion of oxygen through the paper into the smoke stream (Terrell and Schmeltz, 1970). This phenomenon is also reflected in an increased CO delivery with ascending number of puffs because the available surface area of the paper diminishes as the cigarette is smoked. With increasing length of the cigarette, the overall yields of tar, nicotine, PAH, and other particulate components increase (DeBardeleben *et al.*, 1978). A circumference of cigarettes smaller than the regular 24.8–25.5 mm (*e.g.*, 23 mm or less) translates into less tobacco being burned and a greater volume of oxygen available during combustion. Thus, the smoke yields of tar, nicotine, and other particulate components are lowered (DeBardeleben *et al.*, 1978; Lewis, 1992; Brunnemann *et al.*, 1994; Hoffmann and Hoffmann, 1997). Cigarettes with small circumference also have a lower ignition propensity toward inflammable materials than ciga-

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rettes that have a 24.8- to 25.5-mm circumference. It has been estimated that in all fire deaths in the U.S. in 1997, 30% were caused by smoking, and worldwide, 10% (Lecstikoo *et al*., 2000).

The number of cuts per inch (width of tobacco strands) applied to the filler tobacco of cigarettes has an impact on smoke yields and/or on the carcinogenicity of the tars. The first investigation on the importance of tobacco cuts per inch, with regard to smoke yields and tumorigenicity of the resulting tars, was published in 1965 (Wynder and Hoffmann, 1965). It compared the smoke yields of tar and BaP when 8, 30, 50, and 60 cuts per inch of tobacco were applied. Tar yields per cigarette decreased from 29.1 to 23.0 mg and B*a* P from 37 to 21 ng. The tumorigenicities of tars derived from cigarettes made with 8, 30, or 50 cuts per inch of tobacco declined from 27 percent to 16 percent and 13 percent of tumor-bearing mice. In a large-scale study of cigarettes filled with an identical blend, cut 20 and 60 times per inch, the smoke yields per cigarette of tar, nicotine, volatile aldehydes, BaA, and BaP were significantly reduced for the fine-cut. However, hydrogen cyanide was insignificantly increased. Gram-to-gram comparison of tumorigenicities of both tars on mouse skin revealed statistically insignificant differences (NCI, 1977a). As the large-scale bioassay was repeated twice, one has to conclude that, in terms of mouse skin carcinogenicity, activities of tars obtained from coarse-cut and fine-cut tobaccos are comparable.

Tobacco Types The botanical genus *Nicotiana* has two major subgenera: *N. rustica* and *N. tabacum*. *Nicotiana rustica* is primarily grown in Russia, the Ukraine, and other East European countries, including Georgia, Moldavia, and Poland. It is also grown in South America and, to a limited extent, in India. In the rest of the world, *Nicotiana tabacum* is grown as the major tobacco crop; it is classified into flue-cured type (often called bright, blond, Virginia or Maryland tobacco), air-cured type (often called burley tobacco; light air-cured tobacco grown in Kentucky, and dark air-cured type grown in parts of Tennessee and Kentucky, South America, Italy, and France) and sun-cured type (often called oriental tobacco; primarily grown in Greece and Turkey). In addition, there are special classes of air-cured tobaccos for cigars, chewing tobacco, and snuff (Tso, 1990).

Prior to the last two decades, flue-cured tobaccos were used exclusively for cigarettes in the United Kingdom and in Finland; they were also the predominate type used in Canada, Japan, China, and Australia. Air-cured tobaccos are preferred for cigarettes in France, southern Italy, some parts of Switzerland and Germany, and South America. Cigarettes made exclusively from sun-cured tobaccos are popular in Greece and Turkey. In the rest of Western Europe and in the United States, cigarettes contain blends of flue-cured and air-cured tobaccos as major components. Today, in many countries, such as the United Kingdom, France, and other developed nations, the U.S. blended cigarette is gaining market share. In the United States, the composition of the cigarette blend has undergone gradual changes. In the 1960s and early 1970s, 45–50 percent of the cigarette blend were flue-cured (Virginia) tobaccos, 35 percent were air-cured (burley) tobaccos, and a few

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percent were Maryland air-cured and oriental tobaccos. By 1980, the average blend was composed of 38 percent flue-cured, 33 percent air-cured, and a few percent each of Maryland and oriental tobaccos. In the early 1990s, these proportions were about 35 percent, 30 percent, and, again, a few percent of Maryland and oriental tobaccos (Hoffmann and Hoffmann, 1997; Spears and Jones, 1981). The blended cigarette is preferred in many countries, in part because each of the three major *N. tabacum* types adds a certain aroma to the smoke. Some isoprenoids, and a relatively high number of agents with carboxyl content, are associated with the aroma of flue-cured tobacco. Other isoprenoids, and especially the composition of the acidic fraction, are related to the special aroma of air-cured tobaccos (Roberts and Rowland, 1962; Enzell, 1976; Spears and Jones, 1981; Tso, 1990). 3-Methylbutanoic acid (isovaleric acid) is considered to impart the most important flavor characteristic to oriental tobacco (Stedman *et al.*, 1963; Schumacher, 1970).

However, in regard to the toxicity and carcinogenicity of tobacco and tobacco smoke, the difference in the nitrate content of the tobaccos is of primary significance. Flue-cured tobacco can contain up to 0.9 percent of nitrate; yet, as it is used for regular cigarettes, it contains less than 0.5 percent of NO_3. In oriental tobaccos, one finds up to 0.6 percent of NO_3, in air-cured tobaccos between 0.9 percent and 5.0 percent, but generally below 3 percent in commercial cigarettes. The highest concentration of nitrate is present in the ribs, and the lowest concentration is in the laminae, especially in the laminae harvested from the top stalk positions of the tobacco plant (Neurath and Ehmke, 1964; Tso *et al.*, 1982). With the utilization of a greater proportion of air-cured tobacco in the U.S. cigarette tobacco blend, the nitrate content of the blended U.S. cigarette tobacco has risen from about 0.5 percent in the 1950s to 1.2–1.5 percent in the late 1980s (U.S. DHHS, 1989).

The concentrations of nitrogen oxides (NO_x) and methyl nitrite in smoke depend primarily on the nitrate concentrations in the tobacco, even though a portion of the nitrogen oxides is also formed during smoking from amino acids and certain proteins (Philippe and Hackney, 1959; Sims *et al.*, 1975; Norman *et al.*, 1983). Cigarettes made with flue-cured tobaccos deliver up to 200 µg of NO_x and 20 µg methyl nitrite in the smoke. Smoking U.S. blended cigarettes produces up to 500 µg NO_2 and 200 µg methyl nitrite, and the smoke of air-cured tobacco cigarettes contains up to 700 µg NO_x and 400 µg methyl nitrite. The major source of nitrate is air-cured tobacco and, thus, the major source of NO_x in its smoke is the nitrogen fertilizers (Sims *et al.*, 1975). The stems of air-cured tobaccos are especially rich in nitrate (≤6.8 percent). Consequently, stems, as components of expanded and reconstituted tobaccos, contribute in a major way to NO_x in the smoke (Brunnemann *et al.*, 1983).

Freshly generated smoke, as it leaves the mouthpiece of a cigarette, contains NO_x virtually only in the form of nitric oxide (NO), and contains practically no nitrogen dioxide (NO_2). However, nitrogen dioxide is quickly formed upon aging of the smoke. It has been estimated that, within 500 seconds half of the NO in undiluted smoke is oxidized to NO_2 (Neurath,

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1972). Of major importance is the high reactivity of NO_x upon its formation in the burning cone and in the hot zones of a cigarette. The thermically activated nitrogen oxides serve as scavengers of C,H- radicals, whereby they inhibit the pyrosynthesis of carcinogenic polynuclear aromatic hydrocarbons. Table 5-8 presents data on the smoke yields of tar, nicotine, phenol, and BaP, and the tumorigenicities of the tars on mouse skin (Wynder and Hoffmann, 1963).

Freshly generated nitrogen oxides also react with secondary and tertiary amines to form volatile *N*-nitrosamines (VNA) and several *N*-nitrosamines from amino acids, as well as from additives. The NO_x also form tobacco-specific *N*-nitrosamines (TSNA) by *N*-nitrosation of nicotine and of the minor tobacco alkaloids (Brunnemann *et al*., 1977; Brunnemann and Hoffmann, 1981; Tsuda and Kurashima, 1991; Hoffmann *et al*., 1994). BaP declined while NNK increased in the smoke of a leading U.S. non-filter cigarette between 1974 and 1997. Both trends correlate with the use of tobaccos with higher nitrate content. Recently, it was suggested that the formation of tobacco-specific nitrosamines in flue-cured tobacco in the United States is, in part, due to the use of propane gas heaters in the curing process. Oxides of nitrogen generated during the burning of the liquid propane react with nicotine in the tobacco leaf to form TSNA. This change in the curing method, introduced in the mid 1960s, is a likely contributor to the increase of TSNA levels in cigarette tobacco. Other important factors are the proportionally greater use of air-cured tobacco and the use of reconstituted tobaccos in the cigarette tobacco blend (Neurath and Ehmke, 1964; Brunnemann *et al*., 1983; Peel *et al*., 2001). Increased amounts of TSNA in tobacco compound the carcinogenic potency of the resulting cigarette smoke (Hoffmann *et al*., 1994) and are considered to contribute to the rise of adenocarcinoma, which has become the dominant form of lung cancer in both male and female smokers during the last three decades (Vincent *et al*., 1977; Cox and Yesner, 1979; el-Torkey *et al*., 1990; Devesa *et al*., 1991; Stellman *et al*., 1997). Increasing concentrations of nitrate in tobacco have also led to an

Table 5-8
Smoke Yields and Tumorigenicity of the Tars from the Four Major *N. tabacum* Varieties

Factors	Flue-Cured Tobacco	Sun-Cured Tobacco	Air-Cured Tobacco	
			Kentucky[a]	Maryland
A: Yields/Cigarette				
Tar (mg)	33.4	31.5	25.6	21.2
Nicotine (mg)	2.4	1.9	1.2	1.1
Phenol (µg)	95	120	60	43
Benzo(*a*)pyrene (ng)	53 (1.6)[b]	44 (1.4)[b]	24 (0.94)[b]	18 (0.85)[b]
B: Tumorigenicity[c]				
Percentage of mice with skin tumors	34	35	23	18

[a]*Low-nicotine, air-cured tobacco (Kentucky)*
[b]*Number in parentheses = µg BaP/g dry tar*
[c]*Bioassayed on a gram-to-gram basis of tar*
Source: Wynder and Hoffmann, 1963.

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increase in cigarette smoke of the human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl and of other aromatic amines (Patrianakos and Hoffmann, 1979; Grimmer *et al.*, 1995).

An important aspect relative to the toxicology of cigarette smoke is the correlation between the nitrate content of tobacco and the pH of cigarette smoke. Even though the different processes used to flue-cure and air-cure tobaccos have a significant impact on the smoke composition of the major types of tobacco, the role of nitrate is of major importance in determining the pH of the smoke. Whereas flue-cured tobacco and U.S. cigarette tobacco blends deliver weakly acidic smoke (pH 5.8–6.3), the smoke of cigarettes made from air-cured tobacco delivers neutral to weakly alkaline smoke (pH 6.5–7.5). A major reason for the range of pH values encountered in the smoke of the two major tobacco types is the concentration of ammonia in the smoke, which is directly tied to the concentration of nitrate in the tobacco. When pH levels of the smoke rise to greater than 6.0, the percentage of free, unprotonated nicotine increases to about 30 percent at pH 7.4 and to about 60 percent at pH 7.8 (Brunnemann and Hoffmann, 1974). Protonated nicotine is only slowly absorbed in the oral cavity; yet, unprotonated nicotine, which is partially present in the vapor phase of the smoke, is quickly absorbed through the mucosal membranes of the mouth (Armitage and Turner, 1970). The pH of cigar smoke rises with increasing puff numbers from pH 6.5 to 8.5; consequently, the rapid oral absorption of the free nicotine in the vapor phase gives a primary cigar smoker immediate nicotine stimulation so that he has no need for inhaling the smoke. Similarly, the smoker of black, air-cured cigarettes tends not to inhale the smoke at all, or only minimally (Armitage and Turner, 1970; NCI, 1998).

In 1963, the first comparative study on the tumorigenicity on mouse skin of tars from the four major types of *N. tabacum* revealed the highest activity for tars from flue-cured and sun-cured tobaccos, and the lowest for the two varieties of air-cured tobaccos (Table 5-8; Wynder and Hoffmann, 1963). The concentration of BaP, as an indicator of the concentrations of all carcinogenic PAH, is correlated with the tumor initiation potential of the tars. Upon topical application to mouse skin and human epithelia, carcinogenic PAH induces papilloma and carcinoma. In inhalation studies with Syrian golden hamsters, the smoke of a cigarette made with a particular tobacco blend was significantly more active in inducing carcinoma of the larynx than was the smoke of a cigarette with air-cured (black) tobacco (Dontenwill *et al.*, 1973).

To verify whether a reduction of carcinogenic PAH in the smoke due to the presence of high levels of nitrate in tobacco leads to reduced mouse skin tumorigenicity of the tar, sodium nitrate (8.3 percent) was added to the standard tobacco blend. On a gram-to-gram basis, the tar from the cigarette with added nitrate (0.6 µg BaP per gram tar) induced skin tumors in only 2 of 50 mice, whereas the tar from the control cigarette (without the addition of nitrate; 1.05 µg BaP per gram tar) induced skin tumors in 25 of 100 mice (Hoffmann and Wynder, 1967). In inhalation experiments with Syrian golden hamsters, smoke from the control cigarette plus 8.0 percent of sodium

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nitrate induced laryngeal carcinomas in only 25 of 160 animals (15.6 percent), compared to this type of neoplasm in 60 of 200 animals (30 percent) in assays with the control cigarette (Dontenwill *et al.*, 1973). Thus, all of these bioassays on the skin of mice and the inhalation studies with hamsters support the concept that increased nitrate content of the tobacco inhibits the pyrosynthesis of the carcinogenic PAH and that the tars of these cigarettes, and their smoke as a whole, have a reduced potential for inducing benign and malignant tumors in epithelial tissues when compared to the tar or whole smoke of cigarettes with tobacco that is low in nitrate.

Reconstituted Tobacco and Expanded Tobacco

In the early 1940s, the technology for making reconstituted tobacco (RT) was developed. Manufacturing RT enables the utilization of tobacco fines, ribs, and stems in cigarette tobacco blends (Halter and Ito, 1979). Prior to this technology, tobacco fines and stems had been discarded. With the utilization of RT as part of the tobacco blend, less top quality tobacco is needed and, thereby, the cost of making cigarettes has been reduced. Laboratory studies (Wynder and Hoffmann, 1967) have shown that cigarettes made entirely of RT deliver a smoke with significantly reduced levels of tar, nicotine, volatile phenols, and carcinogenic PAHs.

The two major technologies for making RT for cigarettes are the slurry process and the paper process. Either process leads to RT with low density. The advantage of RT lies in the creation of a high degree of aeration of the tobacco which enhances combustibility. Most of the tested tars from reconstituted tobaccos had significantly reduced carcinogenic activity on mouse skin (Wynder and Hoffmann, 1965; NCI, 1977a). In inhalation assays with Syrian golden hamsters, diluted smoke from cigarettes made of reconstituted tobacco induced significantly fewer carcinomas in the larynx (19/160) than the diluted smoke from control cigarettes (60/200). The cigarette with RT gave only 7 puffs per cigarette and yielded 20.8 mg tar and 16 ng of BaP compared to 10 puffs, 33.7 mg tar, and 35.4 ng BaP for the control cigarette (Dontenwill *et al.*, 1973). This result supports the concept that, at least in the experimental setting, the carcinogenic PAH, with BaP as a surrogate, are correlated with the induction of papilloma and carcinoma in epithelial tissues. The procarcinogenic TSNA, on the other hand, are not activated by enzymes to their reactive species in epithelial tissues; thus, they induce few, if any, tumors in such tissues. Tobacco ribs and stems, the major components of RT, are richer in nitrate (and this applies especially to the ribs and stems of air-cured tobaccos) than the laminae of tobacco (Neurath and Ehmke, 1964; Brunnemann *et al.*, 1983; Brunnemann and Hoffmann, 1991; Burton *et al.*, 1992). Therefore, in general, the nitrate content of today's blended U.S. cigarette, which may contain 20–30 percent RT, is at 1.2–1.5 percent—much higher than the nitrate level in cigarettes during the fifties and sixties when it was ≤0.5 percent (U.S. DHHS, 1989; Spears, 1974). Cigarettes with RT emit in their smoke significantly greater amounts of TSNA than cigarettes of the past. These TSNA include the adenocarcinoma-inducing NNK, which is metabolically activated to carcinogenic species in target tissues like the lungs (Hoffmann *et al.*, 1994). One major U.S. cigarette manufacturer was awarded a patent in December 1978 for developing

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a process that reduces more than 90 percent of the nitrate content of the RT made from ribs and stems (Kite *et al.*, 1978; Gellatly and Uhl, 1978). It is unclear to which extent this patented method has been applied to the RT manufacture for U.S. commercial cigarettes.

There are at least three methods for expanding tobacco by freeze-drying (NCI, 1977b). As a result of freeze-drying, expanded tobacco has greater filling power than natural tobacco, meaning that less tobacco is needed to fill a cigarette. An 85-mm filter cigarette, filled entirely with expanded tobacco, requires 630 mg tobacco; while a regular non-filter control cigarette of the same dimensions requires 920 mg tobacco. The tar yields in the smoke of both types of cigarettes amounted to 12.4 mg and 22.1 mg, respectively (NCI, 1977b, 1980). In 1982, incorporation of all possible modifications in the makeup of the cigarette required only 785 mg leaf tobacco; in contrast, in 1950, the blended U.S. cigarette required 1,230 mg leaf tobacco (Spears, 1974). Table 5-9 presents analytical data for the smoke of experimental cigarettes filled with puffed tobacco, expanded or freeze-dried tobacco, and a control cigarette. Levels of most components measured in the smoke of cigarettes with puffed tobacco, expanded tobacco, or freeze-dried tobacco were reduced, compared with data for the control cigarette (NCI, 1977b, 1980).

The changes that have occurred between 1950 and 1995 in the makeup of U.S. cigarettes, have significantly altered smoke composition. Table 5-10 compares data for individual components in the smoke of U.S. blended cigarettes of the 1950s with corresponding data for the cigarette smoke composition profiles that have been established between 1988 and 1995. All of these cigarettes were smoked using the FTC method (Pillsbury *et al.*, 1969).

Additives

Humectants

Humectants serve to retain moisture and plasticity in cigarette and pipe tobaccos. They prevent the drying of tobacco, which would lead to a harsh tasting smoke; importantly, they also preserve those compounds that impart flavor to the smoke. Today, the principal humectants in cigarette tobacco are glycerol (propane-1,2,3-triol) and propylene glycol (PG; propane-1-2-diol); of lesser importance are diethylene glycol (2.2'-di[hydroxyethyl]ether) and sorbitol (Voges, 1984). In the past, ethylene glycol (ethane-1,2,-diol) has been used as a humectant for cigarette tobacco. However, because this compound leads to the formation of ethylene oxide, which is carcinogenic to both animals and humans, its use has been prohibited (IARC, 1994a). In 1972, Binder and Lindner reported the presence of 20 µg ethylene oxide per cigarette in the smoke of the untreated tobacco of one cigarette brand (Binder and Lindner, 1972). In this context, it is noteworthy that Törnqvist and colleagues (1986) found significant levels of the *N*-hydroxyethylvaline moiety of hemoglobin in the blood of smokers ranging between 217 and 690 pmol/g Hb, averaging 389 ± 138 pmol/g, while levels in nonsmokers' blood ranged between 27 and 106 pmol/g Hb and averaged 58 ± 25 pmol/g Hb. The authors suggest that most of the ethylene oxide in the hemoglobin adduct is derived from endogenous oxidation of ethene in cigarette smoke (50–250 µg/cigarette) (Törnqvist *et al.*, 1986).

Humectants may comprise up to 5 percent of the weight of cigarette

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Table 5-9
Smoke Analyses of Cigarettes Made from Puffed, Expanded, and Freeze-Dried Tobacco and from a Control Cigarette

Smoke Component	Puffed Tobacco	Expanded Tobacco	Freeze-dried Tobacco	Expanded Stems	Control
CO (mg)	9.33	11.8	12.3	23.1	18.0
Nitrogen oxides (µg)	247.0	293.0	235.0	349.0	269.0
HCN (µg)	199.0	287.0	234.0	248.0	413.0
Formaldehyde (µg)	20.7	21.7	33.4	58.0	31.7
Acetaldehyde (µg)	814.0	720.0	968.0	803.0	986.0
Acrolein (µg)	105.0	87.7	92.4	93.0	128.0
Tar (mg)	16	18	16	23	37
Nicotine (mg)	0.8	0.7	0.8	0.4	2.6
BaA (ng)	13.7	11.8	15.3	19.5	37.1
BaP (ng)	11.8	8.2	9.2	16.2	28.7

Abbreviations: CO=carbon monoxide; HCN=hydrogen cyanide; BaA=banz(a)anthracene; BaP=benzo(a)pyrene.
Source: National Cancer Institute, 1980.

Table 5-10
Changes in the Yields of Selected Toxic Agents in the Smoke of U.S. Cigarettes (FTC Smoking Conditions)

	Earlier Cigarettes[a]		Current Cigarettes[a]	
Smoke Component	**Year**	**Concentration**	**Year**	**Concentration**
Carbon monoxide (CO)	1953	33-38 mg (NF)	1994	11 mg (F)
Nitrogen oxides (HNO_x)	1965	330 µg (NF)	1994	500 µg (NF)
Benzene	1962	30 µg (NF)	1988	48 µg (NF)
	1962	25-30 µg (F)	1990	42 µg (F)
Acetaldehyde	1960	1,000 µg (NF)	1992	400 µg (F)
NDMA	1976	43 ng (NF)	1989	65 ng (NF)
Tar	1953	38 mg (NF)	1994	12 mg (F)
Nicotine	1953	2.7 mg (NF)	1994	0.85 mg (F)
	1959	1.7 mg (F)	1994	1.1 mg (F)
Phenol	1960	100 µg (NF)	1994	70 µg (NF)
	1960	46 µg (F)	1994	35 µg (F)
Catechol	1965	390 µg (NF)	1994	
	1976	790 µg (F)	1994	140 µg (F)
2-Naphthylamine	1968	22 ng (NF)	1985	35 ng (F)
BaP	1959	50 ng (NF)	1995	19 ng (NF)
	1959	27 ng (F)	1995	8 ng (F)
NNN	1978	220 ng (NF)	1995	300 ng (NF)
	1978	240 ng (F)	1995	280 ng (F)
NNK	1978	110 ng (NF)	1995	190 ng (NF)
	1978	100 ng (F)	1995	144 ng (F)

[a]*Abbreviations: NF=non-filter; F=filter; NDMA=N-nitrosodimethylamine; BaP=benzo(a)pyrene; NNN=N'-nitrosonornicotine; NNK=4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone*
Source: Pillsbury et al., *1969.*

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tobacco. In a 1964 study, 18 U.S. cigarette tobacco blends that were analyzed for humectants contained between 1.7 and 3.15 percent of glycerol, which is to some extent decomposed to the ciliatoxic acrolein, and between 0.46 and 2.24 percent of PG (Cundiff *et al.*, 1964). The smoke of four American cigarettes contained between 0.34 and 0.96 mg/cigarette of PG (Lyerly, 1967). However, PG may be thermically degrading to yield propylene oxide. This would be of concern because propylene oxide is regarded as possibly carcinogenic to humans (IARC, 1994b). Four U.S. cigarettes contained between 0.34 and 0.96 mg per cigarette (Lyerly, 1967). In 1999, between 12 and 100 ng of propylene oxide were detected in the smoke of cigarettes filled with PG treated tobacco. Several commercial samples of PG, used as a humectant for cigarette tobacco, already contained traces of propylene oxide (Kagan *et al.*, 1999).

Flavor Additives Natural tobacco is composed of a wide spectrum of components that, upon heating, release agents, which contribute to the flavor of the smoke. These include tobacco-specific terpenoids, pyrroles, and pyrazines among others (Roberts and Rowland, 1962; Gutcho, 1972; Senkus, 1976; Leffingwell, 1987; Roberts, 1988). The effective reduction of smoke yields by filter tips and by the incorporation of reconstituted tobacco also brought about a reduction of flavor components in the smoke. To counteract this loss of smoke flavor, the tobacco blends are treated with additives that are essentially precursors to smoke flavors. They include natural agents contributing to minty, spicy, woody, fruity and flowery flavors. In some instances, such additives also include synthetic agents as flavor enhancers. While most of the flavor enhancers are chosen indiscriminately, it is realized that some of them may contribute to toxicity or carcinogenicity of cigarette smoke. A case in point was the cessation of the use of deer tongue extract which contained several percent of the animal carcinogen coumarin (Voges, 1984). It has been suggested that additives to cigarettes are used to reduce the perception of environmental tobacco smoke (ETS; Connolly *et al.*, 2001).

In 1993 and 1994, the tobacco industry convened an expert panel of toxicologists to screen agents that were in use, or considered for use, as tobacco additives. The panel established a list of 599 agents that were generally regarded as safe (GRAS), whereby the term 'safe' applied to each of the additives as such without consideration of the fate and reactivity of these agents during and after combustion (Doull *et al.*, 1994). An exception was menthol, which was known to transfer into the smoke without yielding appreciable amounts of carcinogenic hydrocarbons (Jenkins *et al.*, 1970). A recent toxicologic evaluation of flavor ingredients dealt with 170 such agents that are commonly used in the manufacture of American blended cigarettes, and examined their effects in four sub-chronic, nose-only smoke inhalation studies in rats compared to effects of the smoke of tobacco blends without additives. Control animals were exposed to filtered air (Gaworski *et al.*, 1998). Smoke exposure was monitored with internal dose markers, including carboxyhemoglobin, serum nicotine, and serum cotinine. The mainstream smoke (MS) of flavored and nonflavored cigarette types caused essentially the same responses in the respiratory tracts of the rats; specifically hyperplasia and metaplasia in the nose and larynx. As this

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study involved maximally 65 hours of exposure (while induction of tumors would not be expected until animals reach half their life span), one cannot deduce with certainty that the addition of these flavoring agents to tobacco blends has no impact on the development of tumors.

New Types of Cigarettes

The tobacco companies have undertaken a substantial research effort to develop new types of nicotine delivery devices. These devices were intended to generate an aerosol with nicotine in the range of the levels present in conventional cigarettes but with very low emissions of tar and other toxic agents. Toward the end of the 1980s, the first prototype of these new types of cigarettes was on the test market, a product named "Premier." It was a cigarette that "heats rather than burns tobacco" (R. J. Reynolds Tobacco Company, 1988; DeBethizy *et al.*, 1990; Borgerding *et al.*, 1990a & b, 1998). This 80-mm cigarette is comprised of three sections. The first 40-mm section of this cigarette is made with compressed charcoal, which is immediately linked to an inner aluminum tube containing tobacco, flavor additives, and glycerol. This tube is embedded in tobacco. Section 2 (~10 mm) is a cellulose acetate filter dusted with charcoal powder. The third section (~30 mm) is a cellulose acetate filter tip. Under FTC standard machine smoking conditions, the "Premier" delivers smoke containing 0.3 mg nicotine, 6.3 mg water, 4.6 mg glycerol, 0.4 mg propylene glycol, and 0.7 mg tar. Compared with the reference (conventional) cigarette, and disregarding nicotine, the majority of the known toxic and carcinogenic agents in the smoke are reduced by more than 90 percent. Known exceptions are carbon monoxide (CO) (+3.5 percent), ammonia (–5.6 percent), formaldehyde (–35.3 percent), resorcinol (–73.3 percent), quinoline (–56.6 percent), and acetamide (–18.2 percent). This new type of cigarette did not gain consumer acceptance, possibly because of difficulty in igniting the "Premier," the need for frequent puffing to ensure continuous burning, the lack of flavor, and the low nicotine delivery (0.3 mg/cigarette). Nicotine emission was below the level that would satisfy most smokers' acquired need for this agent even with compensatory smoking.

In 1996, a modified "Premier" came on the market. In the United States, it is known as "Eclipse"; in Germany it is called "HiQ," and in Sweden, it goes by the name "Inside." The "Eclipse" consists of four sections. Section 1, the heat source, is a specially prepared charcoal; section 2 consists of tobacco plus glycerol; section 3 contains finely shredded tobacco; and section 4 is a filter tip. Upon ignition, the special charcoal heats the air stream during puff drawing. The heated air stream enters the tobacco sections and vaporizes glycerol, as well as the volatile and semi-volatile tobacco components, including nicotine. Under FTC smoking conditions, the "Eclipse" delivers 8 mg CO (low-tar filter cigarette: 6–12 mg), 150 µg acetaldehyde (700 µg), 30 µg NO_x (200–300 µg), 180 µg hydrogen cyanide (300–400 µg), 5.1 mg tar (11–12 mg), and 0.2–0.4 mg nicotine (0.7–1.0 mg). The remainder of the smoke particulates consists of 33 percent water, 47 percent glycerol, and 17 percent of various other compounds. The concentrations of the major carcinogens, such as BaP, 2-aminonaphthalene, 4-aminobiphenyl, and the TSNA are lowered by 85–95 percent (Rose and Levin, 1996; Smith *et al.*, 1996). Currently, the "Eclipse" is being test marketed and it appears that

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response is somewhat more favorable than it was to its predecessor, the "Premier." The products labeled, "Eclipse Full Flavor," "Eclipse Mild," and "Eclipse Menthol" produce FTC-standardized smoke yields of 0.2, 0.1, and 0.2 mg nicotine and 3, 2, and 3 mg tar per cigarette. Regular cigarette smokers were asked to switch for 2 weeks to "Eclipse." There were four study groups, each composed of 26–30 volunteers, for a total of 109 smokers. Smoking of "Eclipse" resulted in about a 30 percent larger puff volume, about 50 percent more puffs, which added up to a total puff volume per cigarette that was more than twice that of the total volume drawn from the control cigarettes (Stiles *et al.*, 1999). These data suggest that the volunteers smoked "Eclipse" more intensely than their non-filter cigarettes. This observation is also supported in the uptake of nicotine (Benowitz *et al.*, 1997). The mutagenic activities of the urine of smokers of four types of "Eclipse" were assayed on two bacterial strains and were reduced by 72% to 100%, compared with the mutagenic activities of the urine of the same volunteers after smoking their regular cigarettes (Smith *et al.*, 1996).

An Expert Committee from the Institute of Medicine of the National Academy of Sciences studied the scientific basis for a possible reduction of the "harm" induced by "Eclipse" relative to the "harm" induced by smoking conventional cigarettes. On the basis of the available data, the Committee came to the following conclusions: "Eclipse" offers the committed smoker an option that is currently not available. "Eclipse" does not add to the inherent biological activity of smoke from the range of cigarettes currently on the market. The elevated COHb levels should be regarded as a potential risk factor for cardiovascular diseases. The magnitude of this risk remains to be determined (Gardner, 2000).

The high concentration of glycerol in the "Eclipse" aerosol led to bioassays of glycerol in 2-week (1.0, 1.93, and 3.91 mg/L) and 13-week (0.033, 0.167, and 0.662 mg/L) "nose only" inhalation studies with Sprague-Dawley rats, testing for toxicity and especially for irritating effects. The investigators detected metaplasia of the lining of the epiglottis (Gardner, 2000). The 13-week inhalation studies with rats and hamsters had also resulted in some early histopathological changes in the upper respiratory tract in both laboratory animals. These observations signal the need for lifetime inhalation assays with the smoke of "Eclipse" in rats, preferably Fisher 344 rats, or better yet, in Syrian golden hamsters, possibly with an inbred strain of hamsters susceptible to carcinogens in the respiratory tract (Bernfeld *et al.*, 1974). Pauly *et al.*, from the Roswell Park Cancer Institute, Buffalo, New York, caution that harmful glass fibers have been found to migrate into the filter tip of the "Eclipse" and may be inhaled during puffing (Pauly *et al.*, 1998).

The Health Department of Massachusetts and the Society for Research on Nicotine and Tobacco disputed the claims made for "Eclipse." They requested that the FTC and the FDA institute regulatory procedures to ensure that insufficiently documented health claims are not made for tobacco products. Declaring "Eclipse" the "next best choice," or calling TSNA-reduced tobacco products "safer tobacco" (Anonymous, 2000; Society

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for Research on Nicotine and Tobacco, 2000) is deceiving.

In 1998, Philip Morris USA released a new type of cigarette (EHC) that is heated electrically to release an aerosol. On the basis of chemical analyses and short-term bioassays, it has significantly lower toxicity and mutagenicity than the smoke of the Kentucky reference filter cigarette, 1R4F. The prototype, containing a tobacco filler wrapped in a tobacco mat, is kept in constant contact with eight electrical heater blades in a microprocessor-controlled lighter. This cigarette contains about half the amount of the tobacco of a conventional cigarette. Under FTC-standardized smoking conditions, the cigarette delivers, with an average of 8 puffs, about 1 mg of nicotine, whereas all other smoke constituents analyzed were significantly lower than those in the smoke of the low-yield Kentucky reference cigarette, 1R4F (Terpstra *et al.*, 1998). However, formaldehyde yields were significantly higher in the smoke of the EHC and emissions of glycerol and 2-nitropropane were comparable to those recorded in the smoke of the 1R4F cigarette. Per gram of tar, the smoke of the EHC had significantly lower mutagenic activity than the smoke of the 1R4F reference cigarette in TA98 and TA100 tester strains with metabolic activation (Terpstra *et al.*, 1998).

OBSERVATIONS ON CIGARETTE SMOKERS

In mice, rats, and hamsters, NNK induces adenomas and adenocarcinomas (AC) in the peripheral lung. This effect is independent of route and form of application (Hoffmann *et al.*, 1994). NNK is metabolically activated primarily to the unstable 4-(hydroxymethylnitrosamino)-1-(3-pyridyl) -1- butanone and to 4-(α-hydroxymethylene)-1-(3-pyridyl)-1-butanol, which decomposes into methane diazohydroxide and 4-keto-4-(3-pyridyl)butane diazohydroxide, respectively. The diazohydroxides react with DNA bases to form 7-methyl guanine, O^6-methyl guanine and O^4-methyl thymidine, respectively, and also form a pyridyloxobutyl adduct of presently unknown structure. Upon acid hydrolysis, this adduct releases 4-hydroxy-1-(3-pyridyl)-1-butanone. These adducts have been found in the lungs of mice and rats following treatment with NNK, and they have also been identified in human lungs. The origin of 7-methyl guanine in DNA from human lungs is unclear; conceivably, in addition to TSNA, nitroso compounds such as *N*-nitrosodimethylamine may also have been a source for this DNA-methylation. However, it is clear that higher levels of 7-methyl guanine have been found in the lung of smokers than in the lung of nonsmokers, thus strengthening the evidence that NNK is a major contributor to the methylation of the lung DNA of smokers (Hecht, 1998).

PAH induce squamous cell carcinoma of the lung in laboratory animals and in workers with exposures to aerosols that are high in PAH. NNK metabolites induce primarily AC of the lung in laboratory animals. Reactive PAH metabolites bind to DNA in epithelial tissues. In laboratory animals, metabolically activated forms of NNK react with the DNA of Clara cells in the peripheral lung (Belinsky *et al.*, 1990) to form methylguanine and methylthymidine, as well as pyridyloxobutylated adducts. 7-Methylguanine has been found in smokers' lungs at higher levels than in the lungs of nonsmokers.

Additional support for the observation that adenocarcinoma of the lung

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among cigarette smokers has increased relative to squamous cell carcinoma during the past 25 years, and for the concept that lung cancer risk of smokers of low-nicotine filter cigarettes is similar to that of smokers of non-filter cigarettes, comes from biochemical studies. In the mouse, the O^6-methylguanine pathway of metabolically activated NNK is clearly the major route for induction of lung tumors; this conclusion is consistent with the high percentage of GGT→GAT mutations in the K-*ras* oncogene induced by NNK (Hecht, 1998; Singer and Essigmann, 1991). A study from the Netherlands has shown that mutations on codon 12 of the K-*ras* oncogene are present in 24–50 percent of human primary adenocarcinoma. These mutations occur more frequently in AC of the lung in smokers than in nonsmokers. Twenty percent of the mutations in codon 12 involve GGT→GAT conversions, which supports the concept that NNK plays a role in the induction of AC of the lung in smokers. Histochemical examination of human lung cancer showed cyclooxygenase (COX)-2 expression in 70 percent of invasive carcinoma cases (Hida *et al.*, 1998). COX-2 expression was also identified in adenocarcinoma of the lung in rats treated with NNK (el-Bayoumy *et al.*, 1999). It is anticipated that future studies in molecular biology will fully elucidate the significance of TSNA, especially of NNK, and of the carcinogenic PAH in the induction of lung cancer in tobacco smokers.

SUMMARY Major modifications in the makeup of the commercial cigarette were introduced between 1950 and 1975. Since then, there have been no substantive changes toward a further reduction of the toxic and carcinogenic potential of cigarette smoke beyond reducing MS yields of tar, nicotine, and carbon monoxide. Some of these modifications have also resulted in diminished yields of several toxic and carcinogenic smoke constituents.

Cigarettes with charcoal filter tips deliver MS with significantly lower concentrations of the major ciliatoxic agents, such as hydrogen cyanide and volatile aldehydes. However, except in Japan, South Korea, Venezuela, and Hungary, cigarettes with charcoal filter tips account for less than one percent (USA) and at most for a small percentage of all cigarettes sold worldwide (Fisher, 2000).

Cellulose acetate filters with or without perforation have the capacity for selective reduction of smoke yields of volatile *N*-nitrosamines and semivolatile phenols. The latter are major tumor promoters in cigarette tar. In contrast to cigarettes manufactured in the 1950s, most of the cigarettes on the market today use a highly porous wrapper of paper treated with agents that enhance the burning, thus, contributing to the reduction of machine-measured yields of carbon monoxide, hydrogen cyanide, volatile aldehydes, volatile *N*-nitrosamines, PAH, and TSNA.

Reconstituted tobacco and expanded tobacco today amount to between 25 and 30 percent of the cigarette tobacco blend. Reconstituted tobacco reduces the yields of smoke components such as tar and CO. The tar from cigarettes made entirely of reconstituted tobacco is less carcinogenic on mouse skin and the smoke of these cigarettes reduces significantly the induction of carcinoma in the larynx of hamsters compared to the smoke of reference cigarettes made of natural tobacco. Reconstituted tobaccos and

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expanded tobaccos have a significantly greater filling power than natural tobacco. An 85-mm filter cigarette that is filled entirely with expanded tobacco requires 363 mg tobacco while a regular filter-tipped cigarette requires 667 mg tobacco. The smoke of cigarettes made of expanded tobacco has significantly lower MS yields of tar, nicotine, CO, hydrogen cyanide, PAH, and TSNA. On the basis of weight-to-weight comparisons, the tar from these cigarettes is significantly less tumorigenic on mouse skin than the tar of a reference cigarette made of the corresponding natural tobacco.

Since 1959, each year the levels of tar, nicotine, and benzo(*a*)pyrene in the mainstream smoke of a leading U.S. non-filter cigarette have been monitored. Beginning in 1977, the MS was also analyzed for NNK and in 1981, the determinations of CO in the mainstream smoke were added. For all of these analyses, the MS was generated with the standardized machine smoking parameters that are mandated by the Federal Trade Commission. Table 5-11 documents the decline of tar levels from 29.8 mg to 24.3 mg in the years between 1959 and 1984, while nicotine levels fell from 2.4 mg to 1.6 mg between 1959 and 1977. Since then, the smoke yields of tar and nicotine for this non-filter brand have not changed. Carbon monoxide remained stable at 16 to 18 mg per cigarette since it was first reported in 1981. By 1997, it was clear that significant changes in the smoke yields of the major lung carcinogens BaP and NNK have occurred since 1977 in that BaP levels declined from 49 ng to 19 ng, but NNK increased from 120 ng to 195 ng per non-filter cigarette.

It is important to note that we are lacking analytical data regarding the levels of these major carcinogens and toxins in the mainstream smoke of leading cellulose acetate filter-tipped cigarettes with and without filter perforation, as well as in the MS of charcoal filter cigarettes. These cellulose acetate filter cigarettes were actually the ones dominating the U.S. cigarette market as the use of non-filter cigarettes faded over the years and charcoal filter cigarettes had only a modest market share. Most importantly, we are also lacking data on biological activities of the tars of leading brands of filter cigarettes produced since the 1960s because tumorigenicity and carcinogenicity of tars have not been monitored on a regular basis. There is now also an urgent need for analytical profiles of the toxic and carcinogenic mainstream smoke constituents that are generated under conditions reflecting the puff drawing profiles actually exhibited by humans who smoke these cigarettes that give lower yields as per FTC measurements. Such analytical data would have to be established for major U.S. cigarette brands manufactured since 1960. They would serve as the scientific basis in support of epidemiological observations regarding the risk of cancer of the lung and upper aerodigestive tract for smokers who have exclusively smoked filter-tipped brands as compared to the risk for smokers who used non-filter cigarettes.

Changes in the agricultural, curing, and manufacturing processes of cigarettes have resulted in an increase in tobacco-specific nitrosamines in cigarette smoke that may have contributed to the increase in adenocarcinoma of the lung observed over the past several decades.

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Table 5-11
Tar, Nicotine, CO, B*a*P, and NNK in the Mainstream Smoke of a Leading U.S. NF Cigarette, 1959-1997[a]

Year	Tar (mg)	Nicotine (mg)	Carbon Monoxide[b] (mg)	Ba P (ng)	NNK[b] (ng)
1959	29.8	2.4		40	
1967	27.2	1.6		49	
1971	29.0	1.8		22	
1977	26.0	1.59		19	120
1981	24.3	1.52	16.7	19	130
1988	24	1.5	16	19	140
1991	25	1.7	16	18	190
1997	26	1.7	18	19	195

Abbreviations: NNK=4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; BaP= benzo(a)pyrene.
[a]The analytical data were generated by smoking the leading U.S. NF cigarette according to the FTC-mandated standard machine smoking method (Pillsbury et al.*, 1969).*
[b]The open fields document the lack of analytical data for the years 1959, 1967, 1971, and 1977 for CO and 1959, 1967, and 1977 for NNK
Sources: Wynder and Hoffman, 1960; Federal Trade Commission, 1971, 1977, 1981, 1988, 1991, 1997; Hoffmann and Hoffmann, 1997.

CONCLUSIONS

1. Major modifications in the makeup of the commercial cigarette were introduced between 1950 and 1975, but since that time there have been few substantive changes toward a further reduction of the toxic and carcinogenic potential of cigarette smoke.

2. A variety of changes in cigarette design and filtration have resulted in chemical changes in cigarette smoke, some of which have also demonstrated decreased toxicity in animal assays. Toxicity or carcinogenicity in animal assays has not been monitored to allow evaluation of changes over time that have occurred for cigarette smoke produced by commercial brands of cigarettes.

3. Changes in the agricultural, curing, and manufacturing processes of cigarettes have resulted in an increase over the last several decades in the amounts of tobacco-specific nitrosamines in cigarette smoke. These changes are considered to have contributed to the increase in adenocarcinoma of the lung observed over the past several decades.

4. On the basis of the standard machine smoking method for cigarettes that has been mandated by the FTC, the sales-weighted average nicotine yields of U.S. cigarettes decreased gradually from 2.7 mg per cigarette in 1953 to 0.85 mg by the mid 1990s. Today, the smoker of filter cigarettes will greatly increase his/her smoking intensity to satisfy an acquired need for nicotine. Thus, the inhaled smoke of one cigarette contains 2 to 3 times the amount of tar, nicotine, and carbon monoxide and 1.6 to 1.8 times the level of biomarkers for the major lung carcinogens BaP, and NNK, compared to amounts in the smoke generated by the FTC method.

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Appendix

Abbreviations

AC	Adenocarcinoma
BaA	Benz(a)anthracene
BaP	Benzo(a)pyrene
FTC	Federal Trade Commission
Hb	Hemoglobin
IARC	International Agency for Research on Cancer
MS	Mainstream Smoke
NNK	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	*N*′-Nitrosonornicotine
NO_x	Nitrogen oxides (NO, NO_2, and N_2O)
PAH	Polynuclear Aromatic Hydrocarbons
RT	Reconstituted Tobacco
SCC	Squamous Cell Carcinoma
TSNA	Tobacco Specific *N*-Nitrosamines
VNA	Volatile *N*-Nitrosamines

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Perspective

The Less Harmful Cigarette: A Controversial Issue. A Tribute to Ernst L. Wynder

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The dose−response relationship between number of cigarettes smoked and risk for lung cancer was established in 1950 by epidemiological studies. Laboratory assays with tobacco tar on mouse skin and smoke inhalation experiments with hamsters provided further evidence for this relationship. In cigarette smoke, among 4800 identified compounds, 69 are carcinogens, and several are tumor promoters or cocarcinogens. The major toxic agents are nicotine, carbon monoxide, hydrogen cyanide, nitrogen oxides, some volatile aldehydes, some alkenes, and some aromatic hydrocarbons. Public health information and education have led to a reduction of cigarette smokers among U.S. adults from 40 to 25%. However, in high school students, smoking increased to 35% and in adults with less than a high school education it remains high at 33.3%. Intervention studies were augmented with attempts of risk reduction by changing the tobacco composition and makeup of cigarettes. This led to cigarettes that, according to the FTC, reduced the tar and nicotine yields from an average of 37 and 2.7 mg to 12 and 0.85 mg. The anticipated reduction of mortality rates from chronic diseases among cigarette smokers did not occur, primarily, because of a major adjustment in smoking intensity and depth of inhalation by the habitual smokers. It is, therefore, imperative that smoking control efforts are intensified and that, short of banning cigarette sales, cigarettes delivering smoke with the lowest potential for toxicity, addiction, and carcinogenicity are declared a matter of public health policy.

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I. Introduction

In developed countries, lung cancer is the major cause of mortality from cancer in men and women. Despite curative surgery and with the best therapeutic approaches, less than 14% of all lung cancer patients survive 5 years (*1*−*3*). In the United States, smoking contributes to more than 90% of all deaths from lung cancer in men and to about 80% of all deaths from lung cancer in women (*2*, *4*). Cigarette smoking is also causally associated with cancer of the larynx, oral cavity, esophagus, pancreas, renal pelvis, and urinary bladder, and it is linked to cancer of the cervix (*2*−*5*). In the United States in 1991, more than 30% of 514 000 cancer deaths were attributed to cigarette smoking (*5*, *6*). The Surgeon General's report for the year 1989 concluded that cigarette smoking accounted also for 81.8% of all deaths from chronic obstructive pulmonary disease (COPD),[1] for 21.5% of deaths from coronary heart disease (CHD), and for 18% of deaths from stroke (*2*). In 1990, smoking in 44 developed countries, as a whole, was responsible for 24% of all male deaths and 7% of all female deaths. These rates increased to over 40% in men in some East European countries and 17% in women in the U.S. (*7*).

The most promising avenue for the reduction of early death from cancer, COPD, CHD, and stroke among cigarette smokers is the vigorous implementation of comprehensive preventive strategies (*8*). These encompass increased taxation for all tobacco products, severe restriction or, better yet, elimination of advertisements, preventing minors to gain access to any tobacco product, banning of smoking at work sites, in public buildings, and public conveyances. Moreover, such measures would include a mandate for providing young people from kindergarten classes throughout high school with curricula about the harmful effects of smoking and use of other addictive substances. Whereas, scientists and physicians have only indirectly influenced the enactment of antismoking regulations, they should fully participate in interventions aimed at treating tobacco dependence for those who cannot stop smoking on their own.

Clinical smoking cessation programs should include instruction about the specific hazards of smoking and chewing of tobacco. Such instructions are to be conducted by trained psychologists and, where indicated, be accompanied by hypnosis, acupuncture, or treatment with drugs, including nicotine (*8*). In recent years, the development of chemopreventive agents for smoking-related diseases has advanced (*9*, *10*). Such agents could be especially helpful toward reducing the risk for neoplastic disease among ex-smokers. This is an important goal in view of the fact that there are 45 million ex-smokers in the U.S. alone who will face an increased risk for smoking-related cancers compared to the risk of life-long nonsmokers and who never reach the low risk of a nonsmoker (*7*, *8*).

In 1950, there were 55 million cigarette smokers in a U.S. population of 151.3 million and, in 1990, 50.1 million cigarette smokers among 248.8 million U.S. residents. The annual consumption of cigarettes rose from 511.2 billion in 1964, the year of the Surgeon General's first report, to a high of 640 billion in 1981. Since then, annual consumption has declined to 465 billion in 1998 (*11*, *12*). In 1972, consumption of cigarettes per adult (≥18 years) amounted to 3700 in the US, to 3280 in the U.K., and to 3900 in Canada. By 1990−1992, these figures declined to 2670, 2210, and 2540, respectively, and they continue to fall (*1*, *13*). A similar decline of cigarette consumption has occurred in most West European countries (*7*). While this is encouraging, the figures unfortunately also reflect the limited success of smoking cessation efforts. Contrary to the trend of lower cigarette consumption among adults, there has been, since 1990, a significant increase in cigarette use among teenagers and adolescents in the U.S. In 1999, 9.2% of all middle school students and 34.8% of all high school students had smoked cigarettes in the month prior to being surveyed; overall, smoking and/or smokeless tobacco consumption was reported by 12.8 and 38.8% of the students, respectively (*14*).

The concept of "the less harmful cigarette" has been, and continues to be, an alternate approach toward reducing the morbidity and early deaths caused by cigarette smoking. However, "the less harmful cigarette" can, at best, be considered a compromise (*15*). Nevertheless, it is a necessary compromise for smokers who remain addicted to nicotine or will not give up their habit. The tobacco industry appears now to have decided to work toward a modified cigarette. Research on a "less harmful cigarette" actually began about 50 years ago by E. L. Wynder and his associates but it was always fully realized that there can be no "safe cigarette" (*16*).

This article discusses the controversy that has developed ever since the concept of "the less harmful cigarette" has emerged; with emphasis on the chemistry of tobacco smoke. Public health officials and some physicians and scientists were not and are not willing to accept this concept as a compromise. In fact, some scientists strongly opposed efforts toward the development of "the less harmful cigarette". This is evident from the enforced closing of the Tobacco Working Group of the National Cancer Institute (*17*). The major reasons for opposition to the concept of "the less harmful cigarette" lie in the assumption that any cigarette considered to be "less harmful" would inhibit a smoker's incentive to quit and that more of such cigarettes would be smoked. Moreover, the very term "less hazardous cigarette" may entice even more young people to start the addictive cigarette smoking habit. The counter-argument remains that men and women who continue to smoke should find on the market nothing but products with the least toxicity and the lowest carcinogenic activity that can be achieved with advanced science and technology. Those who view "the less harmful cigarette" as a compromise may agree, at least in part, with the sentiment of a 1989 editorial in a leading U.S. newspaper which reads, "Obviously, not smoking is better than smoking, but the best should not be the enemy of the good. There is a strong social case

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[1]Abbreviations: AC, adenocarcinoma; B*a*A, benz(*a*)anthracene; B*a*P, benzo(*a*)pyrene; CHD, coronary heart disease; COHb, carboxyhemoglobin; COPD, chronic obstructive pulmonary disease; cpi, cuts per inch; CPS, cancer prevention study; CORESTA, Centre de Coopération pour les Recherches Scientifiques Relatives au Tabac; DMNA, *N*-nitrosodimethylamine; EHC, electrically heated cigarette; ET, expanded tobacco; DMBA, 7,12-dimethylbenz(*a*)anthracene; FDA, Federal Drug Administration; FTC, Federal Trade Commission; GRAS, generally regarded as safe; IARC, International Agency for Research on Cancer; MS, mainstream smoke; NAB, *N*′-nitrosoanabasine; NAT, *N*′-nitrosoanatabine; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*′-nitrosonornicotine; PAH, polycyclic aromatic hydrocarbons; PG, 1,2-propylene glycol; RT, reconstituted tobacco; SCC, squamus cell carcinoma; TSG, tobacco study group; TSNA, tobacco-specific *N*-nitrosamines; TWG, tobacco working group; VNA, volatile *N*-nitrosamines.

for encouraging manufacturers to develop safer cigarettes that will sell" (*18*).

As scientists who have studied "the less harmful cigarette" for many years, we have proposed various ideas toward this concept. Working with the late E. L. Wynder, our group was the first to publish a reproducible bioassay method for estimating the carcinogenic potential of the particulate matter of cigarette smoke. We were the first to isolate from cigarette smoke, in crystalline form, a major carcinogen, benzo(*a*)pyrene (B*a*P). Our group was also the first to report that nicotine gives rise to highly carcinogenic nitrosamines that induce cancer of the lung, upper aerodigestive tract, and pancreas (*1*, *2*). These findings were initially challenged by the industry. Scientists outside the industry also demonstrated, for the first time, that charcoal filter tips have the capacity for selective removal of ciliatoxic smoke constituents and that cellulose acetate filter tips selectivity reduce volatile phenols, which are tumor promoting agents. We reported that during tobacco processing and during smoking a portion of the sucker growth inhibitor maleic hydrazide diethanolamine (MH-30) turns into a strong carcinogen, *N*-nitrosodiethanolamine and that in the course of smoking, as also reported by others, the human carcinogen ethylene oxide is formed from the humectant ethylene glycol. These are only a few findings that have contributed significantly to a better understanding of the chemistry, toxicity, and carcinogenicity of cigarette smoke (*1*, *2*).

In Section II, we summarize our present knowledge of the chemical composition of cigarette smoke, list the known carcinogens in cigarette smoke, and discuss those agents that are likely contributors to the disorders induced by cigarette smoking. Section III presents, in some detail, the changes that have occurred since 1950 in the makeup and the chemical composition of the U.S. cigarette and discusses concurrent changes in the smoke.

II. Chemical Composition and Toxic and Carcinogenic Agents in Cigarette Smoke

In 1950, two large-scale case control studies demonstrated that cigarette smoking is associated with cancer of the lung (*19*, *20*). This finding was supported by the induction of skin tumors in mice treated with cigarette "tar" (*21*, *22*).[2] Moreover, in 1973, the formation of benign and malignant tumors in the larynx of hamsters exposed to whole cigarette smoke confirmed the link (*23*). These reports led to intensive research on the chemical composition of cigarette smoke and to the identification of toxic and carcinogenic agents in the smoke. The high interest in the physicochemical nature of tobacco smoke and in its toxicology and carcinogenicity is reflected in the progressive identification of smoke constituents. In 1959, Johnstone and Plimmer reported that about 600 compounds had been found in cigarette smoke (*24*). In 1968, Stedman listed 1000 smoke compounds (*25*). In 1980, Ishiguro and Sugawara claimed 1889 compounds and in 1988, Roberts listed 3794 cigarette smoke constituents (*26*, *27*). In 1996, Green and Rodgman reported that 4800 compounds had been identified in tobacco smoke (*28*). Roberts listed the identified smoke components according to their functional groups; a slightly modified version of this list is presented in Table 1.

Table 1. Compounds Identified in Tobacco and Smoke[a,b]

functional groups	no. in tobacco	no. in smoke	no. in tobacco and smoke
carboxylic acids	450	69	140
amino acids	95	18	16
lactones	129	135	39
esters	529	456	314
amides and imides	205	227	32
anhydrides	10	10	4
aldehydes	111	106	48
carbohydrates	138	30	12
nitriles	4	101	4
ketones	348	461	122
alcohols	334	157	69
phenols	58	188	40
amines	65	150	37
N-nitrosamines	23	18	19
sulfur compounds	3	37	2
N-heterocyclics			
pyridines	63	324	46
pyrroles and indoles	9	88	3
pyrazines	21	55	18
non-aromatics	13	43	7
polycyclic aromatic	1	36	0
others	4	50	2
ethers	53	88	15
hydrocarbons			
saturated aliphatics	58	113	44
unsaturated aliphatics	38	178	10
monocyclic aromatics	33	138	25
polycyclic aromatics	55	317	35
pesticides	28	25	25
miscellaneous	112	110	19
inorganics and metals	105	111	69

[a] D. L. Roberts (*27*). [b] Two additional groups have been added, *N*-nitrosamines and pesticides.

Cigarette smoke is composed of a vapor phase and the particulate phase. The vapor phase is arbitrarily defined as that portion of the smoke aerosol which passes through a Cambridge glass fiber filter. The particulate phase is that portion which is trapped on the glass fiber filter. Its particle sizes range from 0.1 to <1.0 μm in diameter. This definition does not fully reflect the conditions prevailing in freshly generated cigarette smoke. Some semivolatile agents, such as phenol for example, appear to some extent in the vapor phase. Some of the substituted phenols, the semi-volatile *N*-nitrosamines, and volatile compounds, such as hydrogen cyanide and low-boiling aldehydes are partially trapped as aerosol inclusions in the particulate matter. The vapor phase accounts for 90−96% of the weight of the mainstream smoke of a nonfilter cigarette with the following compounds as major constituents: nitrogen ~60%, oxygen ~13%, carbon dioxide 13%, carbon monoxide 3.5%, water 2%, argon 1%, hydrogen 0.1−0.2%, acetone ~1%, nitrogen oxides (NO, NO_2, N_2O) < 0.1%, and volatile sulfur compounds likewise < 0.1% (Table 2). Major components of the particulate phase include nicotine (0.2−0.6% of the weight of the total smoke); the remaining Nicotiana alkaloids amount to ~0.02%, and compounds specific to solanaceae, namely *n*-hentriacontane ($C_{31}H_{64}$) and solanesol (0.1−0.2%). In addition, the particulate phase contains catechols (~1%), 3- and 4-ring noncarcinogenic aromatic hydrocarbons (~0.0003−0.007% = 3−7 ppm) and the carcinogenic PAH 0.00002−0.00007% (0.3−0.7 ppm) (Table 3). These relative proportions of smoke components are approximate figures.

[2]The term "tar" has been chosen as a descriptive noun only. It does not reflect the freshly generated particulate matter in cigarette smoke, but is arbitrarily defined as the portion of the smoke trapped on a Cambridge glass fiber filter CM-20 with water and nicotine deducted.

Table 2. Major Constituents of the Vapor Phase of the Mainstream Smoke of Nonfilter Cigarettes

compd	concentration/cigarette (% of total effluent)
nitrogen	280−320 mg (56−64%)
oxygen	50−70 mg (11−14%)
carbon dioxide	45−65 mg (9−13%)
carbon monoxide	14−23 mg (2.8−4.6%)
water	7−12 mg (1.4−2.4%)
argon	5 mg (1.0%)
hydrogen	0.5−1.0 mg
ammonia	10−130 μg
nitrogen oxides (NO_x)	100−600 μg
hydrogen cyanide	400−500 μg
hydrogen sulfide	20−90 μg
methane	1.0−2.0 mg
other volatile alkanes (20)[a]	1.0−1.6 mg[b]
volatile alkenes (16)	0.4−0.5 mg
isoprene	0.2−0.4 mg
butadiene	25−40 μg
acetylene	20−35 μg
benzene	6−70 μg
toluene	5−90 μg
styrene	10 μg
other volatile aromatic hydrocarbons (29)	15−30 μg
formic acid	200−600 μg
acetic acid	300−1700 μg
propionic acid	100−300 μg
methyl formate	20−30 μg
other volatile acids (6)	5−10 μg[b]
formaldehyde	20−100 μg
acetaldehyde	400−1400 μg
acrolein	60−240 μg
other volatile ketones (3)	80140 μg
methanol	100−650 μg
other volatile ketones (3)	50−100 μg
methanol	80−180 μg
other volatile alcohols (7)	10−30 μg
acetonitrile	100−150 μg
other volatile nitriles (10)	50−80 μg[b]
furan	20−40 μg
other volatile furans (4)	45−125 μg[b]
pyridine	20−200 μg
picolines (3)	15−80 μg
3-vinylpyridine	7−30 μg
other volatile pyridines (25)	20−50 μg[b]
pyrrole	0.1−10 μg
pyrrolidine	10−18 μg
N-methylpyrrolidine	2.0−3.0 μg
volatile pyrazines (18)	3.0−8.0 μg
methylamine	4−10 μg
other aliphatic amines (23)	3−10 μg

[a] Parentheses show the number of individual compounds identified in a given group. [b] Estimate.

Table 3. Major Constituents of the Particulate Matter of the Mainstream Smoke of Nonfilter Cigarettes

compd	μg/cigarette
nicotine	100−3000
nornicotine	5−150
anatabine	5−15
anabasine	5−12
other tobacco alkaloids (1.7)[a]	n.a.[d]
bipyridyls (4)	10−30
n-hentriacontaine (n-$C_{31}H_{64}$)	100
total nonvolatile hydrocarbons (45)[b]	300−400[b]
naphthalene	2−4
naphthalenes (23)	3−6[b]
phenanthrenes (7)	0.2−0.4[b]
anthracenes (5)	0.05−0.1[b]
fluorenes (7)	0.3−0.5[b]
pyrenes (6)	0.3−0.45[b]
fluoranthrenes (5)	0.1−0.25
carcinogenic polynuclear aromatic hydrocarbons (11)[c]	80−160
phenol	60−180[b]
other phenols (45)[b]	200−400
catechol	100−200[b]
other catechols (4)	200−400[b]
other dihydroxybenzenes (10)	15−30
scopoletin	n.a.
other polyphenols (8)[b]	40−70[b]
cyclotenes (10)[b]	0.5
quinones (7)	600−1000
solanesol	200−350
neophytadienes 94)	30−60
limonene	n.a.
other terpenes (200−500)[b]	100−150
palmitic acid	50−75
oleic acid	40−110
linoleic acid	150−250
linolenic acid	150−250
lactic acid	60−80
indole	10−15
skatole	12−16
other indoles (13)	n.a.
quinolines (7)	2−4
other aza-arenes (55)	n.a.
benzofurans (4)	200−300

[a] Parentheses show the number of individual compounds identified in a given group. [b] Estimate; n.a., not available.

In 1954, Cooper, Lindsey, and Waller identified the polycyclic aromatic hydrocarbon (PAH) B*a*P as the first carcinogen in cigarette smoke (*29*). Advances in chemical analytical techniques and increased knowledge of genotoxic environmental agents brought the number of carcinogens identified in tobacco smoke to 69 by the year 2000. These include, in addition to B*a*P, another nine PAH, and four aromatic amines, among them two known human bladder carcinogens; they also include nitrosamines, aldehydes, and several other organic and inorganic compounds (Table 4). The carcinogenic potential of these compounds has been assessed according to the classification of carcinogens by IARC, the International Agency for Research on Cancer (*30*). Accordingly, there are among the identified smoke constituents 69 animal carcinogens; 48 of these are possibly also carcinogenic to humans, 8 are probably carcinogenic to humans, and 11 are proven human carcinogens. Two of these compounds have not yet been evaluated for their carcinogenicity by the IARC (*15*, *30*).

Of the 69 carcinogens listed in Table 4, all but 1,2-propylene oxide have been identified independently by at least two research teams. Scientists in the industry have confirmed the presence in tobacco smoke of at least 50 of the 69 carcinogens even though they published their findings in many cases several years after the first reports on the identification of such carcinogens in the literature. For example, vinyl chloride, first reported as a tobacco smoke constituent at the 28th Tobacco Chemists' Research Conference in 1975 and published in 1976, was not acknowledged by industry scientists until the 51st Tobacco Chemists' Research Conference in 1997 (*31*, *32*).

However, the turn of events and changing policies of the industry are reflected in the fact that, in 1999, scientists from the Research Laboratories of the R. J. Reynolds Company listed all but 2 of the 69 cigarette smoke carcinogens in their publications. The exceptions were polonium-210 and 1,2-propylene oxide (PO) (*33*−*36*). Levels of ^{210}Po in the lungs of cigarette smokers were found to be generally three times higher than those in the lungs of nonsmokers (*37*). The U.S. National Council on Radiation Protection and Measurement ascribed about 1% of the risk for lung cancer after 50 years of cigarette

Table 4. Carcinogens in Cigarette Smoke[d]

agent	concentration in smoke of nonfilter cigarette	IARC evaluation of carcinogenicity		group[a]
		in lab animals	in humans	
PAH				
benz(*a*)anthracene	20−70 ng	sufficient		2A
benzo(*b*)fluoranthene	4−22 ng	sufficient		2B
benzo(*j*)fluoranthene	6−21 ng	sufficient		2B
benzo(*k*)fluoranthene	6−12 ng	sufficient		2B
benzo(*a*)pyrene	20−40 ng	sufficient	probable	2A
dibenz(*a*,*h*)anthracene	4 ng	sufficient		2A
dibenzo(*a*,*l*)pyrene	1.7−3.2 ng	sufficient		2B
dibenzo(*a*,*e*)pyrene	present	sufficient		2B
indeno(1,2,3-*cd*)pyrene	4−20 ng	sufficient		2B
5-methylchrysene	0.6 ng	sufficient		2B
heterocyclic hydrocarbons				
furan	18−37 μg	sufficient		2B
quinoline[b]	1−2 μg			
dibenz(*a*,*h*)acridine	0.1 ng	sufficient		2B
dibenz(*a*,*j*)acridine	3−10 ng	sufficient		2B
dibenzo(*c*,*g*)carbazole	0.7 ng	sufficient		2B
benzo(*b*)furan	present	sufficient		2B
***N*-nitrosamines**				
N-nitrosodimethylamine	2−1000 ng	sufficient		2A
N-nitrosoethylmethylamine	3−13 ng	sufficient		2B
N-nitrosodiethylamine	ND−2.8 ng	sufficient		2A
N-nitrosodi-*n*-propylamine	ND−1.0 ng	sufficient		2B
N-nitroso-di-*n*-butylamine	ND−30 ng	sufficient		2B
N-nitrosopyrrolidine	3−110 ng	sufficient		2B
N-nitrosopiperidine	ND−9 ng	sufficient		2B
N-nitrosodiethanolamine	ND−68 ng	sufficient		2B
N′-nitrosonornicotine	120−3700 ng	sufficient		2B
4-(methylnitrosamino)-1-(3-pyridyl)−1-butanone	80−770 ng	sufficient		2B
aromatic amines				
2-toluidine	30−337 ng	sufficient		2B
2,6-dimethylaniline	4−50 ng	sufficient		2B
2-naphthylamine	1−334 ng	sufficient	sufficient	1
4-aminobiphenyl	2−5.6 ng	sufficient	sufficient	1
N-heterocylic amines				
AaC	25−260 ng	sufficient		2B
MeAαC	2−37 ng	sufficient		2B
IQ	0.3 ng	sufficient		2A
Trp-P-1	0.3−0.5 ng	sufficient		2B
Trp-P-2	0.8−1.1 ng	sufficient		2B
Glu-P-1	0.37−0.89 ng	sufficient		2B
Glu-P-2	0.25−0.88 ng	sufficient		2B
PhIP	11−23 ng	sufficient	possible	2B
aldehydes				
formaldehyde	70−100 μg	sufficient	limited	2A
acetaldehyde	500−1400 μg	sufficient	insufficient	2B
phenolic compounds				
catechol	90−2000 μg	sufficient		2B
caffeic acid	<3 μg	sufficient		2B
methyleugenol[b]	20 ng			
volatile hydrocarbons				
1,3-butadiene	20−75 μg	sufficient	insufficient	2B
isoprene	450−1000 μg	sufficient		2B
benzene	20−70 μg	sufficient	sufficient	1
styrene	10 μg	limited		2B
nitrohydrocarbons				
nitromethane	0.5−0.6 μg	sufficient		2B
2-nitropropane	0.7−1.2 μg	sufficient		2B
nitrobenzene	25 μg	sufficient		2B
misc. organic compounds[c]				
acetamide	38−56 μg	sufficient		2B
acrylamide	present	sufficient		2B
acrylonitrile	3−15 μg	sufficient	limited	2A
vinyl chloride	11−15 ng	sufficient	sufficient	1
DDT	800−1200 μg	sufficient	probable	2B
DDE	200−370 μg	sufficient		2B
1,1-dimethylhydrazine	present	sufficient		2B
ethyl carbamate	20−38 μg	sufficient		2B
ethylene oxide	7 μg	sufficient	sufficient	1
propylene oxide	0−100 ng	sufficient		2B

Table 4. (Continued)

agent	concentration in smoke of nonfilter cigarette	IARC evaluation of carcinogenicity		group[a]
		in lab animals	in humans	
inorganic compounds				
hydrazine	24−43 ng	sufficient	inadequate	2B
arsenic	40−120 μg	inadequate	sufficient	1
beryllium	0.5 ng	sufficient	sufficient	1
nickel	ND−600 ng	sufficient	sufficient	1
chromium (only hexavalent)	4−70 ng	sufficient	sufficient	1
cadmium	7−350 ng	sufficient	sufficient	1
cobalt	0.13−0.2 ng	sufficient	inadequate	2B
lead	34−85 ng	sufficient	inadequate	2B
polonium-210	0.03−1.0 pCi	sufficient	sufficient	1

[a] IARC Monographs on the Evaluation of Carcinogenic Risks. Vol. 1−77 and Suplements 1−8, 1972−2000. (1) Human carcinogens; (2A) probably carcinogenic in humans; (2B) possibly carcinogenic to humans; (3) not classifiable as to their carcinogenicity to humans. [b] Unassigned line in column IARC Evaluation Carcinogenicity in lab animals; so far not reviewed. [c] In 1982, IARC assigned di(2-ethylhexyl)phthalate as sufficient to Group 2B. However, more recently, its carcinogenicity was reevaluated and it was classified as not carcinogenic (IARC, 1982; 2000). [d] Abbreviations: ND, not detected; PAH, polynuclear aromatic hydrocarbons; AaC, 2-amino-9H-pyrido[2,3-*b*]indole; MeAaC, 2-amino-3-methyl-9H-pyrido[2,3-*b*]indole; IQ, 2-amino-3-methylimidazo[4,5-*b*]quinoline; Trp-P-1, 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole; Trp-2, 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole; Glu-P-1, 2-amino-6-methyl[1,2-*a*:3′,2″-*d*]imidazole; Glu-P-2, 2-aminodipyrido[1,2-*a*:3′,2″-*d*]imidazole; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine.

Table 5. Probable Causative Agents for Cigarette Smoke-Related Disorders[a]

disorder	contributing agents	possible enhancing or associated agents
tobacco dependence	major: nicotine minor: secondary *Nicotiana* alkaloids, flavor components	acetaldehyde
cardiovascular disease	major: carbon monoxide, nitrogen oxides, hydrogen cyanide, tar minor: cadmium, zinc, carbon monoxide, tar	nicotine, alkylating species
chronic obstructive lung disease	hydrogen cyanide, volatile aldehydes, nitrogen oxides, carbon monoxide, tar	
lung and larynx cancer	major: PAH, NNK minor: ^{210}polonium, formaldehyde, acetaldehyde, butadiene, metals (Cr, Cd, Ni)	catechol, tumor promoters acetaldehydes, diet, alkylating species
oral cavity cancer	major: NNN, NNK minor: PAH	*herpes simplex*, irritation ethanol, diet
esophageal cancer	NNN	ethanol, diet
urinary bladder	4-aminobiphenyl, 2-naphthylamine, other aromatic amines	
pancreas cancer	NNK, NNAL	diet

[a] Abbreviations: PAH, polynuclear aromatic hydrocarbons; NNK, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; NNN, *N*′-nitrosonornicotine; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

smoking to ^{210}Po inhaled as a smoke constituent (*38*). Propylene oxide was identified in cigarette smoke in 1999. It is derived, in large part, from 1,2-propylene glycol which is present in cigarette tobacco at a level of ∼1%. However, the 1,2-propylene glycol used as a tobacco humectant already contains traces of PO (*36*).

Table 5 presents a list of disorders induced in cigarette smokers, the major and minor contributing agents, and the possible enhancing agents. This table serves as a guide for studies on "the less harmful cigarette"; it makes no claims for completeness (*39*).

III. The Changing Cigarette

Epidemiological studies in the 1950s reported an association of cigarette smoking with cancer of the lung. Mounting epidemiological evidence in the following 3 decades revealed that cigarette smoking was not only causally related to lung cancer but that it was also causally associated with cancer of the larynx, oral cavity, esophagus, pancreas, kidney, and urinary bladder; moreover, it showed an association with cancer of the cervix (*3*). Shopland et al. estimated that out of 514 200 deaths from cancer at all sites, a total of 157 200 (∼ 31%) were attributable to cigarette smoking. There were 123 100 (∼ 24%) cases of lung cancer among the 514 200 deaths (*5*). Thus, studies on tobacco carcinogenesis have focused primarily on lung cancer (*39*).

Factors regarded to be of major importance in the identification of key lung carcinogens include (1) the unambiguous identification of lung carcinogens in biologically significant amounts, (2) the uptake of significant doses of the suspected lung carcinogen as deduced from reliable biomarkers of exposure in physiologic fluids, (3) the induction of AC or SCC of the lung by the suspected carcinogen in 2 animal species, and (4) in vivo adduct formation of metabolite(s) of the suspected carcinogen with DNA in the lungs of mice and/or rats or at least in vitro DNA adduct formation in human lung cell culture.

On the basis of these criteria, the carcinogenic PAH in cigarette smoke as well as certain TSNA, typified by NNK and NDMA, can be viewed as important and highly relevant lung carcinogens for cigarette smokers.

In addition, consideration needs to be given to several elements that play a role as lung carcinogens in occupational environments. These are arsenic, beryllium,

nickel, chromium, cadmium, cobalt, and polonium-210, albeit most of these are present in tobacco and in cigarette smoke at low concentrations (Table 4). Another group of smoke carcinogens with a likely role as contributors to lung cancer risk in humans are free radicals that induce oxidative DNA damage.

In the 1950s, studies in the U.K. and the U.S.A. reported on the identification of the carcinogen B*a*P in cigarette smoke. These reports were challenged as merely representing B*a*P-like UV absorption spectra (*40*). Subsequent tedious analytical work finally led to the isolation and chemical identification of crystalline BaP from the smoke of several thousand cigarettes (*41*). Chemical-analytical studies led to the isolation and identification of the nicotine-derived nitrosamines NNN and NNK that proved to be highly carcinogenic in bioassays (*42*). For more than 10 years, the tobacco industry challenged the evidence for nicotine-derived carcinogens while research data emanating from groups outside the industry clearly pointed to organ-specific carcinogenicity and routes of metabolic activation of the tobacco-specific *N*-nitrosamines NNN, NNK, and five other alkaloid-derived nitrosamines. NNK induces primarily adenoma and adenocarcinoma of the lung in mice, rats, hamsters and mink independent of its route of application, i.e., regardless of whether it is injected intraperitoneally, intravenously, intravesically, or given by gavage, swabbed onto oral surfaces, or administered in the drinking water. NNK also induced tumors in the nasal cavity of rats and hamsters and in the pancreas of rats (*43*, *44*).

While the industry now has acknowledged the existence of TSNA (*45*) and even endeavors to prevent or at least reduce TSNA formation in smoke, it suggests that any possible carcinogenic action of TSNA is counteracted by inhibitors, including nicotine, nornicotine, and other smoke constituents. This contention is based on significant reduction of mutagenic activity of NNK and NDMA, but not NNN, by nicotine, nornicotine, or cotinine in in vitro assays. Similarly, SEC induction in mammalian cells by NNK was also markedly reduced by co-application of nicotine or cotinine (*46*). The concurrent application of NNK with nicotine or NNK with cotinine to perfused rat liver resulted in significant inhibition of NNK clearance, and in decreased metabolic activation by α-hydroxylation; it also caused a significant increase in *N*-oxidation of NNK and in the formation of NNAL-glucuronides (*47*).

In contrast, neither the NNK clearance from perfused rat lung nor its pattern of metabolites were substantially affected by the co-administration of nicotine or cotinine (*47*). Isolated rat lungs perfused with NNK revealed only small differences in pulmonary clearance and pattern of NNK metabolites between fed and starved animals (*47*). Rats on a high-fat diet who were given NNK in their drinking water developed lung adenoma and adenocarcinomas sooner but the overall incidence of lung tumors was similar to that in rats given NNK and a low-fat diet. However, the role of induction of carcinoma of the pancreas by NNK was significantly higher in the group of rats on the high-fat diet than in those on a low-fat diet (*48*). As to underlying mechanisms in NNK lung carcinogenesis, it is thought that 11β-hydroxysteroid dehydrogenase reduces the carbonyl group of NNK to yield NNAL whose secondary alcohol group is subject to glucuronidation so that it gets excreted as a urinary constituent. Inhibition of 11β-hydroxysteroid dehydrogenase raises the rate of α-hydroxylation of NNK, thus, increasing its carcinogenicity. On the other hand, activation of the 11β-hydroxysteroid dehydrogenase decreases α-hydroxylation of NNK, thus diminishing its carcinogenic potential (*49*). When rats were treated with a low dose of NNK and given drinking water that contained 0.002% nicotine, the alkaloid did not diminish DNA methylation (*50*). Additional well-designed bioassays are needed to clarify how nicotine and other smoke constituents affect the carcinogenicity of NNK.

The impetus for changing the makeup of cigarettes can be traced back to the landmark articles by Ernst L. Wynder and Evarts A. Graham in the United States and by Richard Doll and A. Bradford Hill in the United Kingdom in 1950 (*19*, *20*). Both studies revealed a dose−response relationship between the number of cigarettes smoked and the risk for developing lung cancer. In 1953 and 1957, these findings were supported by bioassays showing a dose−response between the amount of tar applied to mouse skin and the induction of skin tumors (*21*, *22*). In 1973, inhalation studies with hamsters at the Research Institute of the West German Cigarette Industry demonstrated a dose−response between the amount of cigarette smoke inhaled and the induction of tumors in the upper respiratory tract (*23*). On the basis of the epidemiological data and the bioassays with mice and hamsters, initial emphasis was placed on reducing the smoke yields of tar and nicotine as a measure that should lead to a less harmful cigarette. Because tar as a whole is the major carcinogen, and nicotine is the major toxic and addictive agent in tobacco smoke, measures of tar and nicotine were chosen as analytical parameters for each marketed brand.

The Federal Trade Commission (FTC) adopted, with some modifications, the standard machine smoking conditions for cigarettes developed by Bradford et al. in 1936 (*51*, *52*). These prescribe taking one puff per minute with a 35 mL volume over 2 s. The butt lengths for nonfilter cigarettes were set at 23 mm and those for filter cigarettes at the length of the filter, plus overwrap, plus 3 mm. CORESTA, the International Organization for Research on Tobacco, developed a standard machine-smoking method in 1968 that is widely used in most of the developed countries (*53*). The CORESTA method differs from that of the FTC only in respect to the butt length to which filter cigarettes are smoked (CORESTA, length of filter, plus 8 mm). The standard machine-smoking conditions are otherwise identical to those of the FTC (*52*, *53*). The data presented here are based on the FTC standard smoking conditions, except when otherwise specified.

A. Filter Tips

Figure 1 displays the sales-weighted average smoke yields for tar and nicotine of U.S. cigarettes for 1953−1996. The tar yields decreased from 38 to 12 mg and the nicotine yields from 2.7 to 0.85 mg (*39*). Figure 1 also approximately marks the year for the introduction of specific changes in the makeup of commercial U.S. cigarettes. Filter cigarette sales increased from 0.5% of all cigarettes on the U.S. market in 1950 to more than 97% as of 1997 (*11*, *12*, *54*, *55*). Similar consumer acceptance of filter cigarettes has been recorded in other developed countries with the exception of France, where it had been delayed. In 1975, only about 70% of all French

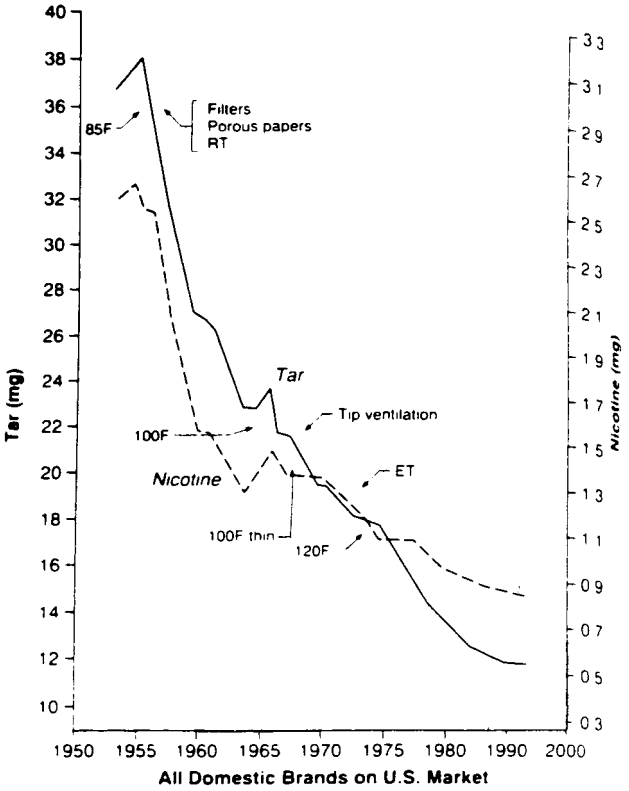


Figure 1. Sales-weighted average tar and nicotine deliveries, 1953−1993, U.S.

cigarettes had filter tips (*56*). There are basically three types of filter tips for cigarettes.[3] These are filters made from paper, from cellulose acetate (*57*) and filter tips that contain charcoal. The latter consist either of two or three sections, cellulose and granulates of activated charcoal, or cellulose acetate, activated charcoal and cellulose acetate. In addition, instead of granulates of charcoal in one section of the filter tip, charcoal has been dusted onto the cellulose acetate of the inner section.

In 1959, Haag et al. reported that charcoal filter tips selectively remove certain volatile agents from the smoke (*58*). Some of these are strong ciliatoxic agents, such as hydrogen cyanide, formaldehyde, and acrolein (*59*−*62*). In vitro studies have demonstrated that the smoke from cigarettes with charcoal filter tips is less ciliatoxic than smoke from other types of filter cigarettes and smoke from plain cigarettes. Thus, the movement of the cilia in the bronchi and trachea is significantly less impaired by the smoke of charcoal filter cigarettes than by the smoke of the other types of cigarettes (*59*−*62*). In the United States, and in most other countries, cigarettes with charcoal filters amount to less than 1−2% of total sales. However, of all the cigarettes on the market in Japan and Venezuela, 95% have charcoal filter tips, and so have 90% in South Korea and Hungary (*63*, *64*).

Cigarettes with cellulose filters account for less than 1% of all cigarettes sold in the developed countries, whereas cigarettes with cellulose acetate filter tips, primarily made from secondary cellulose acetate, amount to more than 90% of all cigarettes (with the exception of Japan, Venezuela, South Korea, and Hungary) (*12*). Cellulose acetate filters retain up to 80% of semivolatile phenols. The retention of phenols was desirable because these compounds are active as tumor promoters in the experimental setting (*65*−*67*). Cigarette smoke contains the parent phenol and about 20 additional volatile phenols. Their total amount in the smoke of an 85-mm nonfilter cigarette amounts to about 300 μg. The individual, semi-volatile phenols range from 80 to 200 μg from phenol itself to less than 1 μg of *o*-chlorophenol (*26*). Boutwell and Bosch bioassayed some volatile phenols for their tumor-promoting activity on mouse skin initiated with 7,12-dimethylbenz[*a*]anthracene. The highest tumor-promoting activity was found for the following semivolatile phenols that had been identified in cigarette smoke: phenol, *o*-, *m*-, and *p*-cresol; 2,4-, 2,6-, 3,4-, and 3,5-dimethylphenol (*68*, *69*); *o*-chlorophenol, 2-ethylphenol, and 2-*n*-propylphenol had lower tumor-promoting activities (*68*, *69*). When bioassayed and compared for effects on a gram-to-gram basis, the tars from cellulose acetate filter-tipped cigarettes were slightly more toxic but less carcinogenic than tars collected from the smoke of plain cigarettes or from cigarettes with charcoal filter tips (*69*). Cellulose acetate filter tips also remove from the smoke up to 75% of the carcinogenic, volatile *N*-nitrosamines (VNA) (*70*). Twice daily exposure of Syrian golden hamsters for over 60 weeks to the air-diluted total MS from cellulose filter cigarettes induced a significantly lower incidence of tumors of the larynx than did exposure to the air-diluted total MS from nonfilter cigarettes. In contrast, whole smoke from cigarettes with charcoal filter tips induced carcinoma of the larynx to a similar extent as the whole smoke from nonfilter cigarettes (*23*).

Around 1965, perforation of the filter tips of cigarettes was introduced as a measure toward reducing toxins in the smoke. The smoke of cigarettes with filter perforation is indicated to be consumer acceptable up to about 50% air dilution. The velocity of the air flow through the burning cone of these filter cigarettes slows down as part of the negative pressure generated by the puff drawing. These changes result in more complete combustion of the tobacco (*71*−*73*). In 1999, more than 65% of all U.S. cigarettes had filter tips with various degrees of perforation. In the 70s, the analysis of the smoke of the experimental cigarette was completed for the Tobacco Working Group of the National Cancer Institute by M. R. Guerin, R. A. Jenkins et al. from the National Laboratory in Oak Ridge, TN (*69*, *74*−*76*) (a) with cellulose acetate filter tips, (b) with perforated cellulose acetate filter tips, (c) with porous paper and with a perforated cellulose acetate filter tip, and (d) a nonfilter cigarette. The same tobacco blend was used as a filler for all four cigarettes. Table 6 shows that the smoke of filter cigarettes with perforation delivers the lowest yields of CO, hydrogen cyanide, nitrogen oxides (NO_x), acetaldehyde, and acrolein of all types of cigarettes. However, the yields of carcinogenic PAH in the smoke of the cigarettes with perforated filter tips were comparable with those from cigarettes without filter tips. Thus, the perforation of the filter tip results in a selective reduction of volatile, toxic agents but no major changes in the yields in particulate components (*77*, *78*).

B. Cigarette Paper

Since about 1960, higher cigarette paper porosity and treatment of paper with citrate has significantly contributed to the reduction of the yields of several smoke

[3] In the People's Republic of China the leading material for the filter tip is polypropylene; there is little use in other countries for this polymer as filter material for cigarettes.

Table 6. Comparison of Experimental Cigarettes (yields/cigarette)[a,b,c]

smoke components	nonfilter cigarette (72−75)	cellulose acetate filter cigarette (91)	cellulose acetate filter 2/perforation (89)	cellulose acetate filter w/perforation and highly porous paper (96)
carbon monoxide (mg)	16.2	19.2	8.52	6.66
hydrogen cyanide (μg)	338	296	201	109
nitrogen oxides-NO_x (μg)	439	438	364	224
formaldehyde (μg)	36.0	20.9	31.7	21.4
acetaldehyde (μg)	1170	1290	608	550
acrolein (μg)	109	104	58.6	48.6
tar (mg)	27.2	14.7	19.2	19.5
nicotine (mg)	1.8	0.94	1.31	1.50
phenol (μg)	170	61.7	122	129
benz(*a*)anthracene (ng)	40.6 (1.40)	35.3 (2.25)	38.5 (1.88)	40.1 (1.91)
benzo(*a*)pyrene (ng)	29.9 (1.09)	19.6 (1.25)	29.2 (1.13)	23.9 (1.14)

[a] U.S. National Cancer Institute (*69*). [b] The composition of the cigarette tobacco is identical in all four experimental cigarettes. [c] Numbers in parentheses (*μg of benz*[*a*]anthracene or benzo[*a*]pyrene in 1 g dry tar).

components. During and between puff drawing, porous paper enhances the outward diffusion through the paper of hydrogen, NO, CO, CO_2, methane, ethane, and ethylene. On the other hand, it accelerates the diffusion of O_2 and N_2 from the air into the tobacco column; this, in turn, causes more rapid smoldering during puff intervals (*15*, *77*). Table 6 compares smoke data from cigarettes with perforated filter tips but regular cigarette paper vs cigarettes with perforated filter tips and highly porous paper, with the tobacco blends in both cigarettes being identical (*69*). Whereas porous cigarette paper causes a significant decrease of volatile toxic agents, it hardly changes the smoke yields of tar, nicotine, BaA, and B*a*P. Importantly, the significant reduction of nitrogen oxides in the smoke of these cigarettes reduces the formation and, thus, significantly lowers the yields of VNA and TSNA (*77*−*79*).

In several countries, the use of hand-rolled cigarettes has risen significantly (*80*, *81*). Making hand-rolled cigarettes requires sturdy cigarette paper. Such papers have low porosity. Rickert et al. compared the smoke yields of hand-rolled cigarettes with those of manufactured cigarettes, some of these two types of cigarettes contained the same tobacco; all cigarettes were machine-smoked under the same conditions. The handmade cigarettes, weighing 26% more, delivered mainstream smoke yields that were 100, 85, and 86% higher in tar, nicotine, and carbon monoxide, respectively, than those of manufactured cigarettes (*80*).

C. Cigarette Construction

Smoke yields also depend on physical parameters, such as length and circumference of the cigarette, and the width of the cut (number of cuts per inch; cpi) of the tobacco filler. Extending the cigarette length from 50 to 130 mm produces an increase in the level of oxygen in the mainstream smoke, while the levels of hydrogen, CO, CO_2, methane, ethane, and ethylene decrease. The major reason for this occurrence lies in the diffusion of oxygen through the paper into the smoke stream (*82*). This phenomenon is also reflected in increased CO delivery with ascending number of puffs, while the available surface area of the paper diminishes. With an increase in the length of the cigarette, the overall yields of tar, nicotine, PAH, and other particulate components also rise (*83*, *84*). Circumference of cigarettes below the regular 24.8−25.5 mm (e.g., 23 mm or less) translates not only into less tobacco being burned but also into greater volume of oxygen available during combustion (*83*, *84*). Thus, the smoke yields of tar, nicotine, and other particulate components are lowered (*15*, *83*, *84*). Cigarettes with small circumference also have a lower ignition propensity toward inflammable materials than cigarettes that have the ∼25 mm circumference (*79*). It has been estimated that in 1980 of the almost 5200 U.S. residents who died from fires, about 1200 of these deaths occurred in fires started by cigarettes (*85*).

The number of cpi applied to the filler tobacco of cigarettes has no major impact on the carcinogenicity of the tars. The first investigation on the importance of tobacco cuts per inch, with regard to smoke yields and tumorigenicity of the resulting tars, was published in 1965. It compared the smoke yields of tar and BaP when 8, 30, 50, or 60 cpi of leaf were applied. Tar yields per cigarette decreased from 29.1 to 23.0 mg and BaP from 37 to 21 ng. In a large-scale study of cigarettes filled with an identical blend, and cuts at 20 and 60 cpi, respectively, the smoke yields per cigarette of tar, nicotine, volatile aldehydes, BaA, and BaP were significantly reduced for the fine-cut (60 cpi), however, hydrogen cyanide was insignificantly increased. Gram-to-gram comparison of tumorigenicities of the two tars on mouse skin revealed statistically insignificant differences (*74*).

D. Tobacco Types

The botanical genus *Nicotiana* has two major subgenera: *N. rustica* and *N. tabacum*. *N. rustica* is primarily grown in Russia, the Ukraine, and other East European countries, as well as in South America, and, to a limited extent, in India. In the rest of the world, *N. tabacum* is grown as the major tobacco crop; it comes as *flue-cured type* (often called bright, blond, or Virginia tobacco), *air-cured type* (often called burley tobacco), light air-cured tobacco (grown in Kentucky), and dark air-cured tobacco (grown in parts of Tennessee and Kentucky, South America, Italy, and France), as well as *sun-cured* (often called oriental or Turkish) tobacco (primarily grown in Greece and Turkey). In addition, there are special classes of air-cured tobaccos for cigars, chewing tobacco, and snuff (*86*).

Until the recent 2 decades, only flue-cured tobaccos were used for cigarettes in the U.K. and in Finland, and they were the predominate type used in Canada, Japan, China, and Australia. Air-cured tobaccos were preferred for cigarettes in France, southern Italy, some parts of Switzerland and Germany, and South America; cigarettes

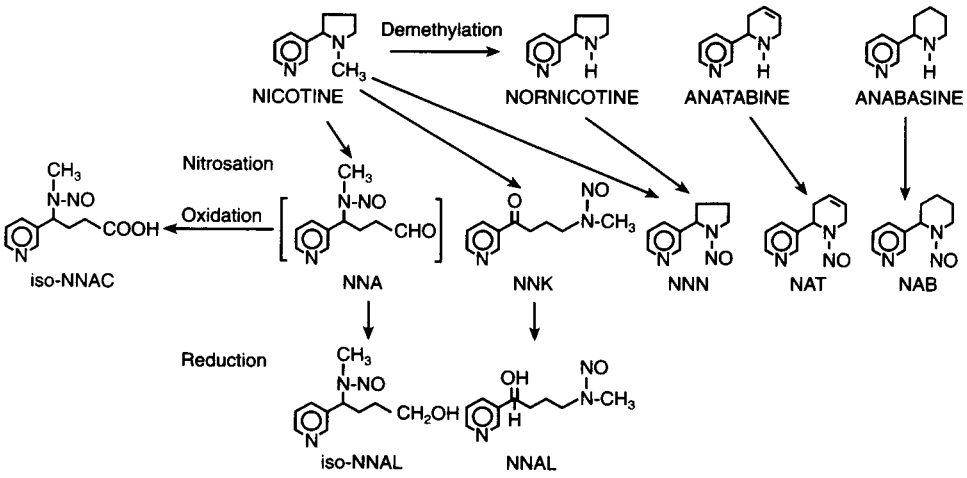


Figure 2. Formation of tobacco-specific *N*-nitrosamines (TSNA), 1994 (*43*).

made exclusively from sun-cured tobaccos are popular in Greece and Turkey. In the rest of Western Europe and in the U.S., cigarettes contain blends of flue-cured and air-cured tobaccos as major components. Today, in many countries, including the U.K, France, and other developed nations, the U.S. blended type of cigarette is gaining market shares. In the U.S., the composition of the cigarette blend has undergone gradual changes. In the sixties and early seventies, 45−50% of the cigarette blends were flue-cured (Virginia) tobaccos, 35% air-cured (burley) tobaccos, and a few percent were Maryland air-cured and oriental tobaccos. By 1980, blends averaged 38% flue-cured, 33% air-cured, and a few percent each of Maryland and oriental tobaccos and up to 30% reconstituted and expanded tobacco. In the early nineties, these proportions were 35%, 30%, and, again, a few percent of Maryland and oriental tobaccos. The blended cigarette is preferred in many countries, in part, because each of the three major *N. tabacum* types lends a specific aroma to the smoke.

In regard to the toxicity and carcinogenicity of tobacco and tobacco smoke, the difference in the nitrate content of the tobaccos is of primary significance. Flue-cured tobacco can contain up to 0.9% of nitrate; yet, as it is used for regular cigarettes, it contains <0.5% of NO_3. In oriental tobaccos one finds up to 0.6% NO_3, in air-cured tobaccos between 0.9 and 5.0%, but generally below 3% in commercial cigarettes. The highest concentration of nitrate is present in the ribs, the lowest concentration is in laminae, especially in laminae harvested from the top stalk positions of the tobacco plant (*87*, *88*). With the utilization of a greater proportion of air-cured tobacco in the blended U.S. cigarette, the average nitrate content of the blended U.S. cigarette tobacco has risen from below 0.5% in the fifties to 1.2−1.5% in the late eighties (*15*, *89*, *90*).

The concentrations of nitrogen oxides (NO_x) and methyl nitrite in smoke depend primarily on the nitrate concentrations of the tobacco; although a portion of the nitrogen oxides is formed during smoking from amino acids and certain proteins (*87*, *91*−*94*). Cigarettes made entirely with flue-cured tobaccos deliver up to 200 μg of NO_x and 20 μg of methyl nitrite in the smoke. Smoking U.S. blended cigarettes produces up to 350 μg of NO_x and 160 μg of methyl nitrite, and the smoke of air-cured tobacco cigarettes contains up to 700 μg of NO_x and 470 μg methyl nitrite. The stems of air-cured tobaccos are especially rich

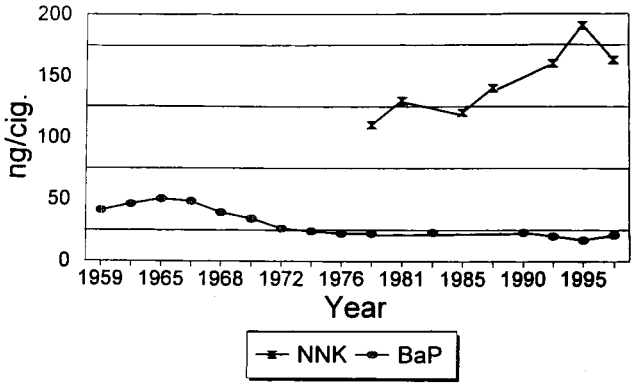


Figure 3. B*a*P and NNK in mainstream smoke of a leading U.S. nonfilter cigarette, 1959−1997.

in nitrate (≤6.8%). Consequently, stems, as components of expanded and reconstituted tobaccos in a cigarette blend, contribute in a major way to NO_x in the smoke (*95*).

Freshly generated smoke, as it leaves the mouthpiece of a cigarette, contains NO_x virtually only in the form of nitric oxide (NO), and only minor amounts of nitrogen dioxide (NO_2) and of nitrous oxide (N_2O) (*92*, *93*). However, nitrogen dioxide is quickly formed upon aging of the smoke. It has been calculated that, within 500 s half of the NO in undiluted smoke is oxidized to NO_2 (*94*). Nitrogen dioxide can cause inflammation of the lungs which may lead to edema. Of major importance is the high reactivity of NO_x upon its formation in the burning cone and in the hot zones of a cigarette. The thermically activated nitrogen oxides serve as scavengers of C,H-radicals, whereby they inhibit the pyrosynthesis of carcinogenic PAH (*94*, *96*, *97*).

The freshly generated nitrogen oxides also react with secondary and tertiary amines resulting in the formation of volatile *N*-nitrosamines (VNA) and of several *N*-nitrosamines from amino acids, as well as from some additives. Furthermore, NO_x also form tobacco-specific *N*-nitrosamines (TSNA) by *N*-nitrosation of nicotine and of the minor tobacco alkaloids (Figure 2) (*44*, *98*). Figure 3 depicts data on the decline of BaP and the increase of NNK in the smoke of a leading U.S. nonfilter cigarette between 1974 and 1997. Both trends are correlated with the use of tobacco blends with higher nitrate content. Increasing concentrations of nitrate in tobacco have also led to an increase in cigarette smoke of nitroalkanes,

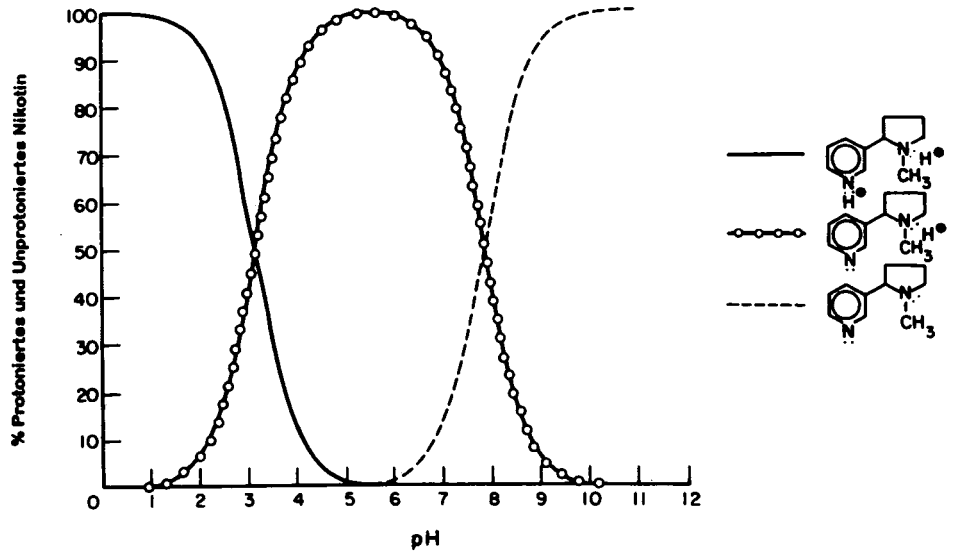


Figure 4. pH of total mainstream smoke of various tobacco products, Brunnemann and Hoffmann, 1974 (*101*).

Table 7. Smoke Yields and Tumorigenicity of the Tars from the Four Major *N. Tabacum* Varieties[a]

factors	flue-cured tobacco	sun-cured tobacco	air-cured tobacco Kentucky[b]	air-cured tobacco Maryland
(A) yields/cigarette				
tar (mg)	33.4	31.5	25.6	21.2
nicotine (mg)	2.4	1.9	1.2	1.1
phenol (μg)	95	120	60	43
benzo(*a*)pyrene[c] (ng)	53 (1.6)	44 (1.4)	24 (0.94)	18 (0.85)
(B) tumorigenicity[d]				
% of mice with skin tumors[e]	34	36	22	18

[a] Wynder and Hoffmann (*96*). [b] Low nicotine, air-cured tobacco (Kentucky). [c] Number in parentheses (μg of B*a*P/1 g of tar). [d] Bioassayed on a gram-to-gram basis of tar. [e] Fifty mice in each group.

including the carcinogenic nitromethane, 2-nitropropane, and nitrobenzene, and of aromatic amines, including the human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl (*15*, *97*, *99*, *100*).

Another important aspect relative to the toxicology of cigarette smoke is the correlation between the nitrate content of tobacco and the pH of cigarette smoke. Even though the different processes used to flue-cure and air-cure tobaccos significantly influence the smoke composition of the major types of tobacco, the amount of nitrate present is also of major importance in determining the pH of the smoke. Whereas flue-cured tobacco and U.S. cigarette tobacco blends deliver weakly acidic smoke (pH 5.8−6.3), cigarettes made from air-cured tobacco deliver neutral to weakly alkaline smoke (pH 6.5−7.5). The major reason for the range of pH values encountered in the smoke of the two major tobacco types is the concentration of ammonia in the smoke, which is primarily tied to the concentration of nitrate in the tobacco. When pH levels of the smoke rise >6.0, the percentage of free, unprotonated nicotine increases to about 30% at pH 7.4 and to about 50% at pH 7.8 (*101*). Protonated nicotine is relatively slowly absorbed in the oral cavity; yet, unprotonated nicotine, some of which is present in the vapor phase of the smoke, is quickly absorbed through the mucosal membranes of the oral surfaces (*102*). This is a distinguishing factor in cigar smoking. The pH of cigar smoke rises with increasing puff numbers from pH 6.5 to 8.5; therefore, the rapid oral absorption of the free nicotine in the vapor phase gives the primary cigar smokers instant nicotine stimulation so that there is no need to inhale the smoke (Figure 4). Similarly, the primary smoker of black, air-cured cigarettes tends not to inhale the smoke or to do so minimally (*13*, *102*, *103*).

In 1963, the first comparative study of the tumorigenicity on mouse skin of the tars from the four major types of *Nicotiana tabacum* revealed the highest activity for tars obtained from flue-cured and sun-cured tobaccos and the lowest for tars from two types of air-cured tobacco (Table 7). The concentration of BaP, a surrogate measure for the carcinogenic PAH, was correlated with the tumor initiation potential of the tars (*96*). Upon topical application to mouse skin and bronchial epithelia, carcinogenic PAH induce papilloma and carcinoma. In inhalation studies with Syrian golden hamsters, the smoke of a cigarette, made with a U.S. tobacco blend, was significantly more active in inducing carcinoma of the larynx than was the smoke of a cigarette with air-cured (black) tobacco (*23*).

To support the concept that the reduction of carcinogenic PAH in the smoke by means of high levels of nitrate in tobacco leads to diminished mouse skin tumorigenicity of the tar, sodium nitrate (8.3%) was added to the standard tobacco blend. On a gram-to-gram basis, the tar from the cigarette with added nitrate (0.6 μg of BaP/g of tar) induced skin tumors in only 2 out of 50 mice, whereas the tar from the control cigarette (without the addition of nitrate; 1.05 μg of B*a*P/g of tar) induced skin tumors in 25 of 100 mice (*104*). In inhalation experiments with Syrian golden hamsters, smoke from the experimental cigarette, made with 8.0% of sodium nitrate, induced laryngeal carcinomas in only 25 of 160 animals compared to this type of neoplasm in 60 of 200 animals in assays

with the control cigarette (*23*). Thus, mouse skin bioassays with tar and smoke inhalation studies with hamsters support the concept that increased nitrate content of the tobacco inhibits the pyrosynthesis of the carcinogenic PAH and that the tars of these cigarettes, and their smoke as a whole, have a reduced potential for inducing tumors in epithelial tissues of the skin and of the upper aerodigestive tract compared to the tar or whole smoke of cigarettes with low-nitrate tobacco.

E. Reconstituted Tobacco and Expanded Tobacco

In the early 1940s, the technology of making reconstituted tobacco (RT) was developed. It was first applied to the manufacture of cigar wrappers. The RT technology enables the utilization of tobacco fines, ribs, and stems in cigarette tobacco blends (*105*). Prior to this technology, tobacco fines and stems had been wasted. The utilization of RT as part of the tobacco blend requires less of the top quality tobaccos for cigarette manufacture. Beginning in 1965, laboratory studies have shown that cigarettes made entirely of RT deliver a smoke with significantly reduced levels of tar, nicotine, volatile phenols, and carcinogenic PAHs. The two major technologies for making RT for cigarettes are the slurry process and the paper process; both lead to RT with low density. It permits a high degree of aeration of the tobacco which enhances combustion. Most of the tested tars from cigarettes made with these reconstituted tobaccos had significantly reduced carcinogenic activity on mouse skin (*74*, *106*). In inhalation assays with Syrian golden hamsters, diluted smoke from cigarettes made of reconstituted tobacco induced significantly fewer carcinoma in the larynx (19/160) than the diluted smoke from control cigarettes (60/200). The cigarette with RT, tested in the smoke inhalation assay, gave per cigarette only 7 puffs and yielded 20.8 mg of tar and 16 ng of BaP compared to 10 puffs, 33.7 mg of tar, and 35.4 ng of BaP for the control cigarette (*23*). Burton, Dye, and Bush analyzed in detail the distribution of nitrite, nitrate, alkaloids, and TSNA in segments of an air-cured, dark tobacco leaf. They reported the highest concentrations of the alkaloids in the tips and the lowest in the base of the leaf, whereas, nitrite and TSNA were present in the highest concentrations in the base of the leaf and decreasing concentrations toward the tip of the leaf. These data indicate a better relationship between nitrite and TSNA than between the alkaloids and TSNA (*107*). Tobacco ribs and stems, the major components of RT, contain more nitrate and nitrite (and this applies especially to the ribs and stems of air-cured tobaccos) than the laminae of tobacco (*95*, *107*, *108*). Therefore, in general, the nitrate content of today's blended U.S. cigarette, which may contain 20−30% RT, is at a level of 1.2−1.5%—significantly higher than the nitrate level in cigarettes during the fifties and sixties when it was ≤0.5% (*89*, *109*). Commercial cigarettes with RT emit in their smoke significantly more TSNA than cigarettes of the past. These TSNA include the NNK which induces AC in rodents. NNK is metabolically activated to carcinogenic species in target tissues such as the lung (*43*). One major U.S. cigarette manufacturer has been granted a patent in December of 1978, presenting a process that reduces more than 90% of the nitrate content of the RT made from ribs and stems (*110*, *111*).

There are at least three methods for expanding tobacco by freeze-drying (*75*). As a result of freeze-drying, the expanded tobacco has greater filling power than natural tobacco; thus, less tobacco is needed to fill a cigarette. An 85-mm filter cigarette, filled entirely with expanded tobacco, required 363 mg of tobacco, while a regular filter-tipped cigarette of the same dimensions required 667 mg of tobacco. The tar yields in the smoke of these two types of cigarettes were 12.4 and 22.1 mg, respectively (*75*, *76*). In 1982, incorporation of all possible modifications in the makeup of the cigarette required only 785 mg of leaf tobacco; in contrast, in 1950, making the blended U.S. cigarette required 1230 mg of leaf tobacco (*109*). Levels of most components measured in the smoke of cigarettes with puffed tobacco, expanded tobacco, or freeze-dried tobacco, were significantly reduced, by comparison to the control cigarette (*75*, *76*).

F. Additives

1. Humectants. Humectants serve to retain moisture and plasticity in cigarette and smoking tobaccos. They delay or prevent the drying of tobacco. Dry tobacco (<8% moisture) gives a harsh tasting smoke. Humectants also preserve those compounds that impart flavor to the smoke. Today, the principal humectants in cigarette tobacco are glycerol (propane-1,2,3-triol) and propylene glycol (PG; propane-1,2-diol); of lesser importance are diethylene glycol (2,2′-di[hydroxyethyl]ether) and sorbitol (*112*). In the past, ethylene glycol (ethane-1,2-diol) has been used as a humectant for cigarette tobacco. During smoking, this compound leads to the formation of ethylene oxide. Workers exposed to this volatile agent face an increased risk for lymphatic leukemia and non-Hodgkin's lymphoma (*113*). For this reason, ethylene glycol is no longer used as a humectant for tobacco. In 1972, Binder and Lindner reported the presence of 7 μg of ethylene oxide in the smoke of a cigarette brand filled with tobacco that had not been treated with ethylene glycol (*114*). The significance of the possible endogenous oxidation of the inhaled ethylene (150−300 μg/cigarette) has not been evaluated (*115*).

Humectants may comprise up to 5% of the weight of cigarette tobacco. In a 1964 study, 18 U.S. cigarette tobacco blends contained between 1.7 and 3.15% of glycerol. To some extent, glycerol decomposes to the ciliatoxic acrolein; U.S. cigarette tobacco contains also between 0.46 and 2.24% of PG (*116*). Four American cigarettes contained between 0.34 and 0.96 mg/cigarette of PG (*117*); during smoking, PG gives rise to the carcinogenic propylene oxide (*118*). Recently, levels of 12−100 ng of propylene oxide have been determined in the smoke of U.S. cigarettes. Several samples of PG that were intended as humectants for cigarette tobacco already contained traces of propylene oxide (*36*).

2. Flavor Additives. Natural tobacco contains a wide spectrum of components that, upon heating, release flavorants. These include tobacco-specific terpenoids, pyrroles and pyrazines among others (*119*−*122*). The effective reduction of smoke yields by filter tips and by the incorporation of reconstituted tobacco also brought about a reduction of flavor components. In 1993 and 1994, the industry convened an expert panel of toxicologists to screen agents that were in use, or considered for use, as tobacco additives. The panel then released a list of 599 agents that were generally regarded as safe (GRAS), whereby the term "safety" applied only to the additives as such without considering the fate and reactivity of

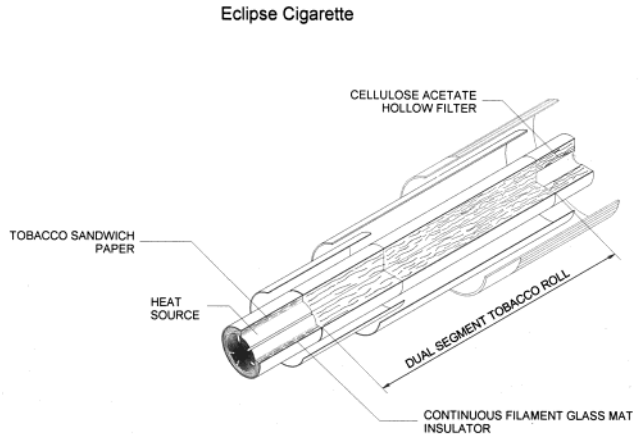


Figure 5. A new type of cigarette: Eclipse, Bombick et al. (*130*).

these agents during combustion (*123*). In inhalation assays, the mainstream smoke (MS) of cigarettes with and without flavor additives induced essentially the same responses in the respiratory tracts of rats; specifically hyperplasia and metaplasia in the nose and larynx (*124*). As this study involved maximally 65 h of exposure, one cannot deduce with certainty that the addition of these flavoring agents to tobacco blends has no additional impact on the development of tumors by cigarette smoke.

G. New Types of Cigarettes

The industry has initiated research toward developing new types of cigarettes, During smoking, such cigarettes were to generate an aerosol with nicotine in the range present in the smoke of conventional filter cigarettes, but low to very low emissions of tar and of toxic and carcinogenic agents. In 1988, the first new type of cigarettes appearing on the test market was called "Premier", a cigarette that "heats rather than burns tobacco" (*125*−*129*). This 80-mm cigarette is comprised of three sections. The first 40-mm section is made with compressed, activated charcoal that is linked to an inner aluminum tube containing tobacco, flavor additives, and glycerol. This tube is embedded in tobacco. Section 2 (∼10 mm) is a cellulose acetate filter, dusted with charcoal powder. The third section (∼30 mm) is a cellulose acetate filter tip. Under standardized smoking conditions (*52*), Premier delivered a MS with low levels of most of the toxic and genotoxic agents compared to concentrations of these agents in the MS of the University of Kentucky reference filter cigarette. Short-term bioassays indicated that the MS of Premier most likely exhibits reduced toxic and genotoxic activities (*125*−*129*). In 1988, Premier was placed on a test market; however, it was not accepted by the consumers.

Undergoing significant changes, the Premier re-emerged as "Eclipse". This product consists of four sections. Section 1, the heat source, is a specially prepared charcoal; section 2 consists of tobacco plus glycerol; section 3 contains finely shredded tobacco; and section 4 is a filter tip (Figure 5). Upon ignition, the special charcoal heats the air stream during puff drawing. The heated air stream enters the tobacco sections and aerosolizes volatile and semivolatile tobacco constituents including nicotine, as well as portions of glycerol. Eclipse is produced in four prototypes; their MS were thoroughly analyzed. Under FTC smoking conditions, the standard Eclipse delivers 8 mg of CO (low-yield filter cigarette, 6−12 mg), 150 μg of acetaldehyde (700 μg), 30 μg of NO_x (200−300 μg) and 180 μg of hydrogen cyanide (300−400 μg), 5.1 mg of tar (11−12 mg) and 0.2−0.4 mg of nicotine (0.7−1.0 mg). The tar consists of 33% water, 47% glycerol, and 17% of various other compounds. The emissions of the major smoke carcinogens, such as B*a*P, 2-naphthylamine, 4-aminobiphenyl, and the TSNA, are lowered by 85−95% (*126*−*129*). The particulate matter of the aerosol generated by smoking Eclipse, according to the FTC standard method, contains as major a constituent about 47% glycerol (in the low-yielding Eclipse this means 2.4 mg glycerol in 5.1 mg smoke particulates) (*129*).

A number of short-term tests were completed with whole smoke, the vapor phase, the tar and/or fractions of the tars of one or several prototypes of Eclipse; the University of Kentucky reference filter cigarette 1R4F and, in some cases, also 1R5F, served as a positive controls. The tars of the two reference cigarettes were cytotoxic, while the tars of two types of Eclipse were not (*130*). Whole smoke of four prototypes of Eclipse had minor cytotoxic activity. However, the activities were significantly less than those of the whole smoke of the Kentucky reference cigarettes (*131*). The tars of the four Eclipse prototypes were not, or at best weakly, mutagenic (with or without activation by the S9 enzyme fraction from rat liver homogenate), but in each case, they were significantly less active than the tars of the reference cigarette (*130*). In the sister chromatid exchange test, the tars of the Eclipse induced only a slightly positive response or no response; the tars from the Kentucky reference cigarettes were significantly more mutagenic (*130*).

The exposure of rats and random-bred Syrian golden hamsters to diluted whole smoke for 5 days a week for 13 weeks led only to moderate changes in the upper respiratory tract of these animals. In each case, the recorded histopathological changes in the short-term assay were less pronounced than the changes observed in the upper respiratory tract of the animals exposed to the diluted smoke of the Kentucky reference cigarette (*132*). The tars of the reference filter cigarette 1R4F and four types of Eclipse were bioassayed at three doses (10, 20, and 40 mg/application) for their tumor promoting activity on the skin of Sencar mice, initiated with DMBA. With one exception, the tumor promoting activities of the tars from the Eclipse cigarettes were reduced by at least two-thirds compared with the tumor promoting activity of the tar from the reference tobacco cigarette (*132*). Using the ^{32}P-postlabeling technique in mice exposed dermally to the tars of four prototypes of Eclipse, resulted in significantly lower DNA-adduct formations in the skin, heart, or lung than DNA adducts in the three organs with the tar from the 1R4F reference cigarette (*133*).

Regular cigarette smokers were asked to switch for 2 weeks from their regular brand to Eclipse and the smoking parameters for these types of cigarettes were determined. There were four study groups, composed of 26−30 volunteers each, for a total of 109 smokers. On the basis of the main values for the four groups, the smoking of Eclipse resulted in about a 30% larger volume per puff, about 50% more puffs per Eclipse adding up to a total puff volume that was more than twice that of the total volume drawn from the control cigarettes (*134*). These data indicate that the Eclipse was very intensely

smoked. This is also reflected in the uptake of nicotine (*135*). The mutagenic activities of the urine of smokers of the four types of Eclipse, assayed on two bacterial strains were reduced by 72% to 100% compared with the mutagenic activities of the urine of the same persons, after smoking their usual cigarette brand (*136*). On request of the Food & Drug Administration, the Institute of Medicine of the National Academy of Sciences assembled an Expert Committee to assess the scientific basis for a possible reduction of the "harm" of the changing cigarette, including Eclipse. The Committee published the evaluation of the Eclipse independent of the entire report on "harm" reduction of tobacco smoke that is to be released in the summer of 2001. The Eclipse evaluation is summarized as follows: "'Eclipse' offers the committed smoker an option that is not currently available." Eclipse does not add to the inherent biological activity of smoke for the range of cigarettes currently on the market. The elevated COHb levels should be regarded as a potential risk factor for cardiovascular diseases. The magnitude of the risk remains to be determined (*132*).

The high concentration of glycerol in the aerosol generated by the Eclipse cigarette motivated scientists to bioassay glycerol in "nose only" inhalation studies with Sprague−Dawley rats. These 2-week (1.0, 1.93, and 3.91 mg/L) and 13-week (0.033, 0.167, and 0.662 mg/L) assays tested for toxicity and especially for irritating effects. The investigators detected metaplasia of the lining of the epiglottis (*132*). The 13-week inhalation studies with rats and hamsters had also resulted in some early histopathological changes in the upper respiratory tract in both types of laboratory animals. These findings, the exposure to the smoke of Eclipse, and to glycerol aerosol, should lead to lifetime inhalation assays with the smoke of Eclipse in rats, preferably Fisher 344 rats, or better yet, in Syrian golden hamsters possibly with an inbred strain of hamsters susceptible to carcinogens in the respiratory tract (*137*). Pauly et al. from the Roswell Park Cancer Institute, Buffalo, NY, caution that harmful glass fibers have been found to migrate into the filter tip of the Eclipse and may be inhaled during puffing (*138*).

The Massachusetts Department of Health and the Society for Research on Nicotine and Tobacco challenged the claim made for Eclipse as the consumer's "next best choice". They request that the FTC and the FDA formulate regulatory procedures. Such procedures should ensure that insufficiently documented health claims for tobacco products such as Eclipse, or for tobaccos with reduced TSNA-levels ("safer tobacco") cannot be used in advertising (*139*, *140*).

In 1998, a second U.S. tobacco company manufactured another new type of cigarette; in this case, an electrically heated cigarette (EHC). The EHC releases an aerosol which, on the basis of chemical analyses and short-term bioassays, induces significantly lower toxicity and mutagenicity than the smoke of the Kentucky reference filter cigarette, 1R4F. The prototype, containing a tobacco filler wrapped in a tobacco mat, is kept in constant contact with eight electrical heater blades in a microprocessor-controlled lighter (Figure 6) (*141*). This cigarette contains about half the amount of tobacco of a conventional cigarette. Under FTC-standardized smoking conditions, the cigarette delivered within an average of 8 puffs about 1 mg of nicotine, whereas all other analyzed smoke constituents were significantly lower than those in the smoke of the University of Kentucky reference cigarette, 1R4F. The carcinogenic PAH were below the detection level (*141*). However, formaldehyde yields were significantly higher in the smoke of the EHC and emissions of glycerol and 2-nitropropane were comparable to those recorded in the smoke of the 1R4F cigarette. Per gram tar, the smoke of the EHC had significantly lower mutagenic activity than the smoke of the 1R4F reference cigarette in TA98, TA100, and TA 1537 tester strains with and without the S9 fraction of rat liver homogenate (*141*).

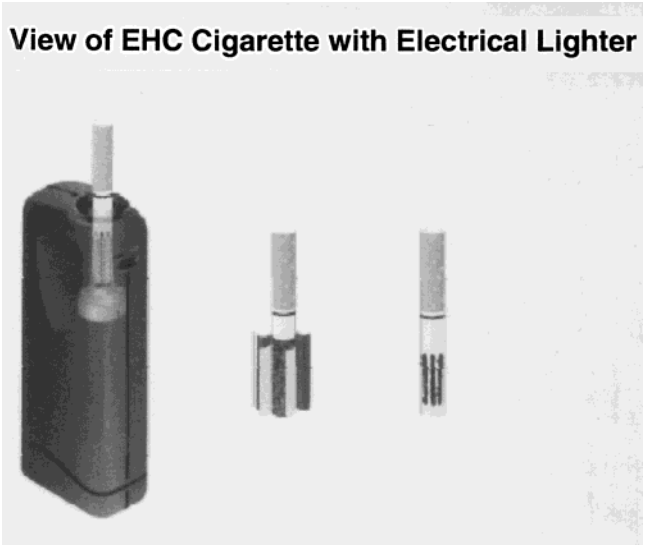


Figure 6. A new type of cigarette: EHC, Terpstra et al. (*141*).

H. Summary of the Changing Cigarette

Table 8 summarizes the changes in the composition of cigarette smoke that resulted from alterations in the makeup and in the composition of the tobacco filler of cigarettes since 1950. In examining these modifications, we gained important, new knowledge about the physicochemical nature of tobacco smoke, the toxic and carcinogenic agents in this aerosol, and their precursors in tobacco. We are now aware of methods that will selectively reduce or even remove specific carcinogenic agents from cigarette smoke. With regard to major carcinogenic agents in cigarette smoke, it has been documented that the gradual increase of the nitrate content of the tobacco blend caused lower smoke yields of the PAH, as shown with B*a*P as a surrogate; however, the smoke yield of the lung carcinogen NNK (and of other TSNA) has increased (Figure 3) (*15*). Around 1990, the nitrate content of U.S. cigarette tobacco amounted to 0.6−1.5% and that of the Canadian cigarette, composed only of bright varieties was ≤0.3%. At that time, the leading U.S. cigarette gave smoke yields of 1.04 ± 0.3 μg of B*a*P/g of tar, while the smoke of the leading Canadian cigarette contained 1.47 ± 0.36 μg of B*a*P/g of tar; the average smoke yields per cigarette of the leading U.S. cigarette amounted to 150 ng of NNN and 100 ng of NNK; and those of the leading Canadian cigarette were 35 ng of NNN and 75 ng of NNK (*142*, *143*).

All analytical data presented in Section III, the "Changing Cigarette", were based on the standard machine smoking method of the FTC (*52*). However, smokers create their own patterns of puff drawing and inhaling smoke primarily for satisfying their acquired need for nicotine. When smoking a low-nicotine cigarette, long-term habitual smokers (≥1 year) tend to smoke more

Table 8. Reduction of Smoke Components[a]

smoke component	charcoal filter	cellulose acetate filter	perforated filter	cigarette paper	reconstituted tobacco	expanded tobacco	flue-cured tobacco[b]	air-cured tobacco[b]
tar	↓	⇓	⇓	↓	↓	↓	+	↓
nicotine	↓	⇓	↓	↓	↓	↓	±	±
CO	↓	±	↓	↓	↓	↓	+	±
HCN	↓	±	↓	↓	±	↓	±	±
acetaldehyde	↓	±	↓	±	±	±	±	±
acrolein	↓	±	↓	±	±	±	±	±
VNA	±	⇓	↓	↓	±	↓	↓	⇑
volatile phenols	±	⇓	↓	±	±	±	↑	↓
BaP	±	±	±	±	↓	↓	↑	↓
TSNA	±	±	±	±	±	↓	↓	⇑
carcinogenicity of tar	±	±	±	±	↓	↓	↑	↓

[a] (±) Insignificant change; (↑) significant increase (≥20%); (↓) significant reduction; (⇓) highly significant decrease (>30%); (⇑) highly significant increase (>30%). [b] For air-cured and flue-cured tobaccos, values are measured against those in the U.S. blended cigarette.

intensely and to inhale the smoke deeper into their lungs. Doing so, they may partially block the perforations of the filter tip or even completely close them (*144*−*148*). These observations were supported by studies in which the smokers used cigarettes that varied from each other in the yields of nicotine but not in other major smoke components. The smokers of the low-nicotine cigarettes compensated for the low dose delivery (low according to smoking by the FTC method) by inhaling a greater volume of smoke than the smokers of (FTC) high-yield cigarettes (*149*, *150*). In the 1980s, the actual puffing parameters of American smokers recorded for the high- and low-nicotine cigarettes substantiated the concept that the smoker of the low-nicotine cigarette takes larger puffs than the smoker of nonfilter cigarettes (*149*−*152*).

In summary, the sales-weighted average nicotine yield in the mainstream smoke of U.S. cigarettes changed from 2.7 mg/cigarette in 1953 to 0.85 mg since 1991 (Figure 1) as determined with the Federal Trade Commission standard machine-smoking method (*52*). Today, reconstituted and expanded tobacco make up 25−30% of the cigarette filler; in addition, the proportion of burley tobacco in the blended U.S. cigarette has increased. Therefore, the nitrate content of the U.S. cigarette has risen, in general, from ≤0.5% to between 1.2 and 1.5%. Other changes pertain to the increased consumption of filter-tipped cigarettes as it rose from 0.5% in 1950 to more than 97% of all U.S. cigarettes since 1997. About two-thirds of all U.S. cigarettes have perforated filter tips that cause air dilution of the smoke to vary between 20 and 45%. In addition, the porosity of the wrapping paper has significantly increased for all manufactured cigarettes.

An important outcome of these changes in the commercial cigarette is the increase in the smoke of the carcinogenic volatile nitrosamines, nitrosamino acids, tobacco-specific *N*-nitrosamines, aromatic amines, and nitroalkanes (*43*, *98*−*100*).

IV. Observations on Cigarette Smokers

A. Comparison of the Smoke of High- and Low-Yield Cigarettes, 1950−1975

On the basis of the laboratory data generated with the FTC standard machine smoking method for cigarettes, it was assumed that the lung cancer risk among cigarette smokers would decrease. Three cohort studies and four case-control studies published between 1968 and 1981 had reported that the long-term smoker of low-yield cigarettes had a 20−50% lower risk for lung cancer than the smoker of the conventional high-yield nonfilter cigarettes (*1*, *153*−*159*). In a longitudinal study that began in 1959, Hammond et al., from the American Cancer Society, followed 1 million men and women over 12 years. Few of the smokers who shifted from high-tar and nicotine to low-tar and nicotine cigarettes increased their daily cigarette consumption. Adjusted for numbers of cigarettes smoked per day, the smokers of low-yield cigarettes showed somewhat reduced total death rates and death rates from coronary heart disease and from lung cancer (*155*). Wynder and Stellman reported in 1979 that long-term smokers of filter cigarettes had reduced risks for cancer of the lung as well as for cancer of the larynx (*158*).

Auerbach et al. examined the bronchial tubes of 211 men (including 154 smokers) from autopsy specimens collected in the years 1955−1960 and bronchial tubes from 234 men (187 smokers) from autopsy material obtained in 1970−1977. Auerbach compared the loss of cilia, and the occurrence of bronchial metaplasia and atypical nuclei. The earlier samples presented significantly more pronounced changes in the bronchial tubes than the samples collected in 1970−1977 (*160*).

A U.S. Surgeon General's Committee on the changing cigarette stated in 1981 that low-tar, low-nicotine cigarettes produce lower rates of lung cancer than the higher tar and higher nicotine predecessors (*78*). In 1986, an IARC expert panel on the epidemiology of smoking-associated cancers, on tobacco toxicology, and on tobacco carcinogenesis concluded that epidemiological studies suggest that "prolonged use of nonfilter, high-tar cigarettes is associated with a greater risk for lung cancer than the prolonged use of filter and low-tar cigarettes" (*1*).

B. Comparison of the Smoke from High- and Low-Yield Cigarettes, 1976−1999

These tentative conclusions about the lower toxicity and carcinogenicity of low-yield cigarettes manufactured during the 1970s and early 1980s were questioned as to their applicability to cigarettes produced in the 1980s and

thereafter. Study groups in the U.K., in the U.S., and elsewhere observed that the machine-smoking schedule chosen by the FTC, CORESTA, and other agencies, did not reflect the smoking patterns observed among most of the cigarette smokers in developed countries during the preceding 2−3 decades (*144*−*149*, *161*, *162*).

In 1978, the tobacco industry was well aware of the fact that the standard machine-smoking schedule did not reflect the smoking habits of most of the cigarette smokers. Schultz and Seehofer, determining nicotine in the butts of cigarettes smoked by men and women, found significantly higher levels of it in these butts than in those from identical cigarettes that were machine-smoked, whereby the butt lengths were not different from those left by the smokers (*163*).

In 1970, Ashton and Watson, and Benowitz et al., had already observed that smokers of low-yield cigarettes took more puffs than smokers of high-nicotine cigarettes (*149*, *164*). This observation was confirmed by Haley et al. in 1985 (*150*). Kozlowski et al. were the first to report that smokers of low-nicotine cigarettes with perforated filter tips tend to occlude the holes in the filter tip with their lips and/or fingers, thereby increasing the smoke yields of tar, nicotine, and carbon monoxide (*148*, *165*, *166*). This was also confirmed by studies in other laboratories (*167*, *168*). Using the ninhydrin color reaction of the saliva-derived residual protein and amino acids on the perforated filter tips, it was determined in a study examining 1229 cigarette butts that 5.2% of the holes were completely or partially closed and 18.9% were partially closed during smoking (*169*). In a second report, 15% of 300 butts gave evidence of the holes being covered with saliva (*170*).

Assays on nicotine uptake by smokers demonstrated that there is no significant relationship between plasma cotinine, a major nicotine metabolite, and the nicotine yield of cigarettes smoked according to the FTC method (*171*). Benowitz et al. reported that the cotinine level in plasma was virtually the same for all cigarettes smoked and inhaled, except for ultra-low-yield cigarettes (*172*). Gori and Lynch found no correlation between expired carbon monoxide from cigarette smokers and the FTC yields of carbon monoxide (*173*).

The development of a tobacco smoke inhalation testing system (TSITS) in the late 1980s enabled assays of the smoking intensities of smokers of cigarettes with different nicotine yields (*174*, *175*). This system was utilized for the determination of smoking profiles of long-term smokers (≥1 year) of a specific brand of cigarettes that had FTC nicotine yields of 0.6−0.8 mg/cigarette (56 volunteers) and of 0.9−1.2 mg of nicotine/cigarette (76 volunteers). The observed average values were puff volumes of 48.6 and 44.1 mL (FTC, 35 mL), puff duration of 1.5 s (FTC, 2.0 s), and a total puff volume per cigarette between 615 and 523 mL (FTC, 280−350 mL). The average smoke yields for nicotine were 1.74 mg (FTC, 0.7) and 2.39 mg (1.11), for tar 22.3 mg (8.5) and 29 mg (15.4), and for carbon monoxide 17.3 mg (9.7) and 22.5 mg (14.6), respectively. This study revealed also that, compared with FTC data, smokers of cigarettes with low or medium smoke yields actually not only inhaled significantly higher quantities of tar, nicotine and carbon monoxide but also of the major lung carcinogens, PAH (B*a*P = 1.6−1.8 times higher) and of the TSNA (NNK = 1.7 times higher) (*176*).

Unfortunately, the public generally assumes that the smoke yields published by the FTC are reflecting the degree of exposure to harmful smoke constituents inherent in smoking a given brand of cigarette. Thus, it is believed that smoking low-yield and ultra-low-yield brands carries less of a risk than smoking high-yield nonfilter cigarettes. However, the suggestion that there is a meaningful quantitative relationship between FTC-measured smoke yields and actual uptake of smoke carcinogens by the cigarette smoker is misleading (*171*). It has, therefore, been stated that "the time has come for (requiring) meaningful information on the smoke yields of cigarettes" (*177*, *178*). While the tobacco industry has not taken a stand on this issue, the FTC principally agrees that a better and more comprehensive test program for cigarettes is needed (*179*).

C. Epidemiological Studies

As cited in subsection V. A., seven independent epidemiological studies published between 1969 and 1981 in the U.K. and in the U.S. reported a 20−50% lower risk of lung cancer for long-term smokers of filter cigarettes than for smokers of nonfilter cigarettes (*1*, *153*−*159*). One may assume, on the basis of previous reports, that during the years 1950−1975, when filter cigarettes gave relatively high yields of nicotine (in 1962, sales weighted average = 2.0 mg), smokers had not significantly increased their smoking intensities, in the way smokers did in later years. Therefore, they may have benefited from the reduction of tar in the smoke of filter cigarettes between 1950 and 1975 as is reflected in a somewhat reduced risk for lung cancer.

The sales-weighted average FTC nicotine yields of the U.S. cigarette decreased since 1980 from 1.0 mg to 0.85 mg and that of filter cigarettes declined from 0.9 mg to 0.80 mg/cigarette (*180*). Because smokers compensate for nicotine uptake (*175*, *176*), the consumers of low-nicotine cigarettes are likely to smoke these cigarettes more intensely and inhale the smoke more deeply into the lung than do smokers of nonfilter cigarettes.

Since 1983, at least 10 epidemiological studies have reported that the lung cancer risk of smokers of low-tar, low-nicotine cigarettes is comparable to, or only slightly lower than that of smokers of nonfilter cigarettes (*181*−*189*). The large prospective study, CPS I (Cancer Prevention Study I), by the American Cancer Society, involving more than one million men and women, compares lung cancer mortality and morbidity rates, CHO, COPD, and stroke during the period 1959−1965 with corresponding data from the CPS II study for the years 1982−1988 (*187*, *190*). The smokers in the CPS II group had a significantly higher lung cancer risk than the smokers of filter cigarettes in the CPS I group, and only a slightly lower risk than the smokers of nonfilter cigarettes in the CPS II study (*191*). These epidemiological data are supported by laboratory data from smokers of low- and high-yield cigarettes (*144*−*152*, *161*−*176*). Over the years, the changing cigarette led to a decline in sales-weighted average FTC-nicotine yields for the U.S. cigarette. In 1970, it was 1.31 mg; since 1990, it declined further from 0.94 to 0.85 mg of nicotine (*180*). Since 1990, more than 60% of all U.S. cigarettes delivered ≤1.2 mg of nicotine under the FTC machine-smoking conditions. During the past 2 decades, most of the cigarette-smoking men and women in the United States smoked their cigarettes

rather intensely. There are many indications, though no actual measurements have been reported that smokers of cigarettes yielding ≤1.2 mg of nicotine/cigarette do, in fact, inhale the smoke more deeply than smokers of cigarettes with higher yields.

One indication for differences in depth of smoke inhalation between smokers in earlier and recent decades is the apparent shift in the prevalence of adenocarcinoma in the peripheral lung in both men and women who smoked cigarettes. In the first large-scale epidemiological study on cigarette smoking and lung cancer, the tumors were classified as bronchiogenic carcinoma and adenocarcinoma (AC). Bronchiogenic carcinoma included squamous cell carcinoma (SCC) and small cell carcinoma. Of the 605 men with lung cancer, 566 had bronchiogenic carcinoma and only 39 had AC, i.e., there was a ratio of 15:1. Among the 592 male cigarette smokers with lung tumors in this study, there were 561 cases of bronchiogenic carcinoma and 31 AC (16:1) (*19*). These assessments were completed before the WHO's acceptance of the classification system by Kreyberg in 1967 (*193*). Thus, caution is necessary in comparisons of the SCC to AC ratios of the studies conducted in the 1950s and in later years. Nonetheless, there has clearly been a gradual change in that the prevalence of lung tumors leaned more and more toward AC in the peripheral lung while there initially was a preponderance of SCC in the major bronchi. The SCC:AC ratios for lung cancer cases changed from 3.1:1.0 in men and 1.0:1.64 in women in the years 1964 to 1971 to 1.4:1.0 in men and 1.0:1.8 in women in 1984−1986 (*185*, *194*−*200*). The prevalence of centrally originating bronchiocarcinoma declined from 69.3% in specimens examined before 1978 to 57.3% in specimens collected between 1986 and 1989 (*201*).

In Section III,D, we discussed that the average nitrate content of the U.S. blended cigarette tobacco increased gradually from less than 0.5% in the 1950s to between 1.2 and 1.5%; since the 1980s. Increased nitrate content is a major factor for the increased formation of TSNA during tobacco processing and during smoking (*43*, *107*). NNK, a TSNA, formed by the nitrosation of nicotine, is an organ-specific carcinogen that induces lung adenocarcinoma in mice, rats, and hamsters (*43*). Literature data support the potential contribution of NNK in the development of human lung cancer in smokers (*200*). Carbonyl reduction of NNK is the major metabolic pathway. α-Hydroxylation leads to the formation of intermediates that can damage lung DNA (*43*, *202*). These data support the concept that smoking low-yield cigarettes enhances the formation of adenocarcinoma of the lung. It appears that efforts to render cigarettes less harmful have had an impact on changes in the type of lung tumors caused by cigarette smoking but have not led to a reduction of the overall lung cancer risk for smokers.

V. Future Directions

The Surgeon General's report on Smoking and Health for the year 2000, entitled "Reducing Tobacco Use", reviews past achievements and outlines the most promising methods for the treatment of nicotine addiction (*203*). It is encouraging that the prevalence of cigarette smoking among adults has decreased from 40% in the 1960s to about 25% in the late 1990s. However, the decline of smoking prevalence progressed only at the rate of 0.5%/year. It is of great concern that, during the last 10 years, cigarette smoking among junior high school students has increased to 9.2% and among high school students to 34.8%. In addition, snuff dipping prevalence in these groups of students increased to 3.6 and 10.0%, respectively (*14*, *203*). It is also of great concern that in certain subgroups in our society the percentage of smokers is now significantly higher than in the rest of the U.S. population. In 1997, among men and women with less than 12 years of education, 35.4% smoked cigarettes compared to 11.6% among college graduates. Among those in the lower income strata (income below the poverty level), cigarette smoking prevalence is 33.3% (*196*).

The most promising approaches toward reducing tobacco smoking are four types of intervention: (1) education (school curricula and by mass media), (2) clinical approaches (prescription of drugs, including nicotine, and other treatment for behavioral changes); (3) regulatory intervention (product controls, restriction of product sales to minors, smoking bans at the workplace), and (4) economic measures (taxation) (*203*).

The Surgeon General's report for the year 2000 neither discusses nor mentions the concept of "the less harmful cigarette". As discussed earlier, from a public health standpoint, the only harmless cigarette is the one that is not smoked. Adherence to this view may have been reinforced by the lack of significant progress over the past three decades toward "the less harmful cigarette". However, several scientists outside the industry see it as a mandate that cigarettes with significantly reduced overall toxicity, carcinogenicity and with less addictive potential are made available. After all, smoking control and prevention has not reached the many millions of cigarette smokers who remain dependent on nicotine and are, therefore, at high risk for tobacco-related diseases. These smokers include the large segment of economically disadvantaged, healthcare-underserved men and women in our society.

There are a number of possibilities for changing tobacco products toward overall reduction of toxicity, carcinogenicity and their addictive nature. It needs to be strongly emphasized that there will never be a safe cigarette (*16*, *203*). However, "the less harmful cigarette" is a necessary compromise for those smokers who cannot overcome their nicotine addiction. It is suggested that the first step toward such renewed efforts will be the inception of a Tobacco Study Group (TSG) composed of individual experts in the tobacco-related sciences and disease research areas. This TSG will not be a revival of the Tobacco Working Group (TWG) that was active at the National Cancer Institute between 1968 and 1979. The first step for the proposed TSG will be the establishment and adoption of the conditions that will ensure its credibility. The group will be composed of scientists from academia, tobacco control agencies of state and federal governments, and industry. It will be the primary goal of the TSG to study and to establish the conditions for research strategies that, on the basis of current scientific knowledge, would represent the most promising approaches toward the "less harmful cigarette". In the second step, the smoke of the research cigarettes will be analyzed for tar, nicotine, CO, and those smoke parameters and components that contribute to the toxicity, carcinogenicity, and addictive nature of cigarette smoke. The cigarettes will be smoked under conditions that reflect the average smoking habits of long-term cigarette

smokers. The smoke of these experimental cigarettes will be bioassayed in short-term in vitro and in vivo tests for their mutagenicity and carcinogenic potential and for their cilia toxicity. These tests would be followed by long-term smoke inhalation assays with Syrian golden hamsters for the indication of tumors in the upper aerodigestive tract. Tars will also be assayed on the skin of strain A mice for their potential for induction of skin tumors and lung adenomas. Those experimental cigarettes that deliver smoke with lower potentials for toxicity, carcinogenicity, and nicotine addiction than current U.S. cigarettes with comparable tar and nicotine yields will be smoked by voluntary long-term cigarette smokers who volunteer to participate in this assay. The serum of these smokers will be analyzed for nicotine, cotinine, thiocyanate, NNAL, 1-hydroxypyrene, and for COHb. The urine will be analyzed for the same metabolites determined in serum and, in addition, for *N*-nitrosoproline and total NNAL after hydrolysis, and for muconic acid.

A. Some Thoughts on Cigarettes with Low Nicotine Delivery

To achieve low nicotine delivery, the cigarette tobaccos will consist of a low-nicotine blend and will have efficient filter tips. These filter tips will be constructed in a manner that precludes smokers' compensation and manipulation of the perforation, thus allowing nicotine delivery in the smoke to be no greater than that deemed the lowest appropriate dose per cigarette according to the TSG. Initial aims will be for a nicotine delivery of no more than 0.7−0.8 mg of nicotine/cigarette. This dose may be gradually reduced to between 0.5 and 0.6 mg/ cigarette.

A survey by the American Cancer Society reported that between 1992 and 1998 among 1.2 million men and women in the United States, 7.8% of all male smokers and 13.9% of female smokers, consumed cigarettes that deliver ≤6 mg FTC tar. Of the cigarettes delivering 6 mg of tar (57 cigarette brands), five brands delivered 0.6 mg, 42 brands 0.5 mg, and 10 brands 0.4 mg of nicotine (*180*, *204*).

Benowitz and Henningfield estimated 0.4−0.5 mg of nicotine content in the tobacco of one cigarette to be the upper limit for effective prevention of nicotine addiction in young people (*205*). It is unlikely that a cigarette with such a low nicotine delivery would be accepted by the consumers. The smoker will rather seek products with higher nicotine yield so that any concept of "a less harmful cigarette" would be self-limiting. However, ultimately, the lowest acceptable level of nicotine emission per cigarette has to be part of "the less harmful cigarette".

B. Major Reduction of TSNA

At a 1962 meeting on *N*-nitrosamines in Hamburg, Germany, sponsored by the West German Cigarette Research Council, H. Druckrey and R. Preussman discussed the possibility that nornicotine and possibly nicotine may give rise during smoking to the suspected carcinogen *N*′-nitrosonornicotine (NNN) (*206*). In 1975, Klus and Kuhn, from the Austrian Tobacco Company, determined in the smoke of a cigarette filled with tobacco rich in nornicotine 40 ng of NNN (*207*). On the basis of the absence of publications in the open literature, it appears that the tobacco industry had only limited interest in the analytical and chemical aspects of the TSNA and their carcinogenic activities until the early 1990s (*208*−*210*). Following a large-scale bioassay for the carcinogenic activity of NNN in the 1970s, the tobacco industry did not publish data on the carcinogenicity of any of the seven TSNA identified in tobacco products (*201*).

TSNA are the major carcinogens in chewing tobacco and snuff and are associated with cancer of the oral cavity of snuff dippers (*43*, *211*, *212*). The nicotine-derived NNK is an organ-specific carcinogen that induces adenocarcinoma in the peripheral lung of mice, rats, and hamsters. In addition, NNK and its enzymatic reduction product NNAL are the only environmental agents known to induce cancer of the exocrine pancreas in laboratory animals (*48*, *202*). NNK and NNN are specifically formed by *N*-nitrosation of nicotine. NNN is also formed from nornicotine (*43*). The *N*-nitrosation of nicotine and nornicotine occurs during curing, fermentation, and aging of tobacco and involves reduction of nitrate, primarily by bacteria, leading to the formation of nitrite which is a *N*-nitrosating agent (*86*, *213*, *214*).

Star Scientific, Inc. has succeeded in reducing the formation of *N*-nitrosamines, and especially that of the highly carcinogenic NNK, during curing and aging of tobacco (*215*). However, about 30−50% of the TSNA in cigarette smoke result from pyrosynthesis in the burning cone and the hot zones of the cigarettes and are emitted into mainstream smoke together with the preformed TSNAs that are aerosolized into the smoke stream (*216*, *217*).

On the basis of our current knowledge, a drastic reduction of TSNA levels in chewing tobacco and snuff is expected to lower the risk for oral cancer; in fact, such low levels of TSNA may be below the threshold level for the induction of tumors in snuff dippers. However, it will also be of importance to investigate the possible endogenous formation of the carcinogenic TSNA in consumers of the snuff brands that contain only traces of TSNA (*43*, *218*−*222*).

Inhibition of NNN and NNK formation in the hot zones of burning cigarettes may also be achieved by trapping the nitrogen oxide radicals. The trapping by free radicals will at the same time, at least partially, remove these freshly generated, highly reactive and, therefore, undesirable agents from tobacco smoke.

C. Nicotine Analogues

Nicotine is regarded as the major addictive agent in smokeless tobacco and in tobacco smoke. Nicotine is also the primary substrate for the two highly carcinogenic, tobacco-specific *N*-nitrosamines, NNK, and NNN (*43*, *202*, *223*). Thus, a possible approach toward "the less harmful cigarette" would be the replacement of nicotine with an analogue that has reduced receptor binding but also a low potential for the formation of NNN- and NNK-analogues and that these *N*-nitrosamines are also only weakly carcinogenic or noncarcinogenic. Preliminary data by several investigators supports this approach (*224*−*227*).

VI. Epilogue

The first large-scale epidemiological studies on smoking and disease in 1950 revealed a dose−response

relationship between the number of cigarettes smoked and the risk for lung cancer. These findings were supported by bioassays resulting in a dose−response between the amount of tar applied to mouse skin and the induction of skin tumors. They were further strengthened by inhalation studies with hamsters documenting a dose−response between the amount of cigarette smoke inhaled and the occurrence of tumors in the upper respiratory tract. On the basis of these observations, the initial research toward the less toxic cigarette emphasized the reduction of smoke yields for tar and nicotine and utilized the standard machine smoking method of the FTC to measure such reduction. The emission of tar and nicotine from the U.S. sales-weighted average cigarette was gradually lowered from 38 mg of tar and 2.7 mg of nicotine in 1953 to 18 and 1.2 mg in 1975, and since 1996, to 12 and 0.85 mg, respectively. The tar and nicotine reductions were achieved by using filter tips primarily made from cellulose acetate. The prevalence of filter tipped cigarettes increased from 0.5% of all U.S. cigarettes in 1950 to more than 97% since 1990. Reductions were also achieved by incorporating into the cigarette blend reconstituted and expanded tobacco, by increasing the porosity of the cigarette paper, by changing the tobacco blend, including increasing the portion of air-cured tobacco, and by developing perforated filter tips. It was always recognized that it is highly unlikely that there will ever be a nontoxic cigarette and that there is only one certain way to prevent, respectively to reduce, smoking-related diseases, namely, by not starting the smoking habit or, for smokers, to stop the habit. "The less harmful cigarette" was, and is, only regarded as a compromise for those who cannot or will not give up smoking cigarettes. The group of men and women who continue to smoke includes a large segment of the economically disadvantaged, healthcare-underserved people who also, in general, lack the opportunity to be treated for nicotine addiction.

Between 1969 and 1981, epidemiological studies indicated that the long-term smoker of filter cigarettes has a 20−50% reduced risk for smoking-related diseases compared with the risk of the smoker of nonfilter cigarettes. However, beginning with the 1980s, this difference in risks for cancer, heart disease, chronic obstructive lung disease, and stroke between smokers of low-yielding cigarettes and of smokers of nonfilter cigarettes gradually disappeared. Primarily, three factors are considered to be associated with the disappearance of a reduction in the differences in risks for diseases among smokers of filter cigarettes and among smokers of nonfilter cigarettes. These are the increased smoking intensities and increased depth of inhalation by the smokers of filter cigarettes as a consequence of their acquired need for nicotine. The third major reason is the increased nitrate concentration in the tobacco of the U.S. blended cigarette. The nitrate increase leads to greater concentrations of nitrogen oxides in the smoke and, thereby enhancing formation of carcinogenic *N*-nitrosamines, especially of the nitrosamines formed from nicotine and nornicotine during tobacco processing and during smoking. These TSNA are organ-specific carcinogens that induce adenocarcinoma in the peripheral lung, carcinoma in the upper aerodigestive tract and carcinoma in the pancreas.

For those adults who did not succeed in refraining from smoking, "the less harmful cigarette" has to be developed as the U.S. cigarette of the future. A number of scientists in tobacco control and tobacco-health research regard "the less harmful cigarette" as a "must" for our society.

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Customer:

Dr Michael Moynihan
22nd Century Limited LLC
8201 Main Street
Suite 6 Williamsville
New York
USA 14221

Sample Received: 14 March 2011

Date Testing Commenced: 16 March 2011

Date Reported: 01 April 2011

Samples Received: Magic Menthol

Testing Requirements: One thousand cigarettes in branded packets were submitted to the Scientific Services Laboratory of the Filtrona Technology Centre for testing for mainstream smoke yields.

Test Procedures: All tests have been carried out in accordance with documented in house test methods based on ISO standard methods when available. The reported data is only applicable to the sample received.

Results: The results are given on the page attached

Approved by:

(b) (6)

Laboratory Manager
Filtrona Technology Centre

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Mainstream Smoke Components			
Date	**01/04/2011**		
Brand	**Magic Menthol**		
Bar Code	**FSC 00953788**		
Component	**Yield Mean**		**Yield SD**
Tar	3.5	mg/cig	0.2
Nicotine	0.03	mg/cig	0.00
Carbon Monoxide	5.4	mg/cig	0.2
Benzo [a] Pyrene	0.9	ng/cig	0.1
Carbonyls			
Formaldehyde	5.3	µg/cig	1.5
Acetaldehyde	283.0	µg/cig	13.0
Acetone	*111.7*	*µg/cig*	*7.9*
Acrolein	12.0	µg/cig	0.9
Propionaldehyde	20.0	µg/cig	1.3
Crotonaldehdye	4.6	µg/cig	0.8
Methyl Ethyl Ketone	23.4	µg/cig	2.2
Butyraldehyde	10.4	µg/cig	1.1
Phenols			
Hydroquinone	15.5	µg/cig	1.0
Resorcinol	< 0.5	µg/cig	
Catechol	13.2	µg/cig	0.3
Phenol	5.1	µg/cig	0.3
meta & para-Cresol	3.9	µg/cig	0.2
orto-Cresol	1.5	µg/cig	0.1
Ammonia	24.8	µg/cig	2.0
Hydrogen Cyanide	44.0	µg/cig	4.6
Semi-volatile bases			
Pyridine	3.5	µg/cig	0.3
Quinoline	*0.04*	*µg/cig*	*0.01*
Miscellaneous Organics			
1,3 Butadiene	17.9	µg/cig	1.0
Isoprene	115.9	µg/cig	7.1
Acrylonitrile	5.6	µg/cig	0.2
Benzene	23.0	µg/cig	3.0
Toluene	31.9	µg/cig	4.6
Styrene	3.6	µg/cig	0.4
Nitrosamines			
N-Nitrosonornicotine NNN	39.1	ng/cig	0.2
N-Nitrosoanatabine NAT	5.7	ng/cig	0.4
N-Nitrosoanabasine NAB	1.3	ng/cig	0.1
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK	10.9	ng/cig	1.4
Aromatic Amines			
3-Aminobiphenyl	1.50	ng/cig	0.13
4-Aminobiphenyl	1.02	ng/cig	0.07
1-Aminonaphthalene	7.56	ng/cig	0.09
2-Aminonaphthalene	4.16	ng/cig	0.08
NOx Nitric Oxide	153.0	µg/cig	2.7
pH	7.04	pH units	0.01
Metals			
Beryllium	*< 2*	*ng/cig*	
Cobalt	< 2	ng/cig	
Nickel	< 10	ng/cig	
Lead	*< 5*	*ng/cig*	
Selenium	< 2	ng/cig	
Cadmium	13.8	ng/cig	1.3
Chromium	< 10	ng/cig	
Arsenic	< 1.5	ng/cig	
Menthol	0.34	mg/cig	0.01

Approved by:

(b) (6)

Filtrona Technology Centre

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Customer:

Dr Michael Moynihan
22nd Century Limited LLC
8201 Main Street
Suite 6 Williamsville
New York
USA 14221

Sample Received: 14 March 2011

Date Testing Commenced: 16 March 2011

Date Reported: 01 April 2011

Samples Received: Magic

Testing Requirements: One thousand cigarettes in branded packets were submitted to the Scientific Services Laboratory of the Filtrona Technology Centre for testing for mainstream smoke yields.

Test Procedures: All tests have been carried out in accordance with documented in house test methods based on ISO standard methods when available. The reported data is only applicable to the sample received.

Results: The results are given on the page attached

Approved by:

(b) (6)

Laboratory Manager
Filtrona Technology Centre

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Mainstream Smoke Components			
Date	**01/04/2011**		
Brand	**Magic**		
Bar Code	**FSC 00953771**		
Component	**Yield Mean**		**Yield SD**
Tar	3.7	mg/cig	0.2
Nicotine	0.03	mg/cig	0.00
Carbon Monoxide	6.3	mg/cig	0.4
Benzo [a] Pyrene	2.4	ng/cig	0.1
Carbonyls			
Formaldehyde	5.7	µg/cig	0.6
Acetaldehyde	352.6	µg/cig	40.6
Acetone	*138.1*	*µg/cig*	*19.0*
Acrolein	14.8	µg/cig	2.4
Propionaldehyde	25.3	µg/cig	3.0
Crotonaldehdye	7.5	µg/cig	0.8
Methyl Ethyl Ketone	28.4	µg/cig	2.4
Butyraldehyde	13.2	µg/cig	1.2
Phenols			
Hydroquinone	18.3	µg/cig	1.5
Resorcinol	< 0.5	µg/cig	
Catechol	14.1	µg/cig	1.0
Phenol	6.3	µg/cig	0.3
meta & para-Cresol	4.5	µg/cig	0.3
orto-Cresol	1.7	µg/cig	0.1
Ammonia	23.1	µg/cig	2.1
Hydrogen Cyanide	60.3	µg/cig	4.0
Semi-volatile bases			
Pyridine	6.0	µg/cig	0.4
Quinoline	*0.05*	*µg/cig*	*0.00*
Miscellaneous Organics			
1,3 Butadiene	21.9	µg/cig	2.8
Isoprene	136.1	µg/cig	24.2
Acrylonitrile	6.8	µg/cig	0.8
Benzene	27.6	µg/cig	3.4
Toluene	39.4	µg/cig	3.7
Styrene	4.8	µg/cig	0.1
Nitrosamines			
N-Nitrosonornicotine NNN	47.1	ng/cig	6.2
N-Nitrosoanatabine NAT	9.1	ng/cig	2.7
N-Nitrosoanabasine NAB	1.9	ng/cig	0.8
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK	17.6	ng/cig	4.0
Aromatic Amines			
3-Aminobiphenyl	1.55	ng/cig	0.09
4-Aminobiphenyl	0.89	ng/cig	0.09
1-Aminonaphthalene	8.30	ng/cig	0.20
2-Aminonaphthalene	4.38	ng/cig	0.11
NOx Nitric Oxide	200.4	µg/cig	6.7
pH	7.02	pH units	0.03
Metals			
Beryllium	< 2	ng/cig	
Cobalt	< 2	ng/cig	
Nickel	< 10	ng/cig	
Lead	*5.3*	*ng/cig*	*0.4*
Selenium	< 2	ng/cig	
Cadmium	16.8	ng/cig	0.4
Chromium	< 10	ng/cig	
Arsenic	< 1.5	ng/cig	
Menthol	Not Detected	mg/cig	

Approved by:

(b) (6)

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Customer:

Dr Michael Moynihan
22nd Century Limited LLC
8201 Main Street
Suite 6 Williamsville
New York
USA 14221

Sample Received: 14 March 2011

Date Testing Commenced: 16 March 2011

Date Reported: 01 April 2011

Samples Received: Newport Menthol Box

Testing Requirements: One thousand cigarettes in branded packets were submitted to the Scientific Services Laboratory of the Filtrona Technology Centre for testing for mainstream smoke yields.

Test Procedures: All tests have been carried out in accordance with documented in house test methods based on ISO standard methods when available. The reported data is only applicable to the sample received.

Results: The results are given on the page attached

Approved by:

(b) (6)

Laboratory Manager
Filtrona Technology Centre

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Mainstream Smoke Components			
Date	**01/04/2011**		
Brand	**Newport Menthol Box**		
Bar Code	**FSC 02657512**		
Component	**Yield Mean**		**Yield SD**
Tar	18.7	mg/cig	0.7
Nicotine	1.07	mg/cig	0.02
Carbon Monoxide	19.7	mg/cig	0.7
Benzo [a] Pyrene	9.3	ng/cig	0.1
Carbonyls			
Formaldehyde	33.0	µg/cig	1.0
Acetaldehyde	767.8	µg/cig	28.6
Acetone	*264.8*	*µg/cig*	*12.0*
Acrolein	75.2	µg/cig	1.2
Propionaldehyde	53.7	µg/cig	1.9
Crotonaldehdye	16.9	µg/cig	1.2
Methyl Ethyl Ketone	55.5	µg/cig	3.2
Butyraldehyde	39.9	µg/cig	4.3
Phenols			
Hydroquinone	64.4	µg/cig	2.1
Resorcinol	5.7	µg/cig	0.3
Catechol	59.0	µg/cig	0.8
Phenol	13.4	µg/cig	0.7
meta & para-Cresol	9.2	µg/cig	0.4
orto-Cresol	3.6	µg/cig	0.2
Ammonia	14.0	µg/cig	0.2
Hydrogen Cyanide	291.3	µg/cig	21.7
Semi-volatile bases			
Pyridine	18.0	µg/cig	1.2
Quinoline	*0.20*	*µg/cig*	*0.02*
Miscellaneous Organics			
1,3 Butadiene	60.7	µg/cig	1.9
Isoprene	493.5	µg/cig	23.1
Acrylonitrile	10.4	µg/cig	0.5
Benzene	52.8	µg/cig	1.8
Toluene	78.9	µg/cig	8.3
Styrene	24.6	µg/cig	0.9
Nitrosamines			
N-Nitrosonornicotine NNN	113.0	ng/cig	2.8
N-Nitrosoanatabine NAT	95.6	ng/cig	2.4
N-Nitrosoanabasine NAB	9.7	ng/cig	0.8
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK	57.6	ng/cig	4.7
Aromatic Amines			
3-Aminobiphenyl	0.83	ng/cig	0.09
4-Aminobiphenyl	0.61	ng/cig	0.10
1-Aminonaphthalene	10.48	ng/cig	0.40
2-Aminonaphthalene	2.32	ng/cig	0.12
NOx Nitric Oxide	163.4	µg/cig	11.9
pH	6.13	pH units	0.01
Metals			
Beryllium	< 2	ng/cig	
Cobalt	< 2	ng/cig	
Nickel	< 10	ng/cig	
Lead	*21.2*	*ng/cig*	*0.1*
Selenium	< 2	ng/cig	
Cadmium	63.3	ng/cig	1.4
Chromium	< 10	ng/cig	
Arsenic	4.3	ng/cig	0.3
Menthol	0.58	mg/cig	0.02

Approved by:

(b) (6)

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Customer:

Dr Michael Moynihan
22nd Century Limited LLC
8201 Main Street
Suite 6 Williamsville
New York
USA 14221

Sample Received: 14 March 2011

Date Testing Commenced: 16 March 2011

Date Reported: 01 April 2011

Samples Received: Marlboro Gold Box King

Testing Requirements: One thousand cigarettes in branded packets were submitted to the Scientific Services Laboratory of the Filtrona Technology Centre for testing for mainstream smoke yields.

Test Procedures: All tests have been carried out in accordance with documented in house test methods based on ISO standard methods when available. The reported data is only applicable to the sample received.

Results: The results are given on the page attached

Approved by:

(b) (6)

Laboratory Manager
Filtrona Technology Centre

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Mainstream Smoke Components			
Date	**01/04/2011**		
Brand	**Marlboro Gold Box King**		
Bar Code	**FSC 02838423**		
Component	**Yield Mean**		**Yield SD**
Tar	10.1	mg/cig	0.3
Nicotine	0.72	mg/cig	0.02
Carbon Monoxide	10.5	mg/cig	0.2
Benzo [a] Pyrene	9.7	ng/cig	0.2
Carbonyls			
Formaldehyde	17.7	µg/cig	1.5
Acetaldehyde	473.8	µg/cig	11.2
Acetone	*167.3*	*µg/cig*	*3.2*
Acrolein	43.6	µg/cig	1.9
Propionaldehyde	34.7	µg/cig	0.7
Crotonaldehdye	8.9	µg/cig	0.5
Methyl Ethyl Ketone	35.7	µg/cig	1.1
Butyraldehyde	26.2	µg/cig	1.4
Phenols			
Hydroquinone	37.9	µg/cig	1.6
Resorcinol	3.2	µg/cig	0.1
Catechol	40.8	µg/cig	0.6
Phenol	10.6	µg/cig	0.2
meta & para-Cresol	7.0	µg/cig	0.2
orto-Cresol	2.8	µg/cig	0.2
Ammonia	9.9	µg/cig	2.0
Hydrogen Cyanide	137.0	µg/cig	1.7
Semi-volatile bases			
Pyridine	12.6	µg/cig	1.7
Quinoline	*0.16*	*µg/cig*	*0.02*
Miscellaneous Organics			
1,3 Butadiene	41.9	µg/cig	1.3
Isoprene	315.0	µg/cig	18.9
Acrylonitrile	7.5	µg/cig	0.2
Benzene	37.3	µg/cig	1.6
Toluene	53.2	µg/cig	5.5
Styrene	14.6	µg/cig	0.4
Nitrosamines			
N-Nitrosonornicotine NNN	102.8	ng/cig	2.3
N-Nitrosoanatabine NAT	98.9	ng/cig	3.8
N-Nitrosoanabasine NAB	8.4	ng/cig	1.4
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK	93.1	ng/cig	4.1
Aromatic Amines			
3-Aminobiphenyl	0.99	ng/cig	0.07
4-Aminobiphenyl	0.69	ng/cig	0.11
1-Aminonaphthalene	11.17	ng/cig	0.42
2-Aminonaphthalene	2.97	ng/cig	0.40
NOx Nitric Oxide	155.1	µg/cig	5.7
pH	6.47	pH units	0.02
Metals			
Beryllium	< 2	ng/cig	
Cobalt	< 2	ng/cig	
Nickel	< 10	ng/cig	
Lead	*14.3*	*ng/cig*	*0.3*
Selenium	< 2	ng/cig	
Cadmium	36.7	ng/cig	1.4
Chromium	< 10	ng/cig	
Arsenic	3.1	ng/cig	0.1
Menthol	Not Detected	mg/cig	

Approved by:

(b) (6)

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Customer:

Dr Michael Moynihan
22nd Century Limited LLC
8201 Main Street
Suite 6 Williamsville
New York
USA 14221

Sample Received: 14 March 2011

Date Testing Commenced: 16 March 2011

Date Reported: 01 April 2011

Samples Received: Camel Blue Box King

Testing Requirements: One thousand cigarettes in branded packets were submitted to the Scientific Services Laboratory of the Filtrona Technology Centre for testing for mainstream smoke yields.

Test Procedures: All tests have been carried out in accordance with documented in house test methods based on ISO standard methods when available. The reported data is only applicable to the sample received.

Results: The results are given on the page attached

Approved by:

(b) (6)

Laboratory Manager
Filtrona Technology Centre

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Mainstream Smoke Components			
Date	**01/04/2011**		
Brand	**Camel Blue Box King**		
Bar Code	**FSC 01230739**		
Component	**Yield Mean**		**Yield SD**
Tar	10.8	mg/cig	0.9
Nicotine	0.80	mg/cig	0.05
Carbon Monoxide	12.5	mg/cig	0.8
Benzo [a] Pyrene	6.7	ng/cig	0.7
Carbonyls			
Formaldehyde	19.3	µg/cig	2.5
Acetaldehyde	563.4	µg/cig	13.3
Acetone	*201.8*	*µg/cig*	*5.1*
Acrolein	48.9	µg/cig	4.3
Propionaldehyde	42.4	µg/cig	0.9
Crotonaldehdye	16.4	µg/cig	1.1
Methyl Ethyl Ketone	45.1	µg/cig	2.7
Butyraldehyde	30.3	µg/cig	0.3
Phenols			
Hydroquinone	38.5	µg/cig	3.1
Resorcinol	3.5	µg/cig	0.2
Catechol	41.3	µg/cig	2.2
Phenol	8.8	µg/cig	0.5
meta & para-Cresol	6.1	µg/cig	0.4
orto-Cresol	2.3	µg/cig	0.2
Ammonia	9.5	µg/cig	0.3
Hydrogen Cyanide	157.7	µg/cig	11.9
Semi-volatile bases			
Pyridine	11.5	µg/cig	1.6
Quinoline	*0.11*	*µg/cig*	*0.01*
Miscellaneous Organics			
1,3 Butadiene	46.9	µg/cig	1.5
Isoprene	400.3	µg/cig	7.9
Acrylonitrile	9.3	µg/cig	0.1
Benzene	45.7	µg/cig	4.0
Toluene	72.3	µg/cig	5.3
Styrene	16.9	µg/cig	0.9
Nitrosamines			
N-Nitrosonomicotine NNN	72.3	ng/cig	2.8
N-Nitrosoanatabine NAT	77.6	ng/cig	0.4
N-Nitrosoanabasine NAB	7.6	ng/cig	0.4
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK	66.8	ng/cig	2.1
Aromatic Amines			
3-Aminobiphenyl	0.91	ng/cig	0.01
4-Aminobiphenyl	0.55	ng/cig	0.08
1-Aminonaphthalene	9.85	ng/cig	0.37
2-Aminonaphthalene	2.70	ng/cig	0.24
NOx Nitric Oxide	156.0	µg/cig	5.4
pH	6.49	pH units	0.03
Metals			
Beryllium	< 2	ng/cig	
Cobalt	< 2	ng/cig	
Nickel	< 10	ng/cig	
Lead	*14.3*	*ng/cig*	*0.7*
Selenium	< 2	ng/cig	
Cadmium	40.8	ng/cig	1.4
Chromium	< 10	ng/cig	
Arsenic	2.8	ng/cig	0.3
Menthol	Not Detected	mg/cig	

Approved by:

(b) (6)

Filtrona Technology Centre

Filtrona Technology Centre, Shaftesbury Avenue, Jarrow, Tyne & Wear NE32 3UP

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TEST REPORT

THE DETERMINATION OF SELECTED ANALYTES IN MAINSTREAM SMOKE UNDER ISO SMOKING CONDITIONS

Prepared for:

Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
United States

May 19, 2011

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I. STUDY OVERVIEW

The objective of this study was to determine the deliveries of selected smoke constituents in mainstream cigarette smoke under ISO smoking conditions.

Test cigarettes for this study consisted of one type, which is listed in Table I.

Selected analyte groups that were determined are listed in Table II.

The laboratory control cigarette for this project was the Kentucky Reference 3R4F cigarette.

A minimum of three observations per brand were determined for mainstream smoke and one observation for physicals, as specified by the client.

The results were electronically submitted to the client on May 19, 2011.

Analytical methods and results are included in the attached appendices.

II. TESTING FACILITY

Activities were conducted at Arista Laboratories, 1941 Reymet Road Richmond, VA. 23237.

III. TEST CIGARETTES

A. Receipt, storage and conditioning of test cigarettes

- Three hundred and eighty cigarettes of each type were received on March 11, 2011.
- The brand code designations are given in Table I.
- Cigarettes were stored at ambient conditions until required for testing.
- Before smoking, cigarettes were conditioned according to Arista SOP FAC-035 Handling of Test Items.

Table I. Brand Coding and Sampling

Client Sample I.D.	Arista Brand Code	Number of Cigarettes Received
Quest 3 Menthol Lights Box	E7791	380

B. Constituent List

The analyses requested are listed in Table II. All applicable analytical methods have been fully validated. For lists of specific compounds in each analyte group, refer to the appendices.

Table II. Constituent List

Analyte Group	Arista Analytical Methods	Validation Report
Nicotine, Menthol and Water in MS by GC	AM-001R v.6.0	V-005
Semivolatiles in MS & SS by GC/MS	AM-006 v.9.0	V-004
Carbon Monoxide in MS & SS by Non-Dispersive Infrared (NDIR)	AM-007R v.4.0	V-005-2
Physical Properties	AM-009 v.7.2	N/A
Ammonia in MS & SS by HPLC	AM-011 v.7.2	V-009
Volatiles in MS & SS by GC/MS	AM-015 v.9.2	V-007
Tobacco Specific Nitrosamine (TSNA) in MS by LC/MS/MS	AM-020 v.8.1	V-013
Metals in MS by ICP/MS	AM-021 v.7.1	V-014
Phenols in MS by HPLC	AM-027 v.9.1	V-017
Nitric Oxide & Other Nitrogen Oxides (NO & NOx) in MS by Chemiluminescence	AM-029 v.6.1	V-018
Polycyclic Aromatic Amines (PAA) in MS by GC/MS	AM-030 v.11.0	V-016
Mercury in MS by Cold Vapor Atomic Absorption	AM-036 v.6.0	V-021
Polycyclic Aromatic Hydrocarbons (PAH's) in MS & SS by GC/MS	AM-044 v.4.2	V-031
Carbonyls in MS by UPLC	AM-076 v.3.1	V-072
Eugenol in MS & SS by HPLC	AM-087 v.2.2	V-042
pH in MS by pH Meter-Health Canada Method	AM-093 v.2.0	N/A
Hydrogen Cyanide in MS & SS by CFA	AM-111 v.4.1	V-063

C. Sample Generation and Records

Smoking was performed under ISO smoking conditions. The project was completed with the electronic submission of the final data set.

IV. QUALITY STATEMENT\SIGNATURES

The analytical results in the attached appendices were reviewed for consistency and evaluated for outliers where deemed necessary. All outliers were noted and repeats conducted if cause was determined. All tests were conducted in accordance with Arista Laboratories quality and technical procedures.

QA Review: _____ Date _____

(b) (6), QA Manager

Management Approval: _____ Date _____

(b) (6), PhD, Laboratory Director

APPENDIX A

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE
FOR TAR, NICOTINE AND CARBON MONOXIDE

DETERMINATION OF TAR, NICOTINE AND CARBON MONOXIDE IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The methods used for this study are detailed in Arista Analytical Method AM-001, Determination of Nicotine and Water in Smoke Condensates – Gas Chromatographic Method, and Arista Analytical Method T-007, Determination of Carbon Monoxide in Vapor Phase Cigarette Smoke.

This method applies to the measurements of nicotine and water in total particulate matter (TPM) from cigarette smoke collected on a 44mm Cambridge filter pad. The smoke condensate collected on the pad is dissolved in iso-propanol. Subsequently, an aliquot of the sample solution is analyzed by gas chromatography (GC), and the nicotine and water content of the smoke condensate is determined. Using the nicotine and water values, and the measured wet total particulate matter (WTPM), the tar content is then calculated. The resulting data is reported in milligrams per cigarette (mg/cig) for each smoke sample.

For carbon monoxide determination, the smoke is collected in gas sampling bags attached to the smoking machine. A non-dispersive infrared absorption method (NDIR) is used to measure the CO concentration in the vapor phase in percent by volume (%vol). Using the number of cigarettes, puff counts, puff volume and ambient conditions, the %CO is converted to milligrams per cigarette (mg/cig).

Mainstream TNC Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-001
Smoking Protocol: ISO
Authorized By: A[redacted]
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	CO (mg/cigt)	Water (mg/cigt)	Nicotine (mg/cigt)	Tar (mg/cigt)
Quest 3 Menthol Lights Box	500546	1	E7791	5.8	13.5	13.5	2.48	0.043	11.0
Quest 3 Menthol Lights Box	500546	2	E7791	5.5	13.4	15.5	2.16	0.045	11.2
Quest 3 Menthol Lights Box	500546	3	E7791	5.4	12.6	16.4	1.70	0.042	10.8
			Average	**5.6**	**13.1**	**15.1**	**2.11**	**0.043**	**11.0**
			sd	**0.2**	**0.512**	**1.48**	**0.388**	**0.001**	**0.183**
			%RSD	**3.5**	**3.89**	**9.78**	**18.4**	**3.23**	**1.66**
Lab Control	500546	4	3R4F	8.3	9.76	11.1	0.712	0.730	8.32
Lab Control	500546	9	3R4F	8.3	10.1	10.6	0.869	0.753	8.50
			Average	**8.3**	**9.94**	**10.8**	**0.790**	**0.742**	**8.41**
			sd	**0.0**	**0.255**	**0.375**	**0.111**	**0.017**	**0.127**
			%RSD	**0.0**	**2.56**	**3.46**	**14.1**	**2.24**	**1.51**

APPENDIX B

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE
FOR PYRIDINE, 3-VINYLPYRIDINE AND QUINOLINE

DETERMINATION OF PYRIDINE, 3-VINYLPYRIDINE AND QUINOLINE (SEMIVOLATILES) IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-006 Determination of Pyridine, 3-Vinylpyridine and Quinoline in Mainstream Smoke.

Mainstream (MS) smoke is passed through a 44-mm Cambridge filter and collected in one impinger containing 20 mL MeOH/TEA that is immersed in a dry ice / isopropyl alcohol bath. After smoking, the MS filter is weighed and transferred to an Erlenmeyer flask. The contents of the impinger are added, the internal standard (ISTD) is added, and the sample is shaken for 30 min at 200 rpm. The extract is filtered into an ALS vial and subsequently analyzed by GC/MSD.

Individual analyte concentrations are determined by the internal standard method using gas-chromatography with mass-selective detection. The concentrations of the analytes determined by the GC/MSD are reported in units of mass-to-volume (i.e., µg/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

Mainstream Semivolatiles Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: **11066**
Project Start Date: **11-Mar-11**
Arista SOP #: **AM-006**
Smoking Protocol: **ISO**
Authorized By: **A(b) (6)**
Title: **QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	Pyridine (μg/cigt)	Quinoline (μg/cigt)
Quest 3 Menthol Lights Box	600578	1	E7791	5.4	15.4	11.8	0.378
Quest 3 Menthol Lights Box	600578	2	E7791	5.5	17.1	12.4	0.394
Quest 3 Menthol Lights Box	600578	3	E7791	5.5	15.6	10.9	0.406
			Average	**5.5**	**16.0**	**11.7**	**0.393**
			sd	**0.1**	**0.9**	**0.8**	**0.014**
			% RSD	**0.9**	**5.5**	**6.5**	**3.6**
Lab Control	600578	4	3R4F	8.3	11.6	4.70	0.217

APPENDIX C

MEASUREMENT OF PHYSICAL PROPERTIES

CIGARETTE WEIGHT

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-009 – Physical Properties.

This measurement can either be performed automatically on the QTM stack or manually. The QTM automatically feeds cigarettes from a hopper and analyzes for weight, circumference, pressure drop and ventilation (VO & VC). In the manual method, conditioned cigarettes are weighed individually on a calibrated analytical balance and recorded in grams to the nearest 0.0001g. The average, standard deviation and relative standard deviation are reported for multiple observations.

CIRCUMFERENCE

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-009 – Physical Properties.
Ten cigarettes are placed into the hopper of a QTM Stack with Module QTM 3. The Module should be calibrated before use. Circumference is reported in millimeters.

TIP VENTILATION

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-009 – Physical Properties.
ISO conditioned test cigarettes are placed into the hopper of a Cerulean QTM Stack with module QTM 5U installed, with filters pointing in the direction of the hopper diagram. The cigarette measurement head contains three distensible latex-grip seals that isolate the tipping paper region and the cigarette paper region of the cigarette. Tip ventilation is defined as the air entering the cigarette through the perforated tipping as a proportion of the total flow through the cigarette. Tip ventilation is expressed as percentage i.e.:

$$\%\,\mathrm{TV} = \frac{\mathrm{QT}}{\mathrm{Q}} \times 100$$

Where: %TV = percent tip ventilation
QT = airflow through ventilation holes
Q = total airflow through the cigarette

DRAW RESISTANCE

PRINCIPLE OF METHOD

Ten previously conditioned cigarettes are placed into the hopper of a QTM Stack with module QTM 5U with filters pointing to the direction of the hopper diagram.

The QTM 5U automatically calibrates pressure drop at 17.5 ml/s. A check standard is used to verify, 1.99 mmWg for cigarettes and 803 mmWg for filter rods. Total RTD is defined as the pressure differential developed by a cigarette when air is pulled through it at the rate of 1050 mL/min.

PLUG RESISTANCE

PRINCIPLE OF METHOD

The filter is cut and removed from ten conditioned cigarettes with a razor or knife and dropped into the slot at the top of the QTM 6 unit. Plug RTD is defined as the pressure differential developed by the filter portion of a cigarette when air is pulled through it at the rate of 1050 mL/min. Values are recorded in mm H2O.

Physical Properties Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Analytical Method #: AM-009
Authorized By: A[redacted] (b)(6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	QTM Cigarette Weight (g)	Circumference (mm)	Pressure Drop "open"	Pressure Drop "closed"	Tip Ventilation	PPM 100
Quest 3 Menthol Lights Box	E7791	0.887	25.0	118	118	0.30	66.2
Quest 3 Menthol Lights Box	E7791	0.853	24.9	121	121	0.30	68.3
Quest 3 Menthol Lights Box	E7791	0.861	25.0	114	113	0.30	61.7
Quest 3 Menthol Lights Box	E7791	0.878	24.9	122	122	0.50	50.6
Quest 3 Menthol Lights Box	E7791	0.827	25.0	118	117	0.30	48.6
Quest 3 Menthol Lights Box	E7791	0.820	24.9	114	113	0.30	n/a
Quest 3 Menthol Lights Box	E7791	0.862	25.0	126	125	0.20	n/a
Quest 3 Menthol Lights Box	E7791	0.866	25.0	112	113	2.00	n/a
Quest 3 Menthol Lights Box	E7791	0.872	25.0	124	123	0.40	n/a
Quest 3 Menthol Lights Box	E7791	0.862	24.9	124	124	0.90	n/a
Quest 3 Menthol Lights Box	E7791	0.851	24.9	119	118	0.70	n/a
Quest 3 Menthol Lights Box	E7791	0.821	24.9	108	108	0.20	n/a
Quest 3 Menthol Lights Box	E7791	0.837	25.0	110	109	0.20	n/a
Quest 3 Menthol Lights Box	E7791	0.831	24.9	113	113	0.40	n/a
Quest 3 Menthol Lights Box	E7791	0.842	24.9	109	109	0.20	n/a
Quest 3 Menthol Lights Box	E7791	0.836	25.0	112	112	0.40	n/a
Quest 3 Menthol Lights Box	E7791	0.828	25.0	112	113	3.70	n/a
Quest 3 Menthol Lights Box	E7791	0.838	25.0	114	113	0.20	n/a
Quest 3 Menthol Lights Box	E7791	0.841	24.9	107	106	0.30	n/a
Quest 3 Menthol Lights Box	E7791	0.868	25.0	123	122	0.30	n/a
Totals	**Average**	**0.849**	**25.0**	**116**	**115.6**	**0.605**	**59.1**
	SD	**0.020**	**0.036**	**5.87**	**5.75**	**0.834**	**9.00**
	%RSD	**2.3**	**0.1**	**5.1**	**5.0**	**138**	**15.2**
	Count	**20**	**20**	**20**	**20**	**20**	**5**

APPENDIX D

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR AMMONIA

DETERMINATION OF AMMONIA IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical method AM-011 Determination of Ammonia in Mainstream Smoke.

For mainstream smoke collection, cigarette smoke is passed through a 44-mm Cambridge filter and collected in 2 impingers each containing 30 ml of 10 mmol Methanesulfonic acid (MSA). Immediately after smoking, the filter is transferred to a 125 ml Polymethylpentene Erlenmeyer flask along with the contents of both impingers. The flask is placed on the shaker for 30 min at 200rpm and the extract is subsequently analyzed by High Performance Liquid Chromatography, (HPLC), with conductivity detection.

The concentration of ammonia determined by ion chromatography is reported in units of mass-to-volume (i.e., µg/mL). The measured ammonia concentration, the number of cigarettes smoked, and the sample solution volume(s) are also used to calculate the total amount of ammonia on a per cigarette basis.

Mainstream Ammonia Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-011
Smoking Protocol: ISO
Authorized By: A (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	Ammonia ($\mu g\ NH_4^+$/cigt)
Quest 3 Menthol Lights Box	600556	1	E7791	5.8	13.3	37.8
Quest 3 Menthol Lights Box	600556	2	E7791	5.4	12.4	32.6
Quest 3 Menthol Lights Box	600556	3	E7791	5.3	12.5	32.9
			Average	**5.5**	**12.7**	**34.4**
			SD	**0.3**	**0.49**	**2.89**
			%RSD	**4.7**	**3.8**	**8.4**
Lab Control	600556	4	3R4F	8.3	10.6	7.79

APPENDIX E

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR VOLATILES

DETERMINATION OF VOLATILES IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-015 Determination of Volatiles in Mainstream Smoke. The term Volatiles refers to 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, and styrene.

Mainstream smoke from test cigarettes is passed through a 44-mm Cambridge filter and collected in one fritted impinger containing 20mL methanol that is immersed in a dry-ice/isopropanol bath. After smoking, the filter is weighed and transferred to the impinger. Internal standard is added, the impinger is vortexed briefly and the extract subsequently analyzed using gas chromatography with a mass selective detector (GC/MSD).

Individual volatile concentrations are determined by the internal standard method. The concentrations of the volatiles determined by the GC/MSD are reported in units of mass-to-volume (i.e., µg/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

Mainstream Volatiles Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-015
Smoking Protocol: ISO
Authorized By: S. [redacted]
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	1,3-butadiene (µg/cigt)	Isoprene (µg/cigt)	Acrylonitrile (µg/cigt)	Benzene (µg/cigt)	Toluene (µg/cigt)	Styrene (µg/cigt)
Quest 3 Menthol Lights Box	E7791	600569	1	6.00	17.8	50.8	413	22.6	55.8	102	12.9
Quest 3 Menthol Lights Box	E7791	600569	2	5.88	15.9	50.0	419	21.5	54.3	98.6	12.8
Quest 3 Menthol Lights Box	E7791	600569	3	6.00	15.3	46.0	371	20.1	51.8	91.8	11.4
			Average	**5.96**	**16.3**	**48.9**	**401**	**21.4**	**54.0**	**97.5**	**12.4**
			SD	**0.0693**	**1.33**	**2.55**	**25.7**	**1.28**	**2.02**	**5.23**	**0.799**
			%RSD	**1.16**	**8.12**	**5.21**	**6.41**	**5.99**	**3.75**	**5.37**	**6.46**
Lab Control	3R4F	600569	4	8.46	11.9	42.1	361	9.88	44.9	79.5	6.28

APPENDIX F

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE
FOR TOBACCO SPECIFIC N-NITROSAMINES

DETERMINATION OF TOBACCO SPECIFIC N-NITROSAMINES IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method T-020 Determination of Tobacco Specific N-Nitrosamines in Mainstream Smoke.

The tobacco specific n-nitrosamines (TSNAs) are quantitated from mainstream smoke collected on a 44 mm Cambridge filter as the collection media. LC-MS/MS (liquid chromatography coupled to a triple quadrupole mass spectrometer) allows for the determination of the targeted nitrosamines with minimum interference from other components in mainstream smoke. The LC-MS/MS method uses a high performance liquid chromatograph (HPLC) equipped with a C18 reversed phase column to resolve TSNAs from potential interference. Further selectivity is accomplished using a triple quadrupole mass spectrometer with electrospray ionization (ESI) and selective reaction monitoring of characteristic daughter ions. Deuterated internal standards (d-NNN, and d-NNK) are added to the buffer extraction solution and are used to correct for recovery of nitrosamines.

The concentrations of the TSNAs determined by this method are reported in units of mass-to-volume (i.e., ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are also used to calculate the total analyte mass on a per cigarette basis.

MS Smoke TSNAs Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista Method: AM-020
Smoking Regime: ISO
Authorized By: S. (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	MS TPM (mg/cig.)	NAB (ng/cig.)	NAT (ng/cig.)	NNK (ng/cig.)	NNN (ng/cig.)
Quest 3 Menthol Lights Box	E7791	500545	2	5.52	13.2	1.22	7.84	13.4	85.4
Quest 3 Menthol Lights Box	E7791	500545	3	5.82	13.3	<LOQ	7.77	12.7	78.5
Quest 3 Menthol Lights Box	E7791	500545	4	5.56	13.9	1.43	7.16	10.2	83.8
			Average	**5.63**	**13.4**	**1.33**	**7.59**	**12.1**	**82.6**
			SD	**0.16**	**0.39**	**0.15**	**0.37**	**1.69**	**3.65**
			%RSD	**2.89**	**2.90**	**11.3**	**4.92**	**13.9**	**4.42**
Lab Control	3R4F	500545	5	8.22	10.1	15.4	120	99.6	111
Limit of Quantitation (ng/mL)						***0.195***			
Approximate Limit of Quantitation (ng/cig.)						***0.780***			

APPENDIX G

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR SELECTED TRACE ELEMENTS

THE DETERMINATION OF SELECTED METALS IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The methods used for this study is detailed in Arista Analytical Method AM-021 - The Determination of Selected Metals in Mainstream Cigarette Smoke and Arista Analytical Method AM-036 - The Determination of Mercury in Mainstream Cigarette Smoke.

The Determination of Arsenic, Cadmium, Chromium, Lead, Nickel and Selenium in Mainstream Cigarette Smoke.

Smoking is performed on a Borgwaldt RM 20 CSR analytical smoking machine equipped with an electrostatic precipitation (EP) unit. A quartz EP tube is used in the EP unit for smoke collection. The smoke condensate is rinsed out of the EP tube, using methanol. Next, the methanol is evaporated and the sample is digested using nitric acid, hydrogen peroxide and heat. The digested samples are subsequently analyzed by ICP-MS. The ICP-MS used in the method is a Perkin Elmer ICP-MS equipped with a dynamic reaction cell that allows for the determination of elements, including Chromium and Selenium, which normally suffer from severe polyatomic interferences. Ammonia and methane are used as the reaction cell gas for chromium and selenium, respectively. Samples are introduced by nebulization into a radio frequency plasma where energy transfer processes cause desolvation, atomization, and ionization. The ions are extracted from the plasma through a differentially pumped vacuum interface and detected on the basis of their mass to charge ratio by a quadrupole mass spectrometer. The ions transmitted through the quadrupole are detected by an electron multiplier and the ELAN software processes the ion information. Instrumental drift is corrected for by the use of indium and gallium as internal standards, which are added online.

The metals are reported in units of mass-to-volume (ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are also used to calculate the total analyte mass on a per cigarette basis. The measured concentration of the metals and the number of cigarettes smoked are used to calculate the concentration of each element in units of nanograms per cigarette (ng/cigt).

The Determination of Mercury in Mainstream Cigarette Smoke.

Smoking is performed on a Borgwaldt RM 20 CSR. Particulate phase and gas phase mercury in mainstream smoke is trapped using two impingers connected in-series, each containing an acidic potassium permanganate solution. The impinger solutions containing the smoke are subjected to a microwave digestion in which mercury compounds (organic and inorganic) are oxidized to Hg^{+2}. Mercury ions (Hg^{+2}) in the digestate are reduced by stannous chloride to elemental mercury and analyzed by cold vapor atomic absorption spectrometry.

Mercury is reported in units of mass-to-volume (ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass in units of nanograms per cigarette (ng/cigt).

Mainstream Metals Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-021
Smoking Protocol: ISO
Authorized By: A[redacted]
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run Number	Ports	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	Arsenic (ng/cigt)	Cadmium (ng/cigt)	Chromium (ng/cigt)	Lead (ng/cigt)	Nickel (ng/cigt)	Selenium (ng/cigt)
Quest 3 Menthol Lights Box	2011D0004	C	E7791	5.8	11.8	3.28	76.6	0.514	19.2	1.31	5.63
Quest 3 Menthol Lights Box	2011D0004	D	E7791	5.9	11.6	3.16	77.1	0.787	17.6	1.47	5.29
Quest 3 Menthol Lights Box	2011D0004	E	E7791	5.9	11.4	3.13	72.9	0.803	17.5	1.34	5.51
			Average	**5.9**	**11.6**	**3.19**	**75.5**	**0.701**	**18.1**	**1.4**	**5.5**
			sd	**0.1**	**0.17**	**0.08**	**2.25**	**0.162**	**0.98**	**0.08**	**0.17**
			%RSD	**1.0**	**1.5**	**2.4**	**3.0**	**23.2**	**5.4**	**6.1**	**3.2**
Lab Control	2011D0004	B	3R4F	8.8	9.77	2.89	33.5	<LOQ	10.7	0.846	2.26
Lab Control	2011D0004	F	3R4F	8.8	9.74	2.56	33.3	<LOQ	10.0	0.710	1.99
			Average	**8.8**	**9.75**	**2.73**	**33.4**	**<LOQ**	**10.4**	**0.778**	**2.12**
			sd	**0.00**	**0.02**	**0.23**	**0.14**	**NA**	**0.53**	**0.10**	**0.19**
			%RSD	**0.0**	**0.2**	**8.6**	**0.4**	**NA**	**5.1**	**12.4**	**8.8**
Aproximate Limit of Quantitation (ng/cigt)						***0.51***	***0.49***	***0.51***	***0.58***	***0.52***	***0.50***

Mainstream Mercury Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-036
Smoking Protocol: ISO
Authorized By: S (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM	Mercury (ng/cigt)
Quest 3 Menthol Lights Box	2011D0004	C	E7791	5.8	11.8	3.3
Quest 3 Menthol Lights Box	2011D0004	D	E7791	5.9	11.6	3.0
Quest 3 Menthol Lights Box	2011D0004	E	E7791	5.9	11.4	3.1
			Average	**5.9**	**11.60**	**3.12**
			SD	**0.1**	**0.17**	**0.17**
			%RSD	**1.0**	**1.5**	**5.4**
Lab Control	2011D0004	B	3R4F	8.8	9.8	2.2
Lab Control	2011D0004	F	3R4F	8.8	9.7	2.0
			Average	**8.8**	**9.75**	**2.08**
			SD	**0.0**	**0.02**	**0.14**
			%RSD	**0.0**	**0.2**	**6.5**

APPENDIX H

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR PHENOLICS

DETERMINATION OF PHENOLIC COMPOUNDS IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-027, Determination of Phenolic Compounds in Mainstream Smoke. Phenolics refers to hydroquinone, resorcinol, catechol, phenol, o-cresol and m+p-cresol.

Phenolics in mainstream tobacco smoke are collected on a 44 mm Cambridge filter pad. The pad is extracted with 20 mL of aqueous acetic acid, and the solution is diluted to a known volume. Before analysis by High Performance Liquid Chromatography (HPLC), the solution is filtered. An HPLC equipped with a reversed-phase column and a fluorescence detector is used for the analysis. This system utilizes an increasing methanol fraction in a methanol:water gradient to elute potentially interfering compounds, and the analytes from the column, at different times. All phenolics are well separated except m-cresol and p-cresol, which coelute. Therefore, only one value is reported for m+p-cresol. The eluted compounds are detected with a fluorescence detector. Hydroquinone is detected with an excitation wavelength of 304 nm and emission wavelength of 338 nm. The other compounds are detected with an excitation wavelength of 274 nm and emission wavelength of 298 nm.

The concentrations of phenolic compounds determined by HPLC are reported in units of mass-to-volume (i.e., µg/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are also used to calculate the total mass of phenolics on a per cigarette basis.

MS Smoke Phenols Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista Method: AM-027
Smoking Regime: ISO
Authorized By: A[redacted]
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	MS TPM (mg/cig.)	Hydroquinone (µg/cig.)	Resorcinol (µg/cig.)	Catechol (µg/cig.)	Phenol (µg/cig.)	m- + p-Cresol (µg/cig.)	o-Cresol (µg/cig.)
Quest 3 Menthol Lights Box	E7791	600561	2.00	5.38	13.3	22.6	0.67	26.9	16.5	14.7	4.54
Quest 3 Menthol Lights Box	E7791	600561	3.00	5.36	11.4	21.3	0.58	23.7	13.8	12.4	3.81
Quest 3 Menthol Lights Box	E7791	600561	4.00	5.26	11.6	21.0	0.59	24.3	14.3	12.6	3.98
			Average	**5.33**	**12.1**	**21.6**	**0.61**	**25.0**	**14.9**	**13.2**	**4.11**
			SD	**0.06**	**1.04**	**0.83**	**0.05**	**1.73**	**1.44**	**1.27**	**0.38**
			%RSD	**1.21**	**8.60**	**3.84**	**8.13**	**6.93**	**9.71**	**9.57**	**9.24**
Lab Control	3R4F	600561	5.00	8.18	10.2	31.7	0.69	36.8	7.26	6.27	2.20
Lab Control	3R4F	600561	12.0	8.24	10.4	33.1	0.71	38.0	7.74	6.52	2.36
			Average	**8.21**	**10.3**	**32.4**	**0.70**	**37.4**	**7.50**	**6.40**	**2.28**
			SD	**0.04**	**0.16**	**0.96**	**0.02**	**0.83**	**0.34**	**0.18**	**0.11**
			%RSD	**0.52**	**1.51**	**2.97**	**2.66**	**2.21**	**4.52**	**2.75**	**4.89**

APPENDIX I

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR NITRIC OXIDE **(NO)**

THE DETERMINATION OF NITRIC OXIDE IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-029 - The Determination of Nitric Oxide in Mainstream Cigarette Smoke.

The mainstream smoke from one cigarette is collected puff by puff into a mixing chamber attached to an analytical smoking machine. Once the smoke is collected in the mixing chamber a valve is switched to allow the sample to enter the analyzer. A highly sensitive and selective chemiluminescent gas analyzer measures the chemiluminescence of the smoke sample after the completion of each puff. The concentration of NO is proportional to the intensity of the chemiluminescent reaction. Results are generated from puff by puff sample measurements and reported as parts per million and then corrected to STP (standard temperature and pressure) and finally converted to μg NO per cigarette.

Mainstream Nitric Oxide Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-029
Smoking Protocol: MS
Authorized By: S (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Set #	Run #	Puffs (/cigt)	MS TPM (mg/cigt)	NO (μg/cigt)	NOx (μg/cigt)
Quest 3 Menthol Lights Box	E7791	500548	3	5.70	15.7	312	539
Quest 3 Menthol Lights Box	E7791	500548	4	6.00	14.6	315	601
Quest 3 Menthol Lights Box	E7791	500548	5	6.00	11.7	276	558
			Average	**5.90**	**14.0**	**301**	**566**
			SD	**0.173**	**2.07**	**22.0**	**31.9**
			%RSD	**2.94**	**14.8**	**7.29**	**5.64**
Lab Control	3R4F	500548	2	9.00	11.9	247	330
Lab Control	3R4F	500548	10	8.80	10.8	232	361
			Average	**8.90**	**11.4**	**239**	**346**
			SD	**0.141**	**0.778**	**10.2**	**22.0**
			%RSD	**1.59**	**6.85**	**4.27**	**6.37**

APPENDIX J

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE
FOR POLYCYCLIC AROMATIC AMINES (PAA)

THE DETERMINATION OF 1-NAPHTHYLAMINE, 2-NAPHTHYLAMINE, 3-AMINOBIPHENYL AND 4-AMINOBIPHENYL (PAAS) IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-030 Determination of 1-naphthylamine, 2-naphthylamine, 3-aminobiphenyl and 4-aminobiphenyl (PAAs) in mainstream smoke.

Mainstream (MS) smoke from test cigarettes is passed through a 44-mm Cambridge filter. After smoking, the filter is weighed and transferred to a Polymethylpentene Erlenmeyer flask containing 25 mL of 5% HCl. Internal standard is added and the sample is shaken for 30 min on a wrist action shaker. The extract is filtered into a separatory funnel and extracted with dichloromethane. The dichloromethane is disposed of as chlorinated waste and sodium hydroxide (50% solution in water) is added to the aqueous phase to make the sample basic. The contents are extracted three times with dichloromethane. The combined dichloromethane extract is derivatized with pentafluoropropionic acid anhydride (PFPA), passed through a Florisil Cartridge clean-up step and concentrated to approximately 2 mL.

Individual analyte concentrations are determined by the internal standard method using gas-chromatography followed by negative chemical ionization with Selected Ion Monitoring (SIM) detection. The concentrations of the analytes, determined by the GC/MSD are reported in units of mass-to-volume (i.e., ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

Mainstream Aromatic Amines Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-030
Smoking Protocol: ISO
Authorized By: S. (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	1-Naphthyl Amine (ng/cigt)	2-Naphthyl Amine (ng/cigt)	3-Amino Biphenyl (ng/cigt)	4-Amino Biphenyl (ng/cigt)
Quest 3 Menthol Lights Box	E7791	500544	2	5.64	13.8	11.6	6.87	2.53	1.70
Quest 3 Menthol Lights Box	E7791	500544	3	5.32	11.3	12.8	7.94	2.95	1.99
Quest 3 Menthol Lights Box	E7791	500544	4	5.12	12.3	12.6	7.49	2.62	1.86
			Average	**5.36**	**12.5**	**12.3**	**7.43**	**2.70**	**1.85**
			SD	**0.262**	**1.23**	**0.675**	**0.541**	**0.222**	**0.143**
			% RSD	**4.89**	**9.84**	**5.48**	**7.27**	**8.22**	**7.75**
Lab Control	3R4F	500544	5	8.00	10.1	9.49	6.29	1.68	1.10

APPENDIX K

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR BENZO**[a]**PYRENE **(BaP)**

DETERMINATION OF BENZO[a]PYRENE IN MAINSTREAM SMOKE

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-044 Determination of Selected Polynuclear Aromatic Hydrocarbons (PAHs) in Mainstream Smoke.

Mainstream (MS) smoke from test cigarettes is passed through a 44-mm Cambridge filter. After smoking, the MS filter is weighed and transferred to an amber bottle, then 20 mL of MEOH and internal standard are added and the sample is shaken for 30min. Type-1 water is added and the solution is passed through a C-18 SPE cartridge that has been rinsed with 30% MeOH in Type 1 water. The eluent is discarded and toluene is added to the SPE cartridge for extraction of the B[a]P fraction using vacuum. The toluene extract from the C-18 cartridge is then poured through a Silica Si-1 SPE cartridge and collected in a disposable 15mL culture tube. The sample is transferred to an autosampler vial and diluted 1:1 with acetone for analysis by GC/MSD.

Individual analyte concentrations are determined by the internal standard method using gas chromatography with a DB-17ms column for chromatographic separation of the analytes and selected ion monitoring (SIM) after electron impact ionization. The concentrations of the analytes, determined by the GC/MSD are reported in units of mass-to-volume (i.e., ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

Mainstream B[a]P Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-044
Smoking Protocol: ISO
Authorized By: S. (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	B[a]P (ng/cigt)
Quest 3 Menthol Lights Box	E7791	600549	2	5.98	14.0	5.31
Quest 3 Menthol Lights Box	E7791	600549	3	5.80	13.4	5.76
Quest 3 Menthol Lights Box	E7791	600549	4	5.72	13.1	5.77
			Average	**5.83**	**13.5**	**5.61**
			SD	**0.133**	**0.458**	**0.263**
			%RSD	**2.28**	**3.39**	**4.69**
Lab Control	3R4F	600549	5	8.42	10.6	5.58

APPENDIX L

DETERMINATION OF CARBONYLS IN MAINSTREAM CIGARETTE SMOKE BY UHPLC USING UV DETECTION

DETERMINATION OF CARBONYLS IN MAINSTREAM SMOKE BY UHPLC

I. PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-076 Determination of Carbonyls and Aldehydes in Mainstream Smoke.

Mainstream smoke is collected in two impingers containing acidified 2,4-dinitrophenylhydrazine (DNPH) solution. After smoking, the combined solution from the impingers containing the derivatized carbonyls is stabilized by adding pyridine and subsequently analyzed by UHPLC. Individual carbonyl concentrations are determined by an external standard method using UV detection. Note that for this method, the term carbonyls refers to the following compounds: formaldehyde, acetaldehyde, acrolein, acetone, propionaldehyde, crotonaldehyde, butyraldehyde & methylethylketone.

A UHPLC (Ultra High Pressure Liquid Chromatograph) equipped with a reversed phase column and a fixed wavelength UV detector is used for the analysis of the samples. A gradient is used to separate interfering compounds from the analytes of interest. The eluting compounds are detected on the basis of their absorbance at 355 nm. The detector's responses of the hydrazone derivatives of the carbonyls are calibrated against standard solutions of known concentration to form a linear calibration curve.

The concentrations of the carbonyls determined by UHPLC are reported in units of mass-to-volume (i.e., µg/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are also used to calculate the total analyte mass on a per cigarette basis.

MS Smoke Carbonyls Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista Method: AM-076
Smoking Regime: ISO
Authorized By: A[redacted]
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	Formaldehyde (µg/cig.)	Acetaldehyde (µg/cig.)	Acetone (µg/cig.)	Acrolein (µg/cig.)	Propionaldehyde (µg/cig.)	Crotonaldehyde (µg/cig.)	Methylethylketone (µg/cig.)	Butyraldehyde (µg/cig.)
Quest 3 Menthol Lights Box	E7791	600548	1	6.00	11.8	763	353	51.5	57.1	18.8	90.9	34.4
Quest 3 Menthol Lights Box	E7791	600548	2	6.20	11.9	798	377	52.8	58.8	19.1	95.0	34.1
Quest 3 Menthol Lights Box	E7791	600548	3	6.00	11.5	796	369	55.5	59.1	18.9	93.3	34.7
			Average	**6.07**	**11.8**	**786**	**366**	**53.3**	**58.3**	**18.9**	**93.1**	**34.4**
			SD	**0.12**	**0.24**	**19.5**	**12.3**	**2.08**	**1.06**	**0.14**	**2.04**	**0.30**
			%RSD	**1.90**	**2.01**	**2.48**	**3.35**	**3.90**	**1.82**	**0.72**	**2.19**	**0.87**
Lab Control	3R4F	600548	4	8.80	14.7	758	340	55.6	59.2	14.0	95.7	31.0

APPENDIX M

DETERMINATION OF EUGENOL IN MAINSTREAM AND SIDESTREAM SMOKE

EUGENOL IN MAINSTREAM AND SIDESTREAM SMOKE

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-087 Determination of Eugenol in Mainstream and Sidestream Smoke.

Eugenol is quantitated in mainstream and sidestream smoke from unconditioned cigarettes.

The mainstream smoke is collected on a 44mm Cambridge filter pad. After smoking, the pad is placed into an Erlenmeyer flask and extracted with 50mL of extraction solution. The flask is shaken for 30 minutes using an orbital shaker set at ~200 rpm. The extract is then filtered through a 0.45-µm filter directly into an ALS vial and then analyzed by HPLC with UV detection. The eugenol concentration in mainstream smoke is determined by an external standard calibration and reported in µg/cigarette.

The sidestream smoke is collected on a 44mm Cambridge filter, which is followed by an impinger filled with 30mL of the trapping solution to collect the analytes not retained by the filter pad. The 44-mm Cambridge filter pad in a holder is connected directly to an out-port of a fishtail chimney. The impinger is placed in an ice-bath in which the temperature is maintained between 0-3 °C. A flow rate of 3.0 liters per minute is maintained during smoking. After smoking, the pad and the trapping solution from the impinger are combined into an Erlenmeyer flask. The fishtail chimney is rinsed with 50mL of the extraction solution and the rinse is added into the flask. The flask is shaken for 30 minutes using an orbital shaker set at ~200 rpm. The extract is then filtered through a 0.45-µm filter directly into an ALS vial and then analyzed by HPLC with UV detection. The eugenol concentration in sidestream smoke is determined by an external standard calibration and reported in µg/cigarette.

MS Smoke Eugenol Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista Method: AM-087
Smoking Regime: ISO
Authorized By: A (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	MS TPM (mg/cig.)	Eugenol (µg/cig.)
Quest 3 Menthol Lights Box	E7791	301970	2	4.83	12.7	<LOQ
Quest 3 Menthol Lights Box	E7791	301970	3	5.40	12.5	<LOQ
Quest 3 Menthol Lights Box	E7791	301970	4	5.07	12.8	<LOQ
			Average	**5.10**	**12.6**	**NA**
			SD	**0.28**	**0.16**	**<LOQ**
			%RSD	**5.58**	**1.25**	**<LOQ**
						% Recovery
Lab Control	3R4F Recovery	301970	5	7.40	9.37	102
Limit of Quantitation (µg/mL)						***6.17***
Approximate Limit of Quantitation (µg/cig)						***103***

APPENDIX N

DETERMINATION OF pH IN MAINSTREAM CIGARETTE SMOKE BY THE HEALTH CANADA OFFICIAL

DETERMINATION OF PH OF MAINSTREAM SMOKE

PRINCIPLE OF METHOD

The method used for this study is detailed in Arista Analytical Method AM-093 - The Determination of pH in Mainstream Smoke – Health Canada Official Method T-113.

The mainstream smoke from cigarettes is collected on a puff-by-puff basis. Using a modified pH electrode, the acid-base effect of both the condensate and gas phase is monitored and recorded. Data is directly transferred from the pH meter to an Excel spreadsheet at a fixed print interval. An average pH of the smoke is determined by averaging all of the data points transferred.

Mainstream pH Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-093
Smoking Protocol: MS
Authorized By: S. (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Set #	Run #	pH Meter	Puffs/Cigt	pH
Quest 3 Menthol Lights Box	E7791	502091	3	1	6.00	6.11
Quest 3 Menthol Lights Box	E7791	502091	4	1	6.00	6.05
Quest 3 Menthol Lights Box	E7791	502091	5	1	6.00	6.01
				Average	**6.00**	**6.06**
				SD	**0.00**	**0.0466**
				%RSD	**0.00**	**0.770**
3R4F	3R4F	502091	2	1	8.00	6.11
3R4F	3R4F	502091	6	1	8.00	6.08
				Average	**8.00**	**6.10**
				SD	**0.00**	**0.0232**
				%RSD	**0.00**	**0.381**

APPENDIX O

ANALYSIS OF MAINSTREAM CIGARETTE SMOKE
FOR HYDROGEN CYANIDE (HCN)

DETERMINATION OF HYDROGEN CYANIDE IN MAINSTREAM SMOKE

I. PRINCIPLE OF METHOD

The a method used for this study is detailed in Arista Analytical Method AM-111 Hydrogen Cyanide in Mainstream and Sidestream Smoke by Continuous Flow Analyzer.

HCN is determined from mainstream smoke collected on a Cambridge filter followed by one non-fritted impinger containing 0.1M aqueous sodium hydroxide as the collection media. The Cambridge filter pad is extracted into 0.1M aqueous sodium hydroxide and analyzed separately from the impinger solution. A continuous flow analyzer is used to add the required reagents to a sample of the pad extract and the impinger trapping solutions. Hydrogen cyanide in the sample is converted to cyanogen chloride by the addition of an aqueous solution of chloramine-T. The cyanogen chloride then reacts with pyridine and barbituric acid to produce a reddish-violet color complex that is measured photometrically at 570nm. The Beer-Lambert Law linearly relates formation of the colored complex to concentration.

The concentration of HCN is reported in units of mass-to-volume (i.e., µg/mL). The measured HCN concentration, the number of cigarettes smoked, and the sample solution volumes are used to calculate the total mass of HCN on a per cigarette basis.

Mainstream HCN Test Report for:
Goodrich Tobacco Company
8201 Main Street
Suite 6
Williamsville, NY 14221
Q11066R3

Project Code: 11066
Project Start Date: 11-Mar-11
Arista SOP #: AM-111
Smoking Protocol: ISO
Authorized By: S. (b) (6)
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	Impinger HCN (µg/cigt)	Pad HCN (µg/cigt)	Total HCN (µg/cigt)
Quest 3 Menthol Lights Box	E7791	600550	1	5.53	13.3	202	86.7	289
Quest 3 Menthol Lights Box	E7791	600550	2	5.77	16.0	211	102.3	313
Quest 3 Menthol Lights Box	E7791	600550	3	5.67	14.6	221	98.5	320
			Average	**5.66**	**14.6**	**211**	**95.8**	**307**
			SD	**0.117**	**1.32**	**9.53**	**8.12**	**16.1**
			%RSD	**2.07**	**9.01**	**4.51**	**8.47**	**5.26**
Lab Control	3R4F	600550	4	8.67	11.0	73.1	46.8	120

Reference #15

United States General Accounting Office (GAO). 2003. Pesticides on tobacco: Federal activities to assess risks and monitor residues. GAO-03-485.

The full report is available online at:

http://www.gao.gov/new.items/d03485.pdf.

DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

[Docket No. 01–060–2]

Vector Tobacco; Availability of Determination of Nonregulated Status for Tobacco Genetically Engineered for Reduced Nicotine

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Notice.

SUMMARY: We are advising the public of our determination that the Vector Tobacco (USA) Ltd. tobacco designated as Vector 21–41, which has been genetically engineered for reduced nicotine, is no longer considered a regulated article under our regulations governing the introduction of certain genetically engineered organisms and products. Our determination is based on our evaluation of data submitted by Vector Tobacco (USA) Ltd. in its petition for a determination of nonregulated status, our analysis of other scientific data, and comments received from the public in response to a previous notice. This notice also announces the availability of our written determination document and our finding of no significant impact.

EFFECTIVE DATE: September 16, 2002.

ADDRESSES: You may read a copy of the determination, an environmental assessment and finding of no significant impact, the petition for a determination of nonregulated status submitted by Vector Tobacco (USA) Ltd., and all comments received on the petition and the environmental assessment in our reading room. The reading room is located in room 1141 of the USDA South Building, 14th Street and Independence Avenue SW., Washington, DC. Normal reading room hours are 8 a.m. to 4:30 p.m., Monday through Friday, except holidays. To be sure someone is there to help you, please call (202) 690–2817 before coming.

APHIS documents published in the **Federal Register**, and related information, including the names of organizations and individuals who have commented on APHIS dockets, are available on the Internet at *http://www.aphis.usda.gov/ppd/rad/webrepor.html*.

FOR FURTHER INFORMATION CONTACT: Dr. Susan Koehler, Biotechnology Regulatory Services, Suite 5B05, 4700 River Road Unit 147, Riverdale, MD 20737–1236; (301) 734–4886. To obtain a copy of the determination or the environmental assessment and finding of no significant impact, contact Ms. Kay Peterson at (301) 734–4885; e-mail: *Kay.Peterson@aphis.usda.gov*.

SUPPLEMENTARY INFORMATION:

Background

On May 1, 2001, the Animal and Plant Health Inspection (APHIS) received a petition (APHIS Petition No. 01–121–01p) from Vector Tobacco (USA) Ltd. (Vector) of Durham, NC, requesting a determination of nonregulated status under 7 CFR part 340 for tobacco (*Nicotiana tabacum* L.) designated as Vector 21–41, which has been genetically engineered to produce a very low level of nicotine. The Vector petition states that the subject tobacco should not be regulated by APHIS because it does not present a plant pest risk.

On February 12, 2002, APHIS published a notice in the **Federal Register** (67 FR 6480–6481, Docket No. 01–060–1) announcing that the Vector petition was available for public review. In the notice, APHIS solicited comments from the public on whether this tobacco presents a plant pest risk. APHIS also made available for public comment an environmental assessment for the proposed determination of nonregulated status. APHIS received 45 comments on the petition and the environmental assessment during the 60-day comment period which ended April 15, 2002. The comments were received from tobacco farmers, tobacco companies, State

farmers' organizations, State department of agriculture officials, private individuals, tobacco growers' cooperatives, tobacco marketing organizations, university cooperative extension centers, members of the U.S. Congress, a foundation seed producer, an agronomic consultant, a county chamber of commerce, and a consumer organization. Twenty-three of the comments were in favor of a determination of nonregulated status for Vector 21–41 tobacco, and 22 comments either opposed deregulation or recommended no action on the petition until certain concerns are addressed about the effects of Vector 21–41 deregulation on traditional tobacco growers and markets. A majority of commenters in favor of deregulation stressed that Vector 21–41 did not present a plant pest risk, displayed disease and insect susceptibilities and agronomic characteristics similar to conventionally bred tobacco, and noted the benefits to local economies from growing Vector 21–41. Those commenters not expressing support for deregulation of the subject tobacco at this time generally expressed the following concerns about Vector 21–41: Blue mold and insect susceptibilities, the limited number of years of field testing, the potential for gene transfer to conventional tobacco, and the potential for commingling with conventional tobacco in the absence of growing and processing guidelines. One commenter found the environmental assessment inadequate, alleging that it failed to address the impacts of Vector 21–41 on organic farmers and certain human health effects, including the impacts of an antibiotic resistance gene. We have provided a response to the comments as an attachment to our finding of no significant impact, which is available from the person listed under FOR FURTHER INFORMATION CONTACT.

Analysis

Vector 21–41 tobacco has been genetically engineered to express a quinolinic acid phosphoribosyltransferase (QPTase) in the reverse, or antisense position, which disrupts the normal expression of QPTase, a key enzyme in the biosynthetic pathway leading to the production of nicotine and related alkaloids. The effect of this genetic change is to reduce the nicotine levels of nicotine, nor-nicotine, and total alkaloids in the leaves of Vector 21–41 tobacco. The subject tobacco also contains the *nptII* marker gene derived from the bacterium *Escherichia coli*. The *nptII* gene encodes the enzyme neomycin phosphotransferase type II (NPTII) and is used as a selectable marker in the initial laboratory stages of plant cell selection. Expression of the added genes is controlled in part by gene sequences from the plant pathogen *Agrobacterium tumefaciens*. The *A. tumefaciens* method was used to transfer the added genes into the parental recipient Burley 21–LA tobacco variety.

The subject tobacco has been considered a regulated article under the regulations in 7 CFR part 340 because it contains gene sequences from a plant pathogen. Vector 21–41 tobacco has been field tested since 1999 in the United States under APHIS notifications. In the process of reviewing the notifications for field trials of this tobacco, APHIS determined that the vectors and other elements were disarmed and that the trials, which were conducted under conditions of reproductive and physical containment or isolation, would not present a risk of plant pest introduction or dissemination.

Determination

Based on its analysis of the data submitted by Vector, a review of other scientific data, field tests of the subject tobacco, and comments submitted by the public, APHIS has determined that Vector 21–41 tobacco: (1) Exhibits no plant pathogenic properties; (2) is no more likely to become a weed than tobacco developed by traditional breeding techniques; (3) is unlikely to increase the weediness potential for any other cultivated or wild species with which it can interbreed; (4) will not cause damage to raw or processed agricultural commodities; and (5) will not harm threatened or endangered species or organisms, such as bees, that are beneficial to agriculture. Therefore, APHIS has concluded that the subject tobacco and any progeny derived from hybrid crosses with other nontransformed tobacco varieties will be as safe to grow as tobacco in traditional breeding programs that is not subject to regulation under 7 CFR part 340.

The effect of this determination is that Vector's 21–41 tobacco is no longer considered a regulated article under APHIS" regulations in 7 CFR part 340. Therefore, the requirements pertaining to regulated articles under those regulations no longer apply to the subject tobacco or its progeny. However, importation of Vector 21–41 tobacco or seeds capable of propagation are still subject to the restrictions found in APHIS" foreign quarantine notices in 7 CFR part 319.

National Environmental Policy Act

An environmental assessment has been prepared to examine the potential environmental impacts associated with this determination. The environmental assessment was prepared in accordance with (1) The National Environmental Policy Act of 1969 (NEPA), as amended (42 U.S.C. 4321 *et seq.*), (2) regulations of the Council on Environmental Quality for implementing the procedural provisions of NEPA (40 CFR parts 1500–1508), (3) USDA regulations implementing NEPA (7 CFR part 1b), and (4) APHIS' NEPA Implementing Procedures (7 CFR part 372). Based on that environmental assessment, APHIS has reached a finding of no significant impact with regard to its determination that Vector 21–41 tobacco and lines developed from it are no longer regulated articles under its regulations in 7 CFR part 340. Copies of the petition and the environmental assessment and finding of no significant impact are available upon request from the individual listed under the FOR FURTHER INFORMATION CONTACT section of this notice.

Done in Washington, DC, this 26th day of November 2002 .

Peter Fernandez,

Acting Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 02–30518 Filed 12–2–02; 8:45 am]

BILLING CODE 3410–34–P

Approval of Vector Tobacco (USA) Ltd. Petition (01-121-01p) Seeking a Determination of Non-regulated Status for Reduced-nicotine Tobacco Line Vector 21-41

Environmental Assessment and
Finding of No Significant Impact

September 2002

The Animal and Plant Health Inspection Service (APHIS), United States Department of Agriculture (USDA) has prepared an environmental assessment (EA) prior to approving a petition (APHIS number 01-121-01p) for a determination of nonregulated status received from Vector Tobacco (USA) Ltd. under APHIS regulations at 7 CFR Part 340. The subject of this petition, tobacco line Vector 21-41, is genetically engineered for reduced nicotine content by the insertion of an anti-sense version of the coding region of a tobacco gene encoding the enzyme quinolinic acid phosphoribosyltransferase, a key enzyme in the biosynthetic pathway for the synthesis of nicotine and related alkaloids. It is also genetically engineered to express a selectable marker, the enzyme neomycin phosphotransferase which confers antibiotic resistance. On February 12, 2002, APHIS published a notice in the Federal Register (67 FR 6480-6481, Docket no. 01-060-1) announcing the availability of the petition and EA for public review and comment. During the designated 60 day comment period, APHIS received 45 comments. APHIS' analysis of and response to these comments is included as an attachment to this finding. Based on the analysis in the EA and in our response to the comments, APHIS has reached a finding of no significant impact (FONSI) to the environment from its determination that tobacco line Vector 21-41, and progeny derived from it, shall no longer be considered regulated articles. This determination is attached to the EA as Appendix D.

Cindy Smith
Acting Deputy Administrator
Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture
Date: SEP 16 2002

APHIS' Analysis and Response to Comments Received on Petition 01-121-01p and the EA.

APHIS received 45 comments on the petition and the EA during the 60-day comment period. The comments were received from tobacco farmers, tobacco companies, State farmers' organizations, State department of agriculture officials, private individuals, tobacco growers cooperatives, tobacco marketing organizations, university cooperative extension centers, members of the U.S. Congress, a foundation seed producer, an agronomic consultant, a county chamber of commerce, and a consumer organization. The comments in favor of a determination of nonregulated status for Vector 21-41 tobacco totaled 23, and 22 comments either opposed deregulation or recommended no action on the petition until certain concerns are addressed about the effects of Vector 21-41 deregulation on traditional tobacco growers and markets. A majority of commenters in favor of deregulation stressed that Vector 21-41 did not present a plant pest risk, that it displayed disease and insect susceptibilities and agronomic characteristics similarly to conventionally bred tobacco under typical management conditions, and that there were benefits to local economies from growing Vector 21-41. Those commenters not expressing support for deregulation of the subject tobacco at this time generally expressed concerns about its susceptibility to blue mold and insects, the limited number of years of field testing, the potential for gene transfer to and commingling with conventional tobacco and the subsequent effect on export markets. One commenter found the EA inadequate, stating that it failed to address the impacts of Vector 21-41 on human health, that it inadequately addressed the impact on organic farmers, and that an Environmental Impact Statement should have been prepared. Further characterization of and response to those comments in opposition are given below.

1. Susceptibility to blue mold and insects

Several commenters expressed concern over the susceptibility of Vector 21-41 to the blue mold fungal pathogen. Some indicated that this pathogen is highly adaptable and the potential for increased incidence of this pathogen in Vector 21-41 raises concerns regarding selection pressure on populations of this pathogen in the presence of genetic modifications in the plant. However, no rationale was provided for how the genetic modification in Vector 21-41 would enhance selection pressure for the blue-mold pathogen compared to many other tobacco varieties currently grown which are also susceptible to blue mold. It was further argued that it is irrelevant that the EA states that Vector 21-41 does not have increased susceptibility to diseases or insects when compared to the parental line Burley 21-LA since the parental line is known to exhibit increased susceptibility to blue mold and insect pests.

Relevance of the comparison of insect and disease susceptibility to Burley 21-LA

In response to these comments APHIS notes that the comparison of the reported disease and insect susceptibility of Vector 21-41 to the parental line Burley 21-LA, and Burley 21 (parent of Burley 21-LA) in Section V of the EA is relevant and appropriate to the determination of plant pest risk. The regulations at 7 CFR 340.6 (c) indicate that the required data and information to be submitted to support a determination of non-regulated status includes a description of known or potential differences from the unmodified recipient organism that would substantiate that the regulated article is unlikely to pose a greater plant pest risk than the unmodified organism from

which it was derived, including disease and pest susceptibilities and agricultural or cultivation practices. The petitioner must also certify that the petition includes relevant data and information which are unfavorable to the petition. Because Burley 21-LA was not released as a commercial variety, APHIS included its parent, Burley 21 in the analysis. Burley 21 has not been grown for about 30 years, but is still used as a parent in breeding programs. APHIS also considered the availability and effectiveness of various cultural or chemical control methods to manage disease and insect pests to which Vector 21-41 tobacco is known or likely to be susceptible.

Characterization of the disease and insect susceptibility of Burley 21-LA and Burley 21
APHIS acknowledged in the EA that both Burley 21-LA and Burley 21 have low levels of disease resistance compared to newer Burley varieties and that Burley 21-LA is described as extremely susceptible to insect damage. In particular Burley 21-LA has been observed to be susceptible to blue mold as well as to two other fungal diseases: black shank (caused by *Phytophthora parasitica* var. *nicotinanae*), and black root rot (caused by *Thielaviopsis basicola)*. It is slightly more susceptible to blue mold than Burley 21. Burley 21 has no resistance to black shank, low resistance to black root rot, and high resistance to TMV and wild fire disease (Gary Palmer, Extension Tobacco Specialist, University of Kentucky (personal communication to Susan Koehler, November and December 11, 2001). Most Burley tobacco varieties today have resistance to black root rot and a few have some degree of resistance to black shank and blue mold (Gary Palmer, personal communication to Susan Koehler, and see also http://www.uky.edu/Ag/TobaccoProd/pubs/2001GuidetoBurleyVarieties.pdf). Burley 21-LA is also described as "extremely susceptible to insect damage" (Legg, et al., 1970). In particular, it is highly susceptible to grasshoppers and other leaf-feeding insects (Glenn Collins, University of Kentucky, personal communication to Susan Koehler, November, 2001). As indicated in the EA, this is not unexpected, since nicotine and some other alkaloids are known to have insecticidal activity.

Observed insect and disease susceptibility of Vector 21-41, and the ability of current agricultural practices to effectively manage pests in Vector 21-41
APHIS' analysis documented the fact that in field trials in North Carolina in 2000, both Vector 21-41 and Burley 21-LA were shown to be extremely susceptible to insect pests in the absence of systemic insecticides, but no differences in disease or insect susceptibility or leaf yield were observed between Vector 21-41 or Burley 21-LA plants that received two applications of 1 lb/acre Orthene. This insecticide treatment is one of the options recommended for control of several of the major foliar-feeding insect pests of tobacco (North Carolina State University, 2000). Topping was also conducted 60 days after transplant, prior to flowering, and suckers (leaf buds which develop in the leaf axils after topping occurs) were chemically controlled by treatment with maleic hydrazide. Early topping and good sucker control are recommended for control of budworms and hornworms, since moths of these pests are strongly attracted to flowers to lay their eggs. This practice is also reported to speed the decline of aphids, especially under hot, dry conditions (NC State Univ., 2000). Other biological and cultural control options are described.

Field tests of Vector 21-41 in Pennsylvania in 2001 indicate that it is susceptible to blue mold, a serious disease of tobacco caused by the fungus *Peronospora tabacina.* The North American Blue Mold Warning and Forecast System, a cooperative network of state coordinators, plant pathologists, and meteorologists, alerts growers about the threat of blue mold through their forecasting and tracking activities so that preventative measures can be implemented. In the petitioner's response of October 19, 2001 to APHIS' deficiency letter dated September 26, 2001, they noted that this System reported that blue mold occurred on other tobacco varieties in most of the tobacco production regions of North America during the 2001 growing season (see http://www.ces.ncsu.edu/depts/pp/bluemold/fcst2001/exec2001.htm.). Furthermore, in over 600 farm field trials of Vector 21-41 in Pennsylvania, Illinois, Louisiana, Mississippi, and Iowa, which were extensively monitored for disease and insect pests by farm owners, workers, Vector Tobacco agronomists, and contracted consultants, no other exceptional disease or pest susceptibility was observed. They claimed that the specific rates of insecticide, fungicide, and herbicide application for any one field depended on traditional agronomic factors, the geographic location, climate, and time of transplanting, but were always within approved label amounts. APHIS considered the fact that disease control in tobacco involves an integrated program of numerous practices, including crop rotation, root and stalk destruction, nitrogen management, soil pH management, plant spacing, varieties, and pesticides (see The University of Georgia College of Agricultural & Environmental Sciences Cooperative Extension Service web site on *Tobacco Disease Control* by Paul Bertrand at http://www.griffin.peachnet.edu/caes/tobacco/handbook/disease98.html). At least four of these practices are applicable to control or management of black root rot, black shank and blue mold. Chemicals recommended along with other practices by the University of Kentucky or in the 2002 North Carolina Agricultural Chemicals Manual for the control of these diseases include at least one or more of the following: the fumigant, Chloropicrin, carbamate, methyl bromide, Ridomil Gold EC or WSP, Ultra Flourish 2EC or 2E, Dithane Rainshield, Actigard, or Acrobat MZ (see *Current Blue Mold Controls* by http://www.uky.edu/Agriculture/kpn/kyblue/kyblu01/controls.htm and *Tobacco Disease Control Planning Should Be a Priority* at http://www.uky.edu/Agriculture/kpn/kyblue/kyblu01/related/rtd0001.htm, both by W. Nesmith, Extension Professor, University of Kentucky, and http://ipm.ncsu.edu/agchem/chptr6/605.pdf).

APHIS' analysis in the EA indicated that currently recommended and approved methods for controlling diseases and insects to which Vector 21-41 is susceptible should be effective and applicable for their control in Vector 21-41. These conclusions are supported by comments provided by growers of Vector 21-41 tobacco, and the tobacco company and crop consultant working with them to coordinate activities for planting, growing, and managing the crop.

2. Insufficient field data

Some of the same commenters also asserted there was insufficient field data to predict the long term impact under various and possible extreme weather conditions and wider range of individual farm production practices. APHIS notes that this concern appeared to be primarily aimed at the impacts from Vector 21-41 tobacco on traditional tobacco varieties as a result of out-crossing via pollen or commingling of seeds, plants, or leaf products and the impact on export markets. That concern is addressed below. APHIS notes that the field data or observations described above (and subsequently supported by field data reports received from the petitioner on June 5 and June 20, 2002 for field trials conducted in 2001 listed in Appendix A of the EA) regarding the disease and insect susceptibility of Vector 21-41 were made over 6 states, some representative of traditional tobacco growing areas, and others not. In addition, the petitioner noted in their letter of October 19, 2001 that no abnormal plant morphology or phenotypes due to the transgenes were observed. APHIS' analysis in the EA of data on cured-leaf nicotine levels from Vector 21-41 tobacco grown in four states indicated that it is consistently low as expected. Field data reports received June 5 and 20, 2002, which include analysis of additional samples and samples from two more states, indicate that the absolute average and median values for nicotine content from plants grown in 5 of the 6 states are still consistently lower than those reported for Burley 21 LA and normal wild-type tobacco varieties. Nicotine values from Vector 21-41 plants grown in a small (approximately 34 acre) experimental site in Hawaii, while higher than those from plants grown in the other states, were still below the 0.8% threshold required for the low-nicotine classification of Type 31-V or Type 73 tobacco defined by AMS, and were influenced by a combination of soil fertility, climatic conditions and cultural practices which are known to increase nicotine content. We believe that even though the field trials were conducted in only two years, the number and variety of locations should have presented a sufficiently broad range of weather conditions and individual production practices and pressures to predict with a reasonable degree of certainty that there will be no significant impacts to the environment.

3. Human health effects of tobacco products made with Vector 21-41

One commenter expressed concern that the commercialization of Vector 21-41 tobacco products would encourage smoking by giving a false sense of security. Along the same line, another commenter claimed that APHIS' EA was inadequate because it did not address human health effects (either direct; or later, indirect, reasonably-foreseeable effects) associated with the commercialization of a new tobacco product as required under NEPA and its implementing procedures. More specifically the commenter asserts that "the EA does not project human exposures rates of the tobacco, whether the products made with this tobacco will lead to increased smoking in the public, and many other health and disease impacts associated with smoking tobacco". The commenter also states that the EA does not address the human health impacts that may be caused when the public is exposed to the antibiotic resistance gene product through direct inhalation of smoke from this tobacco product.

In response to these comments APHIS notes that **addressing human health effects associated with the commerical use of the tobacco product is outside the scope of the EA.** The scope of the EA, as indicated in the Summary and under Alternative B, is to compare the environmental impacts of the introduction (importation, interstate movement and release) of Vector 21-41 tobacco and its progeny, without the safeguards afforded by 7 CFR Part 340, to impacts posed by the cultivation and distribution of tobacco not subject to these regulations. APHIS did consider the impacts of exposure to agricultural workers handling the tobacco plants.

Tobacco products, cigarettes, snuff etc., are made from tobacco leaves, which following detachment from the plant and curing, are no longer living. These products are therefore not subject to APHIS regulations at 7 CFR 340 because they do not meet the definitions provided therein of a regulated article or a plant pest. Impacts on human health from exposure to or use of these products, will therefore, not be determined by alternative actions identified in the EA. APHIS recognizes that use of some traditional tobacco products may have adverse consequences to human health, and did consider the potential human health effects from potential products made with Vector 21-41 tobacco, but this analysis was not included in the EA because it is believed to be outside the scope of impacts affected by the Agency's range of alternative actions. Vector 21-41 tobacco is a burley type of tobacco. Traditional burley tobacco is primarily used in cigarettes, but is also an important component of cigar, pipe, and chewing tobacco (Shew and Lucas, 1991). Tobacco is purchased and blended based on certain chemical criteria (including sugar and nicotine content) as well as appearance and smoke flavor. In addition, it is common practice to add sugars and other flavors to balance the smoke flavor, primarily by modifying the sensory impact of nicotine and other tobacco alkaloids (Leffingwell, 1999). It is difficult to predict what the composition of the final product might be, since as noted in the EA, data indicate that cured leaves of Vector 21-41 have significantly lower levels of nicotine and related alkaloids and higher levels of reducing sugars compared to a normal burley tobacco (Burley 21). The company is still working out the product formulation and currently, all the Vector 21-41 tobacco leaves harvested are still in the curing and aging process, which can typically last anywhere from 12 to 60 months (Scott Shore, Vector Tobacco (USA), Ltd., personal communication to Susan Koehler, May 3, 2002).

APHIS considered the information submitted by the petitioner regarding the content of nicotine and other alkaloids, total nitrogen, and reducing sugars in Vector 21-41 cured tobacco leaf, and TSNAs in smoke from cigarettes made from Vector 21-41 tobacco. We could find no reason why these differences would pose a greater human health threat than traditional burley tobacco if used in tobacco products, since the addictive component, nicotine, and carcinogenic TSNAs were reduced. The petition states that "Tobacco products made from Vector 21-41 deliver nicotine below the addictive levels suggested by Benowicz and Henningfield (1994)." Benowicz and Henningfield suggest that an absolute limit of 0.4 to 0.5 mg of nicotine per cigarette should be adequate to prevent or limit the development of addiction in most young people. This threshold

recognizes that nicotine uptake from smoke varies depending on how the cigarette is smoked and assumes a maximal bioavailability of 40%. As noted in the EA, the median value for nicotine content from samples taken from Vector 21-41 cured (oven-dried) leaves available at the time the EA was prepared was 0.05% (500 ppm or 0.5 mg/1000 mg), and assuming that 1000 mg of tobacco is used in the average cigarette, then it would be possible for cigarettes made from Vector 21-41 tobacco to meet this threshold. Additional nicotine data included in final field data reports submitted on June 5 and 20, 2002 do not change the conclusion that it would still be possible to meet this threshold. The effects of reduced nicotine in cigarette products on smoking behavior are debatable. But the stated intent of the petitioner is to develop a product which would help smokers reduce or control their smoking, and they indicate that trials are underway to confirm or quantify this. In as much as the product formulation is not finalized, any definitive conclusions regarding the human health effects of products made from Vector 21-41 tobacco would be speculative.

APHIS does not consider inhalation of the product of the antibiotic resistance gene in tobacco smoke to be an issue. The product of this gene is a protein, and proteins are broken down during curing, aging, and burning of the tobacco (Leffingwell, 1999). Breakdown products and derivatives of this protein would be similar to those derived from other proteins normally found in tobacco leaf.

Furthermore, APHIS identified within the EA the regulatory authority of other federal agencies or commissions relevant to the sale, use, packaging, labeling, and advertising of Vector 21-41 tobacco and its products. In particular, the FDA can assert jurisdiction over products made from Vector 21-41 tobacco if health claims are made regarding the product. The Federal Trade Commission oversees testing of "tar" and nicotine yields of cigarettes, which must be included in cigarette advertising and they would have the authority to address any unfair or deceptive cigarette advertising practices that might affect human health. APHIS' actions in no way prejudice or influence the regulatory authority or actions of these agencies with respect to Vector 21-41 tobacco products.

4) Impacts on organic farming were inadequately addressed in the EA.

One commenter stated that APHIS' EA contained an inadequate analysis of the potential impacts associated with the commercial use of genetically engineered tobacco on organic farming. They assert that we made an unsupported statement that nontransgenic tobacco seed would still be readily available for planting. APHIS checked several tobacco seed supplier websites, including domestic, international, private and public, and those marketing to organic growers (e.g. http://www.attra.org/attra-pub/tobacco.html), and there were plenty of traditional, non-genetically engineered tobacco varieties available, and there was no mention of these varieties not being available if genetically engineered tobacco seed was deregulated. There appears to be

an increasing interest among organic growers for indigenous and heirloom-variety types of tobacco and several possible sources of seed were listed.

The commenter further asserts that APHIS failed to analyze whether the marketplace and market-based standards will actually tolerate "adventitious presence" of genetically-engineered tobacco in organically produced tobacco products and the impact it will have on producers, processors and consumers of such products. APHIS has addressed the potential impacts of the Vector 21-41 tobacco on organic farmers in the EA. We made reference to the National Organic Program (NOP) administered by USDA's Agricultural Marketing Service, which considers that the presence of a detectable residue alone does not necessarily indicate use of a product of excluded methods that would constitute a violation of the standards. (Please refer to the preamble of the NOP final rule at residue testing, changes requested but not made, (3) Threshold for Genetic Contamination for a discussion of "adventitious presence" in relation to organic production at website: http://www.ams.usda.gov/nop/nop2000/Final%20Rule/preamble/pre-residues.htm.) Further, the NOP requires that organic production operations have distinct, defined boundaries and buffer zones to prevent unintended contact with prohibited substances from adjoining land that is not under organic management. The organic system plan enables the production operation to achieve and document compliance with the National Organic Standards, including the prohibition on the use of excluded methods. APHIS' analysis indicates that adventious presence of Vector 21-41 tobacco in organically-produced tobacco leaf of another type could only occur if the farmer planted seed that was commingled with or cross-pollinated by Vector 21-41 tobacco. Several reasons were provided in the EA for why this is extremely unlikely to occur.

Producers, processors, or consumers wishing to check for adventious presence of Vector 21-41 tobacco in their products could enlist the services of commerical laboratories (e.g. Genetic ID and Integrated Biomolecule Corporation) that offer testing for the detection of foreign genetic elements in commodities, including the nopaline synthase terminator used in both of the foreign gene constructs in Vector 21-41 tobacco. USDA's Agricultural Marketing Service and Grain Inspection, Packers and Stockyards Administration published an Advance Notice of Proposed Rulemaking on November 30, 2000 in the *Federal Register* (65 FR 71272- 71273) concerning the possible further development of additional testing and standardization for seeds and commodities designed to differentiate products such as non-biotechnology-derived commodities. Federal, State, private, and international groups involved in seed certification all allow for some level of accidental, incidental, or adventitious presence of off-types even in the purest seed categories, such as foundation and breeder seed.

5) APHIS should prepare an Environmental Impact Statement (EIS).

One commenter suggested that APHIS must prepare a complete environmental impact statement (EIS) to address the full range of impacts associated with the commercial planting of Vector 21-41 tobacco.

In response, APHIS notes that their NEPA Implementing Procedures (7 CFR 372) do not indicate that this type of action is of the class of actions normally requiring the preparing of an EIS. It is characteristic of the class of actions normally requiring an EA, but not necessarily an EIS. APHIS' analysis documented in the EA (and in the response to comments) does not indicate that a significant impact to the human environment is likely; therefore the preparation of an EIS is not necessary. This is the first petition for deregulation for a genetically engineered tobacco product that APHIS has received. APHIS does not believe a decision to deregulate Vector 21-41 tobacco, when combined with previous decisions to deregulate other genetically engineered crops with totally different traits, uses, and markets, will influence or cause a significant cumulative impact to the human environment which would warrant the preparation of an EIS.

6) Gene transfer to and commingling with conventional tobacco and market impacts. Many commenters expressed concern that out-crossing or commingling of Vector 21-41 tobacco with conventional varieties could lead to a loss of export sales estimated at $250 million because purchasers of U.S. tobacco, particularly those that focus on the large export market, have imposed a "GMO" (genetically-modified organism) tolerance level of zero. They request that the Vector 21-41 tobacco continue to be regulated under 7 CFR 340 to prevent cross-pollination and commingling until the Vector 21-41 tobacco is produced in a male-sterile form and/or a system is in place to identify the locations of its production and provide production guidelines or mandated programs that will prevent outcrossing or commingling. A minor concern was raised that if contamination occurs, it could affect the nicotine levels of conventional tobacco and raise concerns about the quality of the tobacco related to this trait.

In response, APHIS believes that such impacts on marketing, which are neither directly or indirectly related to disease, damage or injury to plant products, are not germane to APHIS' decision as to whether Vector 21-41 poses a plant pest risk. Nonetheless, APHIS did address the potential for outcrossing and/or commingling in the EA under the sections on potential impacts from gene introgression and potential impacts on organic farming (section V. C. and E., respectively).

Furthermore, as noted in Section II. C. of the EA, production and marketing of tobacco is subject to regulation by other agencies within the USDA. In particular, APHIS noted that the USDA, Agricultural Marketing Service (AMS) has established a classification and certification system for certain low nicotine types of tobacco (less than 0.8% nicotine oven dry weight in the cured leaf). This includes Type 31-V air-cured Burley tobacco with low nicotine and Type 73 flue-cured tobacco with low nicotine, as defined under 7 CFR 30.38 and 7 CFR 30.42, respectively. Restrictions and controls relating to the production and marketing of Type 31-V tobacco as a prerequisite for certification are described under 7 CFR 30.38 (c). In summary, these restrictions require that the tobacco must be grown under contract filed yearly with the AMS on a specified number of acres, and that it must be separated from other types of tobacco during cultivation,

housing, and handling. It can not be offered for sale, or be sold, marketed or disposed of unless it is clearly represented and identified as being low nicotine tobacco. In addition, the grower can not transfer seed, seedlings or plants furnished under the contract, nor can the grower harvest or save seed produced under the contract. AMS samples tobacco from each grower and assays it to determine whether it meets the low nicotine criteria to meet the classification. Similar restrictions are in place under 7 CFR 30.42 for Type 73 tobacco. Vector 21-41 tobacco is the first tobacco to have ever received this certification.

According to Ken Wall, Senior Marketing Specialist, AMS Tobacco Programs, (personal communication to Susan Koehler, November 14, 2001) Vector 21-41 received certification under this program as both Type 31-V and Type 73 last year. Bill Hawks, Under Secretary for USDA's Marketing and Regulatory Programs indicated in a letter dated April 26, 2002 to Mr. Bill Dickerson, Director of Plant Industry Division, North Carolina Department of Agriculture and Consumer Services, that destination audits were conducted for the 2001-2002 marketing year to confirm that there was no commingling of this tobacco with other types of tobacco, and that more than 7 million pounds of Vector 21-41 tobacco have been certified under this program to date. The petitioner has indicated that contracts have already been filed with AMS to certify as low-nicotine types all of the Vector 21-41 tobacco being grown during the 2002 growing season for marketing, and they intend to continue growing under the certification program in future years. All the Vector 21-41 tobacco previously grown, or scheduled to be grown in 2002, in the United States with the intent of marketing has been in non-quota areas or states, including Mississippi, Pennsylvania, Iowa, Illinois, and Louisiana, (Scott Shore, personal communication, May 21, 2002). (Hawaii, another non-quota state, is also being evaluated by the petitioner as a viable production site.) In the vicinity of where Vector 21-41 has been grown in LA, MS, IL, and IA, there are no other types of tobacco being grown. The petitioner purposefully chose these locations to avoid any concerns regarding commingling, and the grower contracts stipulate that the tobacco must be topped and suckers controlled (Scott Shore, personal communication to Susan Koehler, May 21, 2002).

Type 31-V and Type 73 tobacco, when classified and certified as such, are currently excluded from the quota system. They can be grown in non-quota areas and not be subject to penalties when marketed. If Vector 21-41 tobacco did <u>not</u> receive the Type 31-V or Type 73 certification, then it would just be considered Type 31 Burley (if air-cured) or Types 11-14 (if flue cured), which are subject to quotas. In that case a substantial penalty can be levied when it is marketed if it is grown in a non-quota area, and it could only be marketed without penalty in a quota area if an allotment is issued for the type. On May 15, 2002, the Farm Service Agency published a notice and request for public comment in the *Federal Register* (67 FR 34673) about whether to include Type 31-V or Type 73 in the definitions of tobaccos subject to quotas for the 2003 and subsequent crop years. The implications of a potential change in quota status of Type 31-V or

Type 73 on the potential for contamination of traditional types of tobacco via cross-pollination is discussed briefly in the notice.

Literature Cited (Includes only those references not already included in the EA.)

Leffingwell, J.C. 1999. Leaf Chemistry. Chapter 8 *in* Tobacco Production, Chemistry, and Technology, D.L. David and M.T. Nielsen eds. Blackwell Science Ltd., Oxford, England.

North Carolina State University. 2000. 2000 North Carolina Burley Tobacco Production Guide. Available at http://ipmwww.ncsu.edu/Production_Guides/Burley/chptr8.html) .

USDA/APHIS Decision on Vector Tobacco (USA) Ltd. Petition 01-121-01P Seeking a Determination of Nonregulated Status for Reduced-Nicotine Tobacco Line, Vector 21-41

Environmental Assessment

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Registrations of pesticides are under constant review by the U.S. Environmental Protection Agency (EPA). Use only pesticides that bear the EPA registration number and carry the appropriate directions.

I. SUMMARY

The Animal and Plant Health Inspection Service (APHIS), United States Department of Agriculture (USDA), has prepared an Environmental Assessment (EA) prior to making its determination on the regulated status of tobacco (*Nicotiana tabacum*) line Vector 21-41 that has been genetically engineered (transformed) to have reduced nicotine. APHIS received a petition (designated 01-121-01P) from Vector Tobacco (USA) Ltd. (Durham, North Carolina) for a determination that Vector 21-41 reduced-nicotine tobacco does not present a plant pest risk, and therefore should no longer be treated as a regulated article under APHIS regulations found at 7 CFR Part 340. The petition contains information in support of such a determination.

The Vector 21-41 reduced-nicotine tobacco has been developed with the intent of producing cigarettes or other tobacco products that will help smokers to reduce or quit their smoking. Nicotine is the major alkaloid in tobacco leaves and is widely believed to be the addictive component of tobacco. Nicotine levels in the leaves were reduced by using recombinant DNA techniques to insert an anti-sense version of the coding region (cDNA) of a tobacco gene encoding the enzyme quinolinic acid phosphoribosyltransferase (QPTase) into the genome of a Burley tobacco variety. The anti-sense gene construct disrupts the normal expression of QPTase. QPTase is one of the key enzymes in the biosynthetic pathway leading to the production of nicotine and related alkaloids. Because these alkaloids are also the precursors for the production of tobacco-specific nitroasmines (TSNAs), which are potent mutagens and potential carcinogens, Vector 21-41 tobacco also has reduced levels of TSNAs. Vector 21-41 tobacco has also been transformed to express the *nptII* selectable marker gene derived from the enteric bacterium *Escherichia coli* transposon Tn5. The *nptII* gene encodes the enzyme neomycin phosphotransferase that confers resistance to the aminoglycoside antibiotic kanamycin. This gene was inserted only as a tool to allow selection of tobacco tissue transformed to contain the new gene constructs. Vector 21-41 tobacco is a regulated article under APHIS regulations at 7 CFR Part 340 because the plant pest *Agrobacterium tumefaciens* was used as a donor organism for some DNA sequences used to regulate the expression of the new gene constructs and also as a vector to introduce the new gene constructs into the tobacco genome.

As a regulated article, the importation, interstate movement, or cultivation in the United States of Vector 21-41 tobacco has been conducted under authorizations from APHIS that require conditions of physical and reproductive confinement to preclude the regulated article from becoming mixed with nonregulated plants or products or persisting in the environment outside the field site. This EA has been prepared prior to issuing a determination of nonregulated status for Vector 21-41 tobacco in order to specifically addresses the potential for impact to the human environment that might be incurred through the cultivation and use in agriculture of this tobacco without the restrictions imposed by 7 CFR Part 340.

II. BACKGROUND

A. Development of Vector 21-41 tobacco.

The Vector 21-41 reduced-nicotine tobacco was developed at the North Carolina State University, Department of Genetics under a research grant to Dr. Mark Conkling from a private company called Alternative Cigarettes. Vector Group, the parent company of Vector Tobacco (USA) Ltd.[1] and the Liggett Group cigarette company, has sublicensed the technology with the intent of producing cigarettes or other tobacco products that will help smokers to reduce or quit their smoking. Nicotine, is the major alkaloid found in *N. tabacum* (Tso, 1972, see Chapter 23, Alkaloids), and is widely believed to be the addictive component of tobacco (Benowitz and Henningfield 1994). It is synthesized in the root and transported to the leaves (Tso, 1972). Figure 1 of the petition shows the biosynthetic pathway for nicotine in tobacco. Nicotine is synthesized from two metabolic precursors, nicotinic acid and N-methylpyrroline, each of which is synthesized by two separate pathways. Quinolinic acid phosphoribosyl-transferase (QPTase) is the key rate-limiting, regulatory enzyme in the biosynthetic pathway that leads to nicotinic acid. It converts quinolinic acid to nicotinic acid mononucleotide, which is then converted directly or indirectly into nicotinic acid. To develop a reduced nicotine tobacco, the petitioner states that they started with a non-commerical tobacco variety developed through traditional breeding to have reduced levels of alkaloids, Burley 21 LA, and genetically engineered it by inserting the coding region (cDNA) of the tobacco gene *NtQPT1,* which encodes the QPTase enzyme, in the anti-sense orientation behind its own root-specific promoter. The anti-sense gene construct was designed to disrupt the normal expression of QPTase in the root, thereby lowering the pool of nicotinic acid available for the production of nicotine, nor-nicotine, and other alkaloids derived from the pyridine ring of nicotinic acid. Nicotine, nornicotine, and other minor tobacco alkaloids give rise to the production of tobacco-specific N-nitroasmines (TSNAs) during tobacco processing and during smoking (Bush et al., 1993). Some TSNAs been demonstrated to be potent mutagens and potential carcinogens, and are thought to contribute to the increased risk of cancer of the upper digestive tract in tobacco chewers and for the increased risk of lung cancer in smokers (Hoffman et al., 1994). The petition includes data that demonstrates that Vector 21-41 tobacco has reduced levels of nicotine, nor-nicotine, and total alkaloids in the leaves, and reduced levels of specific TSNAs in smoke from cigarettes derived from it.

Vector 21-41 tobacco has also been transformed to constitutively express the *nptII* selectable marker gene derived from the *Eschericia coli* bacterial transposon Tn5. This gene encodes the enzyme neomycin phosphotransferase (NPTII) that confers resistance to the antibiotic kanamycin and allowed tissue that was transformed to express the new genes to be selected on medium that contains kanamycin. Regulatory DNA sequences derived from the nopaline synthase (*nos*) gene from the plant pathogenic bacterium, *Agrobacterium tumefaciens*, were fused to both of these gene constructs to facilitate their transcription in the transgenic plant. *A. tumefaciens* was also

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[1]In January 2001, Dr. Conkling left the University to work for Vector Tobacco (USA) Ltd., and on November 14, 2001, Vector Tobacco (USA) Ltd. was changed to Vector Tobacco, Inc.

used as a vector to introduce the anti-sense *NtQPT1* and *nptII* gene constructs into the genome of the recipient tobacco variety to create the transgenic line Vector 21-41. Because this plant pathogen was used as a vector and donor organism in the production of the genetically engineered Vector 21-41 tobacco, this tobacco is considered to be a regulated article under APHIS regulations at 7 CFR Part 340, and authorization for its importation, interstate movement and field testing in the United States and its territories is required.

Vector 21-41 tobacco has been field tested in a wide variety of locations, in at least 7 States under notifications from APHIS issued since 1999 that are listed in Appendix A. It has also been field tested in Argentina. This field testing was conducted, in part, to confirm that Vector 21-41 tobacco exhibits the desired agronomic and quality characteristics and does not pose a greater plant pest risk than the unmodified recipient from which it was derived. Although these field tests were conducted in agricultural settings, APHIS performance standards for notifications (7 CFR 340.3 (c) 1-6) stipulate that the regulated article not be planted with nonregulated plant material that is not part of the release, that it be contained or devitalized when no longer in use, and that the regulated article and its offspring must not persist in the environment after completion of the test. Therefore, measures were employed to ensure physical and reproductive confinement from other sexually compatible plants and to manage volunteers. Reports for those field tests completed under APHIS authorization that were due at the time of the petition submission, and other information contained in the petition, have been submitted to APHIS to support a determination that Vector 21-41 tobacco does not pose a plant pest risk (see Appendix C for a list of supporting data and information).

B. APHIS Regulatory Authority.

APHIS regulations under 7 CFR Part 340, which are promulgated pursuant to authority granted by the Plant Protection Act (Title IV, Pub. L. 106-224, 114 Stat. 438, 7 U.S.C. 7701-7772) regulate the introduction (importation, interstate movement, or release into the environment) of certain genetically engineered organisms and products. A genetically engineered organism is considered a regulated article if the donor organism, recipient organism, vector or vector agent used in engineering the organism belongs to one of the taxa listed in the regulation and is also a plant pest, or if there is reason to believe that it is a plant pest. Vector 21-41 tobacco has been considered a regulated article because a plant pathogen was used as a vector agent and as a donor organism for some noncoding DNA regulatory sequences.

Section 340.6 of the regulations, entitled "Petition for Determination of Nonregulated Status", provides that a person may petition the Agency to evaluate submitted data and determine that a particular regulated article does not present a plant pest risk and should no longer be regulated. If APHIS determines that the regulated article is unlikely to pose a greater plant pest risk than the unmodified organism from which it is derived, the Agency can grant the petition in whole or in part. Therefore, APHIS permits or notifications would no longer be required for field testing, importation, or interstate movement of that article or its progeny.

C. Regulatory Authority of Other Federal Agencies Relevant to the Production and Use of Vector 21-41 Reduced-Nicotine Tobacco and Its Products.

Production and Marketing of Tobacco: Production and marketing of tobacco, including Vector 21-41 reduced-nicotine tobacco, is subject to regulation by other agencies within the USDA. The Agricultural Stabilization and Conservation Service and the Commodity Credit Corporation set production quotas and price levels for tobacco leaf under the federal tobacco support program ("No Net Cost Tobacco Program"). Under the quota system, limits are placed on the amount of different types of tobacco that can be grown. Under 7 CFR Part 30, the USDA's Agricultural Marketing Service (AMS) classifies tobacco based on distinctive characteristics determined by the variety, growth conditions, and methods of cultivation, harvesting, and curing. Two types of low nicotine tobacco (less than 0.8% nicotine oven dry weight in the cured leaf) are excluded from the quota system, when classified and certified as such by the AMS under their regulations at 7 CFR 30.38 and 7 CFR 30.42. Special restrictions and controls relating to the production and marketing of these types of tobacco are described under these regulations. Vector 21-41 is the first tobacco variety to have received this certification (Kenneth Wall, Senior Marketing Specialist, AMS Tobacco Programs and Mark Conkling, personal communication to Susan Koehler, 11/14/01).

Product Sale and Use: Currently, tobacco is not generally considered a food, feed, drug, or dietary supplement by the U.S. Food and Drug Administration. (FDA). But the FDA has asserted jurisdiction over cigarettes as a "drug" when health claims were made by vendors or manufacturers, and the courts have sustained the agency's assertions of jurisdiction. Should health claims be made on cigarettes made with Vector 21-41 tobacco, the FDA would have jurisdiction over them as a drug. In 1996 the FDA asserted jurisdiction over tobacco products under the Food, Drug, and Cosmetic Act (FFDCA) to regulate tobacco advertising and promotional campaigns as well as labeling and purchasing restrictions. But the legal authority of the FDA to regulate tobacco products in the absence of health claims was challenged by the tobacco industry and in June 2000, the United States Supreme Court ruled that Congress had not expressly given the FDA legal authority to regulate the tobacco industry.

Packaging, Labeling and Advertising of Tobacco Products: The Bureau of Alcohol, Tobacco and Firearms regulations cover packaging and require the disclosure of certain information on every tobacco product carton or package and prohibit certain promotional practices. The Federal Cigarette Labeling and Advertising Act bans cigarette advertising on television, radio, and other electronic media, and requires cigarette packages and advertising to carry specified health warnings, such as the Surgeon General's warning. The Department of Justice, the Federal Communications Commission and the Federal Trade Commission (FTC) ensure compliance with this Act. The FTC oversees testing of "tar" and nicotine yields of cigarettes, which must be included in cigarette advertising, and they have the authority to address unfair or deceptive cigarette advertising practices under the Federal Trade Commission Act.

III. PURPOSE AND NEED

In compliance with the National Environmental Policy Act (NEPA) of 1969 (42 U.S.C. 4321 *et seq.*) and the pursuant implementing regulations (40 CFR 1500-1508; 7 CFR Part 1b; 7 CFR Part 372), APHIS has prepared this EA before making a determination on the status of Vector 21-41 tobacco as a regulated article under APHIS regulations. Vector Tobacco (USA) Ltd., (Durham, North Carolina) submitted a petition requesting a determination from APHIS that Vector 21-41 reduced-nicotine tobacco no longer be considered a regulated article under 7 CFR Part 340.

IV. ALTERNATIVES

A. No Action: Continuation as a Regulated Article

Under the "no action" alternative, APHIS would come to a determination that Vector 21-41 tobacco and its progeny should continue to be regulated under 7 CFR Part 340. Permits or acknowledgment of notifications from APHIS would still be required for their introduction. APHIS would choose this alternative if there were insufficient evidence to demonstrate lack of plant pest risk from the cultivation or movement of Vector 21-41 and its progeny without the containment restrictions that would otherwise be imposed under 7 CFR Part 340.

B. Proposed Action: Determination of Nonregulated Status

Under this alternative, Vector 21-41 tobacco and its progeny would no longer be considered regulated articles under 7 CFR Part 340. Permits or notifications to APHIS would no longer be required for introductions in the United States and its territories of Vector 21-41 tobacco or its progeny. A basis for this determination would be established, which would result in a "Finding of No Significant Impact (FONSI) under NEPA. Unrestricted cultivation and movement of this tobacco would be permitted by APHIS. Such a determination, however, does not preclude any restriction which might be placed on the cultivation, distribution, or sale of this tobacco by other regulatory agencies also having authority over this tobacco, e.g. those restriction imposed by the USDA, AMS as described in section II, C above. Importation of Vector 21-41 tobacco seeds and other propagative material would still continue to be regulated and inspected for pests and noxious weeds under APHIS regulations at 7 CFR 319.37 and under the Federal Seed Act at 7 CFR 201.

C. Determination of Nonregulated Status, in Part

The regulations at 7 CFR Part 340.6 (d) (3) (i) state that APHIS may "approve the petition in whole or in part." There are two ways in which a petition might be approved in part:

Approval of only some of the lines requested in the petition. Some petitions request de-regulation of lines derived from more that one independent transformation event. In those cases, supporting data must be supplied for each line; and APHIS could approve certain lines requested in the petition, but not others.

Approval of the petition with geographic restrictions. APHIS might determine that the regulated article poses no significant risk in certain geographic areas, but may pose a significant risk in others. In this case, APHIS may choose to approve the petition with a geographic limitation stipulating that the approved lines could only be grown in certain geographic areas.

V. POTENTIAL ENVIRONMENTAL IMPACTS

The potential environmental impact of each of the alternatives cited in IV. A.- C. will be presented.

Alternative A.

In a decision to choose alternative A., no action, these plants would still require APHIS authorization to be planted, imported, or moved interstate. Such introductions could continue under APHIS authorized notifications. In this case the applicant must certify that they will meet the performance standards that are designed to ensure physical and reproductive confinement of Vector 21-41 tobacco and any progeny derived from it. Thus far, no adverse effects to the environment or human health have been reported as a result of field tests of Vector 21-41 tobacco grown under APHIS authorization.

Growers could choose to grow other tobacco varieties if they choose not to grow Vector 21-41 under contract with the developer under APHIS authorization. However, there are currently no other tobacco varieties that have been commercialized that meet the AMS definition of "low nicotine" tobacco (Kenneth Wall, AMS and Dr. Gary Palmer, Extension Tobacco Specialist, University of Kentucky, personal communication to Susan Koehler, November 2001).

Alternative B.

A decision to choose alternative B, deregulation of Vector 21-41 reduced-nicotine tobacco, is addressed below. The environmental impacts of the introduction of Vector 21-41 tobacco and its progeny into the United States and it territories without the safeguards afforded by 7 CFR Part 340 are compared to any impacts posed by the cultivation and distribution of tobacco not subject to these regulations.

A. Plant pathogenic properties

APHIS considered the potential for the transformation vector or process, the introduced DNA sequences, or their expression products to cause or aggravate disease symptoms in Vector 21-41 tobacco or in other plants, or to cause the production of plant pathogens. We also considered whether data indicate that unanticipated plant pest effects would arise from cultivation of Vector 21-41 tobacco.

The petition states that a disarmed binary vector system based on the tumor-inducing Ti-plasmid of *Agrobacterium tumefaciens* was used to introduce the new genes into Burley 21 LA tobacco (see Petition, pg. 16). The system is considered "disarmed" because (1) the plant hormone genes necessary for the formation of crown gall tumors, which are normally produced upon infection of plants with *A. tumefaciens*, are removed from the T-DNA, that portion of the Ti-plasmid that is normally transferred to plant cells upon *A. tumefaciens* infection; and (2) the virulence functions are provided on a separate Ti-plasmid that lacks the T-DNA. Therefore, the transformation process should not lead to crown gall disease in Vector 21-41 tobacco.

APHIS analyzed molecular genetic and inheritance data provided in the petition that characterize the new genetic material in the transgenic line selected from a single transformation event (T_0 #41) and designated as Vector 21-41(see Appendix C). Data demonstrate that Vector 21-41 tobacco contains within a single locus: (1) two complete copies of the T-DNA insert from the disarmed Ti-plasmid pYTY32 in reverse orientation with respect to each other, each of which contains (a) the *nptII* gene encoding neomycin phosphotransferase, originally derived from *E. coli* Tn5, whose transcription is initiated and terminated by the promoter and termination/polyadenylation sequences, respectively, derived from the nopaline synthase (*nos*) gene from *A. tumefaciens*, and (b) the anti-sense quinolinic acid phosphoribosyl-transferase (QPTase) *Nt-QPT1* cDNA derived from tobacco whose transcription is initiated by its own promoter and is terminated by the *nos* terminator as described above; (2) a small portion of the backbone sequence located outside of the left T-DNA border in pYTY32 that includes truncated versions of the *Pseudomonas aeruginosa* derived *tetA* gene and the *E. coli* plasmid pRK2 derived *trfA* gene; and (3) the T-DNA left and right border sequences from *A. tumefaciens* bordering each T-DNA insert.

Data provided in the petition indicate that both the *nptII* and anti-sense *Nt-QPTI* genetic constructs are expressed in Vector 21-41 and produce the expected traits. Full length copies of the bacterial *tetA* and *trfa* genes would encode proteins that confer resistance to the antibiotic tetracycline and plasmid DNA transfer and conjugations functions respectively, as expressed in their donor organisms. However since only half of these genes are present in Vector 21-41, and they lack regulatory sequences necessary to initiate expression in plants, they would not be expressed in Vector 21-41 tobacco. Molecular genetic data were provided that indicate that no other complete protein coding sequences present outside of the T-DNA border in pYTY32 were inserted into Vector 21-41.

Although some of the donor organisms of the introduced sequences are described as plant or human pathogens, the introduced sequences are not known to cause or aggravate diseases in plants, nor in animals or humans. *A. tumefaciens* is a plant pathogen, but the non-coding regions of the *nos* gene derived from it are commonly used to regulate transgene expression in plants. Neither these sequences nor the T-DNA borders will cause or aggravate disease symptoms in plants. *E. coli* is not a plant pathogen. It is a coliform bacterium found commonly in the guts of humans and animals, and is not generally considered to be a human, animal, or plant pathogen (American Biological Safety Association, 1998; CAB Intl., 2001) . The *nptII* gene has a safe history of use as a selectable marker for plant transformations. *P. aeruginosa* is not a plant pathogen, but is listed as a human pathogen (ABSA, 1998) and as a natural enemy of certain insects (CAB, Intl., 2001). Regardless, of its status as a pathogen, the truncated *tetA* gene derived from it will not be expressed in Vector 21-41 tobacco.

Molecular genetic and inheritance data provided in the petition indicate that the new *nptII* and anti-sense *NtQPT1* genetic constructs are expressed and inherited as dominant, tightly linked traits, consistent with insertion of both transgenes at a single locus. Early generations of transformant #T_0-41 from which Vector 21-41 was selected all exhibit kanamycin resistance, and Vector 21-41 plants were shown to express NPTII protein in the leaves, roots, and stems. These plants also had nicotine levels in their leaves that were consistently lower than those determined for progeny of the original transformant #T_0-41 that lost the transgenes through segregation and for those reported for "wild-type" Burley 21-LA and "promoter control" plants that were grown in North Carolina in 2000. ("Promoter control" plants were reported to be Burley 21-LA transformed to carry only the *NtQPT1* promoter fused to a marker gene.) In the North Carolina experiment, Vector 21-41 leaves also had significantly lower levels of nor-nicotine and total alkaloids compared to both the "wild-type" and "promoter control" Burley 21-LA plants. APHIS notes, however, that the nicotine and total alkaloid levels of leaves derived from both the "promoter control" and the "wild-type" Burley 21-LA plants in the 2000 North Carolina field experiment and the nicotine content derived from the leaves taken from null segregants in the greenhouse are all higher than those reported previously for Burley 21-LA (Legg et al., 1970; and Paul Legg and Lowell Bush, personal communication to Susan Koehler, December 6, 2001). The source of this discrepancy remains unresolved, but could possibly be due to cultural or environmental effects which are known to effect nicotine content (Mark Conkling, letter to Susan Koehler, January 11, 2002.). The nicotine levels measured by AMS from at least 830 leaf samples from Vector 21-41 tobacco grown during the 2001 growing season in over 100 locations from four states (Louisiana, Mississippi, Illinois, and Pennsylvania) did vary slightly between states, with both the average and median values ranging from approximately 0.04 to 0.10 % oven dry weight (400 - 1000 ppm). The average and median values for all samples combined were 0.079% and 0.05%, respectively, and the maximum value reported was 0.40%. The average nicotine content reported for Burley 21-LA and Burley 21 (the normal alkaloid progenitor of Burley 21-LA) is 0.2 to 0.25% and 3.5%, respectively (Legg et al., 1969 and 1970). Therefore the data indicate that the average nicotine content for cured Vector 21-41 tobacco leaves grown over a variety of locations is approximately 2.5- and 44- fold lower, respectively, than the

average previously reported for Burley 21-LA and Burley 21, and only 0.02% of Vector 21-41 samples exceeded the average reported for Burley 21-LA.

Data also indicate that specific TSNAs, which are derived from nicotine and other alkaloids, were 15- to 39-fold lower in smoke from cigarettes made from Vector 21-41 tobacco when compared to standard, full-flavor generic cigarettes. In particular, the levels of N-nitrosonornicotine (NNN) and N-nitrosonicotine keytone (NNK) from Vector 21-41 cigarette smoke are approximately 15- and 18-fold lower, respectively, than those derived from the standard cigarette, and are approximately 12- and 2.7-fold lower, respectively, than those reported from cured Burley 21-LA tobacco leaf (Lowell Bush, Professor of Agronomy, University of Kentucky, personal communication to Susan Koehler, December 6, 2001). Both of these TSNAs are known carcinogens (Hoffman et al., 1994). This data taken together indicate that the anti-sense *NtQPT1* gene construct in Vector 21-41 is functioning as expected to lower the pool of nicotinic acid available in the root for the synthesis of nicotine, nor-nicotine and other alkaloids derived from the pyridine ring of nicotinic acid. However, in addition to reduced levels of nicotine and other alkaloids, Vector 21-41 was also found to have levels of reducing sugars in the leaves that were about twice those of the "wild-type" and "promoter control" Burley 21-LA plants, but which are well within the range of reducing sugars observed among different tobacco varieties. APHIS knows of no information which would lead one to believe that this would cause a plant pest risk.

APHIS analysis of agronomic data and observations provided on field tests conducted in 2000 in Clayton, North Carolina, and in 2001 in Pennsylvania, Illinois, Louisiana, Mississippi, and Iowa using a typical insect and disease management program indicate that Vector 21-41 does not have increased susceptibility to diseases or insects when compared to the parental line, or to that reported previously for Burley 21-LA (Legg et al., 1970) or Burley 21 (Gary Palmer, Extension Tobacco Specialist, and Glenn Collins, University of Kentucky, personal communication to Susan Koehler, November and December, 2001). Both Burley 21 and Burley 21-LA have low levels of disease resistance compared to newer Burley varieties and Burley 21-LA is described as extremely susceptible to insect damage. The petitioner notes that a field experiment was conducted in Clayton, North Carolina in 2000 to compare Vector 21-41 tobacco with the "wild-type" and "promoter control" plants grown in the absence of systemic insecticides, and all plants were destroyed by insects, primarily tobacco horn worms and tobacco bud worms. No difference in insect predation was observed between Vector 21-41 and the controls.

B. Potential impacts based on the relative weediness of Vector 21-41 tobacco compared to currently cultivated tobacco varieties.

APHIS evaluated whether Vector 21-41 tobacco is any more likely to become a weed than the parent tobacco line, or other tobacco currently cultivated. The assessment considers the weediness status and any weediness characteristics of tobacco and the unique characteristics of

Vector 21-41 tobacco. APHIS also evaluated whether Vector 21-41 tobacco is any more likely to transmit weedy characteristics to other cultivated tobacco.

Tobacco (*N. tabacum*) has been grown for commercial purposes in at least 97 countries around the world (Shew and Lucas, 1991). In a search of the major weed references (Holm et al., 1977 and 1979; Muenscher, 1980; Reed, 1977, Weed Science Society of America, 1989), it is listed as a common weed in Hawaii by Holm et al.(1979), but it is not listed as a weed anywhere else in the world, nor is it present on the lists of noxious weed species distributed by the Federal Government (7 CFR Part 360) or on the list of weeds regulated by the states (see http://www.aphis.usda.gov/npb/statenw.html). Its status as a weed in Hawaii is questionable, as the only *Nicotiana* species listed in a recent reference of Hawaiian weeds is *N. glauca* Graham, commonly referred to as tree tobacco (Haselwood and Motter, 1983). APHIS' analysis of the characteristics of tobacco reveals that it possesses few of the characteristics described by Baker (1965) that are thought to contribute to the weediness potential of plants that are notably successful weeds. The only ones identified are self-compatibility and very high seed output in favorable conditions (up to 3,000 seeds per flower) (Shew and Lucas, 1991). One characteristic of weeds not mentioned by Baker, but which is in part responsible for the classification of some Solanaceous plants as weeds, including *N. glauca* and *N. suaveolens*, is the production of alkaloids, including nicotine, which can cause adverse health effects in humans and livestock (Holm et al., 1979; James et al., 1992). Cultivated tobacco is unlikely to become a weed under most agricultural situations because the common practice of topping prevents seed formation. Even if seed were produced, the seeds are very small (0.5 mm in diameter) and usually require germination in a carefully prepared sterile seedbed or in a greenhouse to avoid devastating seedling pathogens, most important of which is blue mold (Shew and Lucas, 1991). Tobacco volunteers are not common, but if found, can be easily controlled by herbicides or mechanical means.

Vector 21-41 tobacco exhibits no characteristics that would cause it to be more weedy than the non-transgenic parent tobacco line or other cultivated tobacco, and therefore is unlikely to transmit weedy characteristics to other tobacco. In particular, as noted above, Vector 21-41 is significantly lower in nicotine and other alkaloids than Burley 21-LA and Burley 21; it is susceptible to blue mold, and is equally susceptible to insects as Burley 21-LA. In addition, Burley tobacco requires higher rates of nitrogen fertilizer than other types of tobacco (Shew and Lucas, 1991). APHIS evaluated data collected from the 2000 field trial in Clayton, North Carolina that show that no significant differences were observed between Vector 21-41 and the non-transgenic parent tobacco line in other agronomic characteristics which might influence the plant's ability to compete as a weed. These characteristics include days from transplant to flowering, height at flowering, leaf number at flowering, leaf size (width and length) and yield. In addition, data were provided that demonstrate that the average and range in the number of seeds produced per pod from greenhouse grown plants of Vector 21-41 tobacco is similar to that

of Burley 21-LA and Tn90, a currently cultivated Burley type of tobacco, and is slightly less than that for two other flue-cured tobacco varieties, Ti121 and Ti57.

C. Potential impacts from gene introgression from Vector 21-41 tobacco into its sexually-compatible relatives.

APHIS evaluated the potential for genes from Vector 21-41 tobacco to introgress into sexually compatible wild relatives and considered whether such introgression would result in increased weediness or other adverse environmental effects. Only six *Nicotiana* species are described as native to the United States, and none of these are listed as threatened or endangered by the U.S. Fish and Wildlife Service. The potential for genes from *N. tabacum* to naturally introgress into these species is extremely low for several reasons (see Appendix B for details). First, all but one of these do not occur in proximity to areas of cultivation or seed production of tobacco in the United States. Second, the species are either not cross compatible with *N. tabacum* or their progeny exhibit sterility or genetic instability. Vector 21-41 is not reported to have flowering characteristics different from those observed for other *N. tabacum,* and there is no reason to believe that it would have a greater ability to produce fertile hybrids with these species.

Several other reasons exist for why gene introgression from Vector 21-41 is extremely unlikely to occur in these indigenous species, or other species of *Nicotiana* that either occur as naturalized weeds in the United States or that are used for ornamental, medicinal or commercial purposes, e.g. *N. alata, N. glauca, N. forgetiana, N. langsdorffii, N. longiflora, N. rustica, N. sauveolens, N. sylvestris, N. sanderae,* and *N. tomentosa* (Shew and Lucas, 1991; see taxonomic information for *Nicotiana* species in the GRIN database at http://www.ars-grin.gov/cgi-bin/npgs/html). (1) As stated in the petition (pg. 4), Vector Tobacco intends to produce all seed in greenhouses that will house only Vector 21-41 plants; and the vents of these greenhouses will be screened and managed in such a way as to prevent the entry or exit of pollen-carrying insects. (2) Restrictions placed on the cultivation of low-nicotine varieties by AMS regulations preclude the harvesting or transfer of seed produced from these plants under contract. (3) Topping and sucker control methods, which are common practice for production of commercial tobacco and Vector 21-41, will reduce or eliminate the availability of Vector 21-41 pollen for cross-hybridization. (4) Even if some flowers were produced, tobacco is primarily self-pollinating (95%) and fertilization generally occurs before the flower opens. It is not wind pollinated and any outcrossing relies on insect pollinators. McMurtrey et al., (1960) reported that outcrossing rates of adjacent plantings of untopped tobacco (including a Burley variety) measured over 3 years in Maryland ranged from 2-11 percent, and outcrossing rates declined with distance, and were usually less than 0.3% at 1/4 mile (1,320 feet, the isolation distance for certified seed of tobacco of different varieties). Since Vector 21-41 tobacco does not exhibit characteristics that might be expected to cause it to be any more competitive or weedy than other cultivated tobacco, or to adversely effect nontarget organisms (see Section D), any impact from gene introgression from Vector 21-41 into wild relatives is not expected to be greatly different from that of other varieties of cultivated tobacco.

D. Potential impact on nontarget organisms, including beneficial organisms and threatened or endangered species.

APHIS evaluated the potential for Vector 21-41 tobacco and its products to have damaging or toxic effects on nontarget organisms representative of the exposed agricultural environment, including those that are recognized as beneficial to agriculture or as threatened or endangered in the United States.

The expression of NPTII in tobacco plants is not expected to have deleterious effects or significant impacts on nontarget organisms, including beneficial organisms and threatened and endangered species, based on information provided in the petition (pg. 18) and APHIS analyses of previously deregulated transgenic plants that express NPTII. The protein is not toxic and it shares no homology with proteins known to be toxic or allergenic (U.S. FDA 1998).

The reduced levels of nicotine and total alkaloids in Vector 21-41 are expected to make this tobacco less toxic to insects or other animals that might feed on tobacco. In general, tobacco is not used as a feed plant because of its vertebrate toxicity. Teratogenic problems resulting from tobacco alkaloids have occurred in the United States when pregnant swine were allowed to forage on tobacco stalks (Crowe, 1969). Nicotine is a naturally occurring insecticide and feeding deterrent in *Nicotiana* species, in particular *N. tabacum* and *N. rustica* (Bush and Crowe, 1989). However as noted earlier, many pests of tobacco have adapted to the alkaloids in tobacco or have ways to avoid it (Tso, 1972, Chapter 23, Alkaloids). APHIS' evaluation of the many insects that feed on tobacco indicate that none of these insects feed exclusively on tobacco or other *Nicotiana* species, and therefore they are unlikely to have a specific requirement for nicotine or its metabolites. Reducing sugars, which were reported to be about two fold higher in Vector 21-41 leaves compared to non-transgenic parent line, are not included among the types of defense compounds produced by plants that have toxic or anti-feeding properties.

APHIS can not identify any threatened or endangered species that specifically feed or live on tobacco, and no *Nicotiana* species are listed as threatened or endangered. Vector 21-41 tobacco does not exhibit traits that would expand or change the range in habitats in which tobacco is normally grown, so its cultivation is not expected to displace any plant species. For these reasons, no effect on species recognized or proposed as threatened or endangered in the United States by the U.S. Fish and Wildlife Service is expected.

E. Potential impacts on agricultural and cultivation practices

APHIS considered potential impacts associated with the cultivation of Vector 21-41 tobacco on current agricultural practices, including potential impacts on organic farming. Potential impacts on minorities, low income populations, and children were also considered.

Potential impacts of Vector 21-41 on pest control and other agricultural practices

As noted in Section V.A. above, Vector 21-41 does not have increased susceptibility to diseases or insects when compared to the parent line or to that reported previously for Burley 21-LA or Burley 21 when using a typical disease and insect management program. Various cultural and chemical control methods have been described by agricultural extension services for the management of disease and insect pests of tobacco to which Vector 21-41 is known or likely to be susceptible. There is no reason to believe that these methods would not also be implemented for Vector 21-41 tobacco. The petitioner notes that "The experience from the over 600 farm field trials conducted in five states this year [2001] indicate that existing approved amounts of pesticides labeled for use on tobacco can control insect, disease, and weed problems.". Pesticide use on U.S. tobacco has been restricted and monitored for many years by the USDA under The Food Security Act of 1985. Growers must certify to the Farm Service Agency that any pesticides used in tobacco production have been approved by the EPA for use on tobacco and were applied in accordance with labeled directions. Failure to comply with requirements can result in loss of price support, fines, or imprisonment (USDA, ERS, 2001).

Potential impacts on organic farming

It is not likely that organic farmers, or other farmers who choose not to plant transgenic varieties or sell transgenic tobacco leaf , will be significantly impacted if a determination for non-regulated status were to be granted for Vector 21-41 tobacco for the following reasons. (1) Nontransgenic tobacco will still be sold and will be readily available to those who wish to plant it. (2) USDA's National Organic Program requires that organic farmers plant certified (nonengineered) seed (http://www.ams.usda.gov/nop/nop2000/Final%20Rule/nopfinal.pdf), and if a grower can verify that this was the case, then any adventitious presence of transgenic material in organically grown products will not keep that product from being certified as organic. (3) According to AMS regulations, the reduced-nicotine Vector 21-41 tobacco would need to be grown under contract with the company, therefore growers will know it is transgenic. (4) Vector Tobacco intends to take several steps to ensure identity preservation of its seed stock of Vector 21-41 tobacco (see Petition, pg. 4.). (5) Cross pollination of other tobacco in the field by Vector 21-41 tobacco is highly unlikely (for the reasons described in Section V. Alternative B. Paragraph C. above). (6) Even if cross-pollination of non-transgenic plants were to occur, only an extremely small percentage of transgenic seed would likely be produced, but the leaves harvested from the cross-pollinated plants to be marketed would not be transgenic.

Potential impacts on humans, including minorities, low income populations, and children

Under Executive Order 13045, we attempted to identify and assess environmental health or safety risks that might disproportionately affect children. We also considered any possible adverse impacts on minorities and low income populations as specified under Executive Order 12898. As noted above, APHIS does not anticipate that there will be a significant change in pest control or cultural practices if Vector 21-41 were deregulated, and pesticide use in tobacco is

closely monitored by the USDA. Because Vector 21-41 tobacco has significantly reduced levels of nicotine compared to traditional tobacco, APHIS does expect there to be some benefit to farm workers or their children who might come into contact with tobacco in the field, particularly during topping of the tobacco plants. A green tobacco syndrome is caused by adsorption of nicotine from skin contact in workers who handle wet tobacco plants. Symptoms, including headache, dizziness, and vomiting, have been reported in up to 50% of tobacco handlers. Fortunately they usually resolve within a few hours after tobacco plant contact ceases and contaminated areas of the body are washed (see *Risks From Chemical Use on the Farm* by Frederick W. Oehme DVM, PhD, Comparative Toxicology Laboratories, Kansas State University, at http://www.vet.ksu.edu/links/agromed/oehmemorning.htm.).

F. Potential impacts on raw or processed agricultural commodities.

APHIS analysis of information and data provided in the petition regarding: (1) the disease and insect susceptibility of Vector 21-41 tobacco; (2) the analysis of air-cured leaves for percent nicotine, nor-nicotine, total alkaloids, total nitrogen and reducing sugars; and (3) the analysis of smoke from cigarettes derived from Vector 21-41 tobacco leaves for TSNAs, reveal no differences between either the reported non-transgenic recipient Burley 21-LA or other tobacco that could have a direct or indirect plant pest effect on any raw or processed plant commodity.

G. Potential environmental impacts outside the United States associated with a determination of nonregulated status as requested by Vector Tobacco (USA) Ltd.

APHIS has also considered potential environmental impacts outside the United States and its territories associated with a determination of nonregulated status for Vector 21-41 tobacco. Any international trade in tobacco subject to this determination would be fully subject to national phytosanitary requirements and be in accordance with phytosanitary standards developed under the International Plant Protection Convention (IPPC). The IPPC has set a standard for the reciprocal acceptance of phytosanitary certification among the nations that are signatory to the Convention (116 countries as of June, 2001). In addition, issues that may relate to commercialization and transboundary movement of particular agricultural biotechnology products are being addressed in IPPC and other international fora. APHIS also continues to play a role in working toward harmonization of biosafety and biotechnology guidelines and regulations included within our regional plant protection organization, the North American Plant Protection Organization (NAPPO), which includes Mexico, Canada, and the United States. NAPPO's Biotechnology Panel advises NAPPO on biotechnology issues as they relate to plant protection. APHIS also participates regularly in biotechnology policy discussions at fora sponsored by the European Union and the Organization for Economic Cooperation and Development. APHIS periodically holds bilateral or quadrilateral discussion on biotechnology regulatory issues with other countries, most often with Canada, Mexico, Japan, and Argentina. We also have participated in numerous conferences intended to enhance international cooperation on safety in biotechnology and sponsored several workshops on safeguards for

planned introductions of transgenic crops (crucifers, maize, wheat, potatoes, rice, tomatoes) most of which have included consideration of international biosafety issues. Of particular relevance to crops with their centers of origin in South and Central America, we sponsored a Latin-American Biosafety workshop on field testing and commercialization of transgenic plants. Mexico and many of the countries in South America where most of the wild relatives of tobacco exist (e.g. Brazil, Argentina, and Uruguay) have procedures in place that require a full evaluation of transgenic plants before they can be introduced into their environment.

Alternative C, Approval of the Petition in Part.

Approval of only some of the lines requested in the petition. The petition received from Vector Tobacco (USA) Ltd. requested a determination of nonregulated status for only a single line, Vector 21-41. Data demonstrate that this line was derived from a single transformation event, transformant #41. Therefore, APHIS can consider only that one line for approval.

Approval of the petition with geographic restrictions. APHIS could identify no impacts to the human environment that are specific to a particular geographical region of the United States or its territories. Even if Vector 21-41 tobacco were grown in regions of the United States where it's wild relatives occur, there are several factors described in Section V, Alternative B, Paragraph C, that make gene introgression unlikely, and any impact from gene introgression into wild relatives is expected to be no worse than that from other cultivated tobacco. APHIS could not identify any risks to non-target organisms or to threatened and endangered species. Therefore, APHIS finds no reason to place geographic restrictions on the cultivation or movement of Vector 21-41 tobacco.

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Appendix A

USDA-APHIS approved field tests of Vector 21-41 tobacco.

APHIS Notification Number	States	Effective Date[1]	Acreage Requested
99-180–05N[2]	NC	7/29/99	5.0
01-024-26N	PA	2/23/01	1838.0
01-061-01N	PA	4/01/01	1061.5
01-081-03N	TX	NOT PLANTED	
01-094-07N	MS	5/04/01	100.0
01-102-01N	MS	5/12/01	210.0
01-102-03N	LA	5/12/01	367.0
01-102-04N	IL	5/12/01	1030.0
01-102-05N	PA	5/12/01	424.0
01-114-02N	LA	5/24/01	81.0
01-116-01N	MS	5/26/01	21.0
01-117-03N	IA	5/27/01	6.0
01-122-01N	PA	6/01/01	5.0
01-143-07N	HI	6/22/01	40.0
01-158-01N	IL	7/07/01	20.0

[1]Plantings must take place within one year of the effective date.

[2]Field data report submitted, and included in the petition. Field data reports are due within 6 months of termination of the field test.

Appendix B. Potential for introgression from *Nicotiana tabacum* to its sexually compatible relatives.

N. tabacum has a somatic chromosome number of 2N = 48 (i.e., 24 pairs of chromosomes) and originated in South America as an amphidiploid species resulting from a hybridization of two progenitor species believed to be *N. sylvestris* (2N=24) and *N. tomentosiformis* (2N=24) (Smith, 1979). The USDA, Agricultural Research Service, Germplasm Resources Information Network (GRIN) database recognizes 68 different taxa at the species level within the genus *Nicotiana,* which is subdivided into three subgenera and 14 sections (Smith 1979). Of these species, 45 species are native to North and/or South America, 17 are native to Australia, one is native to Polynesia, Tonga, and S. Melanesia, and one is native to Africa. Others are listed as cultivars. Only six *Nicotiana* species are listed as native to the United States. Their distribution within the United States (as referenced in the GRIN database and references therein), their somatic chromosome number (Smith, 1979), and their reported ability to produce viable, fertile offspring with *N. tabacum* (as described in the petition, pg. 2; and in Chaplan and Burk, 1979; and confirmed in discussion with Dr. David Zaitlin, tobacco breeder, University of Kentucky, Tobacco and Health Research Instititue, personal communication to Susan Koehler, 12/9/01) are summarized in the table below. The potential for genes from *N. tabacum* to naturally introgress into its sexually compatible relatives in the United States is extremely low for several reasons. First, with the exception of *N. plumbaginofolia*, none of these occur in proximity to major areas of cultivation or seed production of tobacco. In the United States, tobacco is typically grown in the midwest and eastern states. Statistics show that for the years 1997-1999, that the largest acreage occurred in the following states in descending order: North Carolina, Kentucky, Tennessee, South Carolina, Virginia, Georgia, Ohio, Indiana, Pennsylvania, Maryland, Florida, Missouri, Connecticut, Wisconsin, West Virginia, and Massachusettes (USDA, NASS, 2000). Most farmers do not produce their own tobacco seed, but use certified seed produced under conditions of reproduction isolation as specified under 7 CFR 201.76, most of which is grown in the same areas where commerical production of tobacco occurs. Second, the species are either not reported to be cross compatible with *N. tabacum* or their progeny exhibit sterility or genetic instability which would further reduce the potential for gene introgression back into the wild population.

Naturally occurring intergeneric crosses with tobacco as one parent (e.g., tobacco x tomato) have not been reported. Intergeneric hybrid plants using tobacco as one parent have been produced under laboratory conditions by fusion of protoplasts (cells lacking cell walls) and subsequent regeneration of whole plants. Most of these intergeneric hybrids are either sterile or produce nonviable seeds (Steward and Krikorian 1979, and Glen Collins, personal communication to Susan Koehler, Nov. 2001).

Nicotiana species native to the United States	Somatic chromosome number	Distribution within the U.S.	Cross-compatible with *N. tabacum*	Fertility of hybrids
N. attenuata Torr. ex S. Watson	2N=24	Western U.S., Mexico to Canada	No	
N. obtusifolia M. Martens & Galeotti (Syn = *N. palmeri* A. Gray and *N. trigonophylla* Dunal)	2N=24	Texas, New Mexico, Arizona, California, Nevada, Utah	Only in laboratory experiments	
N. repanda Willd. ex Lehm.	2N=48	Texas (gulf coast)	Yes	Male sterile
N. quadrivalvis Pursh (Syn = *N. bigelovii* (Torr.) S. Watson)	2N=48	California, Nevada, Oregon	Yes	Male sterile
N. clevelandii A. Gray	2N=48	California, Arizona, New Mexico	No	
N. plumbaginifolia Viv.	2N=20	Florida	Only under controlled conditions.	Male and female sterile: genetic instability, loss of *N. plumb.* genome

References:
See Literature Cited, Section VI.

Appendix C. Data submitted with the petition or in the October 19, 2001 response to the deficiency letter dated September 21, 2001 (RTDL) in support of nonregulated status for Vector 21-41 Tobacco.

Molecular Genetic Characterization and Inheritance Data
NtQPT1 gene is expressed in the roots: Petition Fig. 2., pg. 11. In situ localization of *NtQPT1* mRNA in parraffin sections of tobacco roots.
NtQPT1 promoter is capable of directing transgene expression in a root-specific manner: Petition Fig. 3, pg. 11. Histochemical localization of GUS activity in trangenic roots; Petition Fig. 4., pg. 12. GUS activities in roots, leaves, and stems of transgenic tobacco plants carrying the CaMV 35S promoter, the promoterless GUS, and 5' nested deletions of the *NtQPT1* promoter fused to GUS.
NtQPT1 gene encodes a functional QPTase: Petition Fig. 5., pg. 13. Complementation of *E. coli* Strain TH266 (*nadC*) by expression of the *NtQPT1* cDNA.
Vector 21-41 contains two copies of the *nptII* gene: Petition Fig. 9., pg. 23. Genomic DNA Blot of Vector 21-41 (probed for *nptII*).
Vector 21-41 contains full length copies of the *nptII* gene and *NtQPT1* promoter in the expected orientation: Petition Fig.10., pg. 24. PCR Analysis of the Transgene in Vector 21-41.
Vector 21-41 contains the full length copies of the anti-sense *NtQPT1* cDNA with its *NtQPT1* promoter and *nos* terminator in the correct orientation: Petition Fig. 11., pg. 26. PCR Analysis of the Transgene in Vector 21-41.
Vector 21-41 contains partial *tetA* and *trfA* sequences flanking the left T-DNA border located between the left T-DNA border of the two inverted repeat copies of the T-DNA inserts. Petition Fig. 12., pg. 28. PCR Analysis of the Transgene in Vector 21-41 and Petition Fig. 13., pg. 30. Amplification Between the Two Tandem Inverted T-DNA Repeats.
Vector 21-41 contains no complete protein coding sequences present outside of the T-DNA border in pYTY32: RTDL, Fig. 1, pp. 6-8.
Progeny from transformant T_0 #41 segregated 3:1 for kanamycin resistance: Petition Table 2., pg. 19. T_0 Segregation Analysis of Tranformant #41.
T_2 seeds from plant T_1-1 derived from T_0 #41 are homozygous for kanamycin resistance: Petition Table 3., pg. 20. Segregation Analysis of T_1 Generation of Transformant #41 (for kan^r).
T_1-1, T_2-1, and later generations (T_3 and T_4) designated Vector 21-41 have low nicotine levels in their leaves compared to null segregants. Petition. Table 4. Pg. 21. Nicotine levels in Generations of Vector 21-41 Tobacco.

Phenotypic Characterization: Intended and Unintended Effects
NPTII expression in Vector 21-41 T_4 plants in leaves, roots, and stems as measured by enzyme-linked immunosorbent assays (ELISAs). Petition pg. 31 (See also Table 2 mentioned above for kanamycin resistance.)
Agronomic traits and chemical traits (nicotine, nor-nicotine, total alkaloids, nitrogen and reducing sugars in cured leaves) of Vector 21-41 tobacco grown in Clayton, NC in 2000 compared to promoter control and wild type (Burley 21-LA) plants. Petition Table. 5., pg. 32. (See also Table 4 mentioned above for nicotine content in NC and other locations, and also RTDL, pg. 3, and pg. 13 for additional agronomic data for 53 field trials in PA in 2001.) (AMS also provided nicotine data to APHIS for Vector 21-41 tobacco grown in 2001 at the request of the petitioner.)
Seed production per pod from greenhouse grown plants of Vector 21-41 tobacco compared to Burley 21-LA and four other tobacco varieties. RTDL, Table 1, pg. 12. (Note: Number of pods in that Table 1 refers to the number of pods from which the data was gathered. The number of pods was limited to 50/plant, M. Conkling personal communication 10/24/01.)
Disease and insect susceptibility of Vector 21-41 tobacco. Petition, pg. 31, & RTDL, pp 10-11.
Yields of Tobacco-Specific Nitrosamines in Mainstream Tobacco Smoke: "Standard" Conditions. (Vector 21-41 vs. a "full-flavor" cigarette) Petition Table 6, pg. 34

Appendix D. Determination of non-regulated status for Vector 21-41 tobacco.

In response to a petition (designated 01-121-01p) from Vector Tobacco (USA) Ltd., APHIS has determined that genetically engineered tobacco line Vector 21-41 and progeny derived from it will no longer be considered regulated articles under APHIS regulations at 7 CFR Part 340. Permits or acknowledged notifications that were previously required for environmental release, importation, or interstate movement under those regulations will no longer be required for Vector 21-41 tobacco and its progeny. Importation of seeds and other propagative material would still be subject to APHIS foreign quarantine notices at 7 CFR Part 319 and the Federal Seed Act regulations at 7 CFR Part 201. This determination is based on APHIS' analysis of field, greenhouse, and laboratory data and references provided in the petition and other relevant information as described in this environmental assessment that indicate that Vector 21-41 will not pose a plant pest risk for the following reasons. (1) It exhibits no plant pathogenic properties - although a plant pathogen was used in the development of this tobacco, these plants are not infected by this organism, nor do they contain genetic material from this pathogen that can cause plant disease. (2) It exhibits no characteristics that would cause it to be more weedy than the non-transgenic parent tobacco line or other cultivated tobacco. (3) Gene introgression from Vector 21-41 tobacco to native, introduced, or naturalized species of *Nicotiana* in the United States is extremely unlikely, and it is not likely to increase the weediness potential of any resulting progeny nor adversely effect genetic diversity any more than would introgression from other cultivated tobacco. (4) Given current tobacco pest management practices and grading and certification systems for tobacco leaf, the disease and insect susceptibility of Vector 21-41 tobacco and the quality characteristics of its cured leaves should not cause a direct or indirect plant pest effect on raw or processed plant commodities, nor should it reduce the ability to control pests in tobacco or other crops, compared to the non-transgenic parent or other tobacco. (5) It has no potential to have a greater damaging, harmful, or toxic effect on organisms beneficial to agriculture than does other cultivated tobacco. In addition to our finding of no plant pest risk, there will be no affect on threatened or endangered species resulting from a determination of non-regulated status for Vector 21-41 tobacco and its progeny.

APHIS also has concluded that there may be new varieties bred from Vector 21-41 tobacco; however, they are unlikely to exhibit new plant pest properties, i.e., properties substantially different from any observed for tobacco descended from Vector 21-41 tobacco, or those observed for other tobacco varieties not considered regulated articles under 7 CFR Part 340.

Cindy Smith
Acting Deputy Administrator
Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture
Date: SEP 16 2002

Reference #17

United States Department of Health and Human Services (HHS). 2010. How Tobacco Smoke Causes Disease. A Report of the Surgeon General.

The full report is available online at:

http://www.surgeongeneral.gov/library/tobaccosmoke/report/full_report.pdf

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CLEARING THE SMOKE

ASSESSING THE SCIENCE BASE FOR TOBACCO HARM REDUCTION

Kathleen Stratton, Padma Shetty, Robert Wallace, and
Stuart Bondurant, Editors

Committee to Assess the Science Base for Tobacco Harm Reduction

Board on Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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Support for this project was provided by the Food and Drug Administration (FDA) prior to the March 2000 decision by the Supreme Court denying FDA comprehensive authority over tobacco products. The views presented in this report are those of the Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction and are not necessarily those of the funding agencies.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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Preface

Tobacco has been used by humans for at least a millennium, and its harmful effects have been suspected for at least 200 years. In the last 50 years, convincing and generally accepted evidence has established the fact that exposure to tobacco products is the major single cause of early human mortality and morbidity in developed nations and in many developing nations as well.

Even nonsmokers suffer morbidity and excess mortality from the toxic effects of inhalation of sidestream smoke. Both smokers and their nonsmoking associates are more likely to be injured in fires and automobile accidents. The personal and social price we pay for establishing and sustaining nicotine addiction through exposure to tobacco smoke is our greatest controllable health cost and one of our greatest social burdens.

It has been scientifically established that reduced exposure to tobacco smoke by lifelong abstinence and avoidance of smoke eliminates the added risk and harm and that cessation, even after many years of smoking, reduces risk and harm both immediately and in the long term for many tobacco-related conditions.

Several smoking cessation programs, some aimed at individuals and some at communities, have been shown to be modestly effective in assisting smokers to quit smoking. These programs have been shown to be more effective with the added use of nicotine replacement by patches for absorption through the skin, by nicotine-containing chewing gum or sprays for absorption through oral or nasal mucous membranes, or by the administration of psychotropic drugs to reduce the desire for nicotine.

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However, with the most intensive application of the most effective known programs for prevention and cessation, approximately 10-15% of the adults in the United States are expected to be regular users of tobacco in 2010, and they will continue to suffer the increased incidence of harmful and lethal consequences. Among this group are many who cannot or will not stop using tobacco, and it is to this group that effective programs and products of harm reduction should be directed.

New tobacco products and nicotine replacement products are being marketed frequently and, along with products now on the market, often have associated direct or implied health claims. Some of the new products differ from traditional products in ways that appear minor, whereas others involve substantial changes in types of tobacco, in additives, or in curing, blending, or processing of the tobacco. New products may also change the composition of the aerosol the consumer inhales compared to cigarette smoke by changing the burning temperature of the tobacco by new methods of combustion, by limiting the release of smoke into the atmosphere, by dilution of the smoke with air, and/or by adding unnatural carriers for smoke particles.

Although many components of tobacco are known to be toxic, little is known of the specific dose-response relations of the individual toxins as they occur in cigarette smoke or of the interactions between the constituents of tobacco smoke. There is little direct evidence that removal of specific substances from tobacco smoke or from tobacco actually reduces risk or harm to human health. In considering the health effects of modified tobacco products it is important to remember that the health consequences of the use of any such product are determined not by the toxic agents removed from the product but by the actual exposure to the toxins that remain. Harm reduction is the net difference in harm between the products as actually used.

There is strong evidence that in the range of exposures involved in smoking, there is a quantitative relationship between the magnitude of exposure and the incidence of cancer, coronary vascular disease, pulmonary disease, and several other tobacco-related illnesses. Rarely if ever is there impartial and thorough assessment of the risk associated with new tobacco products relative to the risk of abstinence or the risk of other tobacco products prior to marketing. Unlike new tobacco products, nicotine replacement products are subject to full disclosure of content, rigorous testing, and the regulation of marketing claims by the of the Food and Drug Administration.

In addition to cigarette smoke, other forms of tobacco such as cigars, chewing tobacco, and snuff are also vectors of nicotine addiction and often have their own sets of serious toxic consequences.

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The latent period between beginning exposure to tobacco and the development of most of the major adverse consequences is so long that empirical, direct evidence (assessment of immediate and long-term toxicity of individual tobacco products in humans) that one tobacco product is less harmful than another will rarely be available in time to be a basis for informing users. In the absence of direct evidence, conflicting claims of the degree of harm reduction are likely and informed usage decisions by smokers and nonsmokers will be difficult.

No one knows the dose-response relations, the specific toxins, the pathogenic mechanisms, or the interrelationship between the many components of tobacco smoke with enough precision to make scientifically reliable quantitative judgments about the risk or actual harm reduction associated with use of any tobacco product. Since we do not know which of many toxins may be the cause of specific harmful effects, we can only infer but we cannot know the health effects of the elimination of any one or several tobacco components. Further, we are just beginning to identify and understand the genetic basis and other causes of the differences in susceptibility to toxic effects among groups or individuals that largely determine the response of an individual to a toxin.

Nonetheless, it is reasonable to expect that some of the new products will reduce exposure to tobacco toxins and possibly reduce harm to some users and to others who are exposed to them. It is, therefore, urgent and important that the assessment of exposure to tobacco toxins resulting from the use of modified tobacco products or drugs be based on the best available evidence, made by the most qualified judges, and communicated to policy makers and the public completely and honestly.

There is little direct evidence available to serve as a basis for judgment as to the potential for harm reduction of specific new tobacco and pharmaceutical products. Therefore, any conclusions as to the relative harm of these products must necessarily be inferred from a base of indirect knowledge. The continuing introduction of new tobacco products with implicit or explicit claims of risk or harm reduction makes it important and urgent that the capacity for the best possible scientific assessment of these claims be put in place.

Since even the availability of harm reduction products may deter some from following the healthier course of abstinence or cessation, assessment of health claims should be based on an estimate of the effect of the product on the prevalence of smoking in the population, as well as the effect on the health risk to the individual smoker.

The most reliable scientific interpretation of necessarily incomplete indirect evidence comes when individuals who are experts in the related fields are not biased and are free of conflict of interest form a consensual

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judgment. Such a judgment based on evidence of high quality should be a requirement for a conclusion that the use of a product is in fact associated with decreased exposure to toxins and that the decreased exposure is likely to be associated with less harmful outcomes.

Further, since these judgments of risk will necessarily be inferential because they are based on indirect and inconclusive evidence, some form of postmarketing surveillance of each product is important.

The charge to the committee is to address the science base for harm reduction from tobacco. The committee concluded early in its deliberations that the science base for harm reduction will evolve over time. There will inevitably be important interactions between the types of products that are developed and the science base. There will also be interactions between any regulatory process and the science base (the science base will influence regulation, and regulation will focus pertinent science) and, obviously, between regulations and products. For these reasons, the committee realized that the science base for harm reduction can be usefully considered only in the context of some sense of the types of specific products and of the consequences of regulation. Accordingly, portions of this report address both general categories of potential harm reduction products and regulatory considerations.

It is the strong sense of the committee that claims of less harm or risk associated with the use of tobacco products or drugs should be available—but only if four conditions are met: (1) There should be strong and widely available programs designed to avoid initiation and to achieve abstinence; (2) There should be premarketing evidence satisfactory to a group of disinterested experts that—as the product will actually be used by consumers—there is less exposure to toxic agents without coincidental increase in harm to the individual from other smoke components or to the population from encouraging initiation or continuation of smoking, the burden of proof of assertions of harm reduction should rest entirely with those making the assertion; (3) The public should be fully informed of the strength of the claims as assessed by an independent panel of experts; and (4) There should be an effective surveillance system in place to determine short-term behavioral and the long-term health consequences of the use of the new products.

The committee wishes to express its great appreciation to the many individuals, listed in Appendix B, who contributed generously and substantially to its deliberations. Representatives of many health agencies as well as tobacco interests responded thoughtfully and extensively to the committee's questions.

Dr. Kathleen Stratton contributed perspective, insight, meticulous attention to detail, and essential oversight to the work and report. This

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report would not be possible without her substantial and important contributions.

Dr. Padma Shetty assumed responsibility for blocks of the report, and both the full report and many specific parts are testimony to her analytic, organizational, and expressive proficiency. Ann St. Claire organized the arrangements for the work of the committee with great finesse and also made useful contributions to the analytical work of the committee. Every member of the committee is deeply appreciative of the work of Dr. Stratton, Dr. Shetty, and Ms. St. Claire.

Stuart Bondurant
Chair

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REVIEWERS

The report was reviewed by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments to assist the authors and the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the review comments and the draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the report review process:

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Judith Wilkenfeld, Campaign for Tobacco Free Kids
Gerald Wogan, Massachusetts Institute of Technology
Raymond Woosley, Georgetown University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **David Challoner**, (review monitor) University of Florida and **Hugh Tilson**, (review coordinator) University of North Carolina. Appointed by the

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National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Executive Summary

BACKGROUND

Tobacco smoke is the cause of the most deadly epidemic of modern times. Smoking causes cancer (e.g., lung, oral cavity, esophagus, larynx, pancreas, bladder, kidney), chronic obstructive pulmonary disease (COPD), myocardial infarction, and stroke. The continuing toll of tobacco use has prompted the search for means of harm reduction for those who cannot or will not stop using tobacco. Numerous products that make implied or explicit claims to reduce the burden of smoking while allowing continued nicotine consumption are now entering the market. This report is concerned with the evaluation of these products.

Nearly one-quarter of adult Americans—an estimated 47 million people—smoke cigarettes (CDC, 2000a). Although this is far lower than the 42% recorded in 1965, the decline in the rates of smoking among adults appears to have leveled off during much of the 1990s (PHS, 2000). In a recent survey, 12.8% of middle school children and 34.8% of high school students reported some form of tobacco use during the month prior to their being interviewed (CDC, 2000b). The vast majority of smokers begin tobacco use during adolescence (IOM, 1994). However, 70% of smokers say they want to quit (CDC, 1994), and 34% of smokers make an attempt to quit each year. Thus, many but not all tobacco users find it very difficult to quit and continually expose themselves to known toxic agents.

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DEFINITION OF HARM REDUCTION

For the purposes of this report, a product is harm-reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants. Many different policy strategies may contribute to harm reduction. However, this report focuses on tobacco products that may be less harmful or on pharmaceutical preparations that may be used alone or concomitantly with decreased use of conventional tobacco. The committee does not use the term "safer cigarette," in particular, in order to avoid leaving the impression that any product currently known is "safe." Every known tobacco-containing product exposes the user to toxic agents; every pharmaceutical product can have adverse effects.

HISTORY OF EFFORTS TO REDUCE HARM FROM CIGARETTES

There have been many efforts in the past to develop less harmful cigarettes, none of which has proved to be successful. One of the first innovations with the promise of harm reduction was the development of cigarettes with filters. Filters attempt to reduce the amount of toxicants that go into the smoke inhaled by the smoker. The next major modification of cigarettes with safety implications was "low-yield" cigarettes. These products emit lower tar, carbon monoxide (CO), and nicotine than other products as measured by the Federal Trade Commission (FTC) assay (the "smoking machine"). Many consumers believed, and still do, that these products pose less risk to health than other cigarettes.

However, data on the health impact of low-yield products are conflicting, in part due to a lack of systematic study early in the introduction of the products. Most current assessments of morbidity and mortality suggest that low-yield products are associated with far less health benefit, if any, than would be predicted based on estimates of reduced toxic exposure using FTC yields. In order to maintain the desired intake of nicotine, many smokers who changed to low-yield products also changed the way they smoked (e.g, compensated by inhaling more deeply than when smoking higher-yield products). Thus, their exposure to tobacco toxicants is higher than would have been predicted by standardized assays and people who have continued to use these products have not significantly reduced their disease risk by switching to them. Moreover, widespread use of these products might have increased harm to the population in the aggregate if tobacco users who might otherwise have quit did not, if former tobacco users resumed use, or if some people who would otherwise not have used tobacco did so because of perceptions that the risk with low-yield products was minimal.

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TYPES OF EXPOSURE REDUCTION PRODUCTS

Tobacco and cigarette-like products have been introduced recently that, under measurement systems such as the FTC smoking machine, result in decreased emission of some toxicants compared to conventional tobacco products. Currently available products include tobacco with reportedly reduced levels of some carcinogens and cigarette-like products that deliver nicotine with less combustion than cigarettes. Two classes of pharmaceutical products approved by the Food and Drug Administration (FDA) for short-term use in smoking cessation might also be used for harm reduction. These include nicotine products, such as in patch, gum, inhaler, and nasal spray preparations, and a nonnicotine product that reduces the craving for tobacco. These cessation drugs could be used long term to maintain cessation or concomitantly with continued but decreased use of conventional tobacco products (see Table 1).

These tobacco and pharmaceutical products could *potentially* result in reduced *exposure* to toxicants. The committee uses *potentially*, because whether exposure to tobacco toxicants is reduced depends on the user's behavior, such as frequency and intensity of use. Reduced exposure, however, does not necessarily assure reduced risk to the user or reduced harm to the population. Therefore, and in order to avoid misinterpretation, the committee uses the generic phrase "potential reduced-exposure products," or PREPs, when discussing the modified tobacco products, cigarette-like products (whether tobacco containing or not), or pharmaceutical products and medical devices (whether nicotine containing or not) used for their tobacco harm reduction potential. More such products are likely to be introduced in the near future, perhaps accompanied by claims that they are less harmful than conventional products.

THE COMMITTEE CHARGE AND ASSUMPTIONS

The Institute of Medicine (IOM) convened a committee of experts to formulate scientific methods and standards by which PREPs (pharmaceutical or tobacco-related) could be assessed. Four questions were imbedded within the charge given to the committee by the Food and Drug Administration in December 1999. Where there are not yet answers, the committee was asked to outline the broad strategy by which the knowledge base might be assembled.

1. Does use of the product decrease exposure to the harmful substances in tobacco?
2. Is this decreased exposure associated with decreased harm to health?

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TABLE 1 Potential Reduced-Exposure Products

Category	Descriptors	Examples
Modified tobacco	Reduced yield of selected toxicants	Advance™, low-nitrosamine tobacco cigarettes, Snus, reduced nitrosamine smokeless tobacco
Cigarette-like products	Less combustion than cigarettes	Premier™ (off market) Eclipse™ Accord™
Pharmaceutical products	Nicotine replacement	Nicotine gum, patches, inhaler, nasal spray
	Antidepressants that reduce nicotine craving	Bupropion SR, nortriptyline
	Other medications	Nicotine antagonists, clonidine

3. Are there surrogate indicators of this effect on health that could be measured in a time frame sufficient for product evaluation?
4. What are the public health implications of tobacco harm reduction products?

The first three questions deal with the adequacy of current scientific methods to determine whether and to what extent these products reduce the risk of morbidity and mortality and the nature of the advice to give to citizens, health professionals, and others. The fourth question is important because it addresses the population impact of these products. That is, although a product might be risk-reducing for an individual's health compared to conventional tobacco products, its use might not be harm-reducing for the population as a whole. The fourth question is also important because the answer lays the groundwork for educational, policy, and regulatory actions.

The committee reviewed the literature and assessed the nature and availability of the data needed to evaluate the feasibility of tobacco harm reduction. Its review encompassed the major disease categories linked by scientific evidence to tobacco consumption, including cancer, cardiovascular disease, respiratory disease, reproductive and developmental disorders, and others. The report is offered to relevant federal and state regulatory and policy bodies, Congress, scientists and health care professionals,

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tobacco and pharmaceutical industries, and—most importantly—the public, who will have to decide whether or not to use these products.

The committee began with fundamental operating precepts, reiterating and reaffirming overwhelming scientific evidence and the conclusions of many scientific and policy advisory bodies:

Precept 1. Tobacco use causes serious harm to human health.

Precept 2. Nicotine is addictive.

Precept 3. The best means to protect individual and public health from tobacco harms are to achieve abstinence, prevent initiation and relapse, and eliminate environmental tobacco smoke exposure.

Precept 4. A comprehensive and authoritative national tobacco control program, with harm reduction as one component, is necessary to minimize adverse effects of tobacco.

PRINCIPAL CONCLUSIONS

The committee does not evaluate specific PREPs in this report, since the currently available tobacco-related PREPs in particular are most likely prototypes of limited life span. Under present regulatory conditions, tobacco-related PREPs can be changed with little assessment and without disclosure of their contents. Therefore, the committee considered the types of PREPs currently or likely to become available in the foreseeable future. After reviewing a large body of scientific documents and data, hearing presentations from many scientific, regulatory and industrial interests, and publicly soliciting comments on the issues at hand, the committee reaches the following principal conclusions regarding the questions posed by the charge:

Conclusion 1. *For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.* This conclusion is based on studies demonstrating that for many diseases, reducing tobacco smoke exposure can result in decreased disease incidence with complete abstinence providing the greatest benefit.

Conclusion 2. *PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use.* One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Carefully and appropriately conducted clinical and epidemiological studies could demonstrate an effect on health. However, the

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impact of *PREP*s on the incidence of most tobacco-related diseases will not be directly or conclusively demonstrated for many years.

Conclusion 3. *Surrogate biological markers that are associated with tobacco-related diseases could be used to offer guidance as to whether or not PREPs are likely to be risk-reducing.* However, these markers must be validated as robust predictors of disease occurrence and should be able to predict the range of important and common conditions associated with conventional tobacco products. Furthermore, the efficacy of PREPS will likely depend on user population characteristics (e.g., those defined by gender, genetic susceptibility, ethnicity, tobacco history, and medical history).

Conclusion 4. *Currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.* Many techniques exist to assess exposure reduction, but the report contains many caveats about the use of all of them, including usually an unknown predictive power for harm.

Conclusion 5. *Regulation of all tobacco products, including conventional ones as recommended in IOM, 1994, as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected.* Regulation is needed to assure that adequate research (on everything from smoke chemistry and toxicology to long-term epidemiology) is conducted and to assure that the public has current, reliable information as to the risks and benefits of PREPs. Careful regulation of claims is needed to reduce misperception and misuse of the products. If a PREP is marketed with a claim that it reduces (or could reduce) the risk of a specific disease(s) compared to the risk of the product for which it substitutes, regulation is needed to assure that the claim is supported by scientifically sound evidence and that pertinent epidemiological data are collected to verify that claim.

Conclusion 6. *The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.* The effect on public health will depend upon the biological harm caused by these products and the individual and community behaviors with respect to their use. Regulation cannot assure that the availability of risk-reducing PREPs will lead to reduced tobacco-related harm in the population as a whole. However, a regulatory agency can assure that data are gathered that would permit the population effects to be monitored. If tobacco use increases or tobacco-related disease increases, these data would serve as a basis for developing and implementing appropriate public health interventions.

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PRINCIPAL RECOMMENDATIONS

The committee believes that harm reduction is a feasible and justifiable public health policy—but only if it is implemented carefully to achieve the following objectives:

- Manufacturers have the necessary *incentive* to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;
- Consumers are fully and accurately *informed* of all of the known, likely, and potential consequences of using these products;
- Promotion, advertising, and labeling of these products are firmly *regulated* to prevent false or misleading claims, explicit or implicit;
- Health and behavioral effects of using PREPs are *monitored* on a continuing basis;
- Basic, clinical, and epidemiological *research* is conducted to establish their potential for harm reduction for individuals and populations; and
- Harm reduction is implemented as a *component* of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

Recommendations about future research needs are based on Principal Conclusions 1-4 and can be found in the following section. They flow primarily from material presented in Section II of the report. Progress in these areas will permit the application of the principles of risk assessment to the evaluation of PREPs in the future. At present, judgement informed by incomplete science will be used to evaluate PREPs. However, immediate actions are required. Therefore, the committee makes recommendations that address Principal Conclusions 5 and 6. These conclusions and recommendations are particularly intertwined, requiring immediate attention and swift action.

The effect of PREPs could be to increase or decrease tobacco-related disease in the population. Assessing a positive public health impact will be difficult and will require extensive surveillance and research to ensure that the impact is positive. Even the strongest surveillance system could not alone provide minimal assurance of safety or protection of the public. Currently there is little public authority over tobacco products of any type. Whatever the current legal or regulatory posture with respect to these products, the committee realized that in order to obtain the best available scientific evaluation of emerging tobacco-related PREPs and to provide the best advice on use of all PREPs to the public, some national authority over these PREPs is needed. Only a comprehensive program of

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regulation and assessment including extensive premarket testing and surveillance offers a reasonable possibility of net gain in health from use of PREPs instead of conventional tobacco product use.

Therefore, the committee recommends development of a surveillance system to assess the impact of promotion and use of PREPs on the health of the public. A national comprehensive surveillance system is urgently needed to collect information on a broad range of elements necessary to understand the population impact of tobacco products and PREPs, including attitudes, beliefs, product characteristics, product distribution and usage patterns, marketing messages such as harm reduction claims and advertising, the incidence of initiation and quitting, and nontobacco risk factors for tobacco-related conditions. There should be surveillance of major smoking-related diseases as well as construction of aggregate population health measures of the net impact of conventional products and PREPs.

The surveillance system should consist of mandatory, industry-furnished data on tobacco product constituents and population distribution and sales. Resources should be made available for a program of epidemiological studies that specifically address the health outcomes of PREPs and conventional tobacco products, built on a robust surveillance system and using all available basic and clinical scientific findings.

The committee further recommends strengthened federal regulation of all modified tobacco products with risk reduction or exposure reduction claims, explicit or implicit, and any other products offered to the public to promote reduction in or cessation of tobacco use. The committee outlines 11 principles to govern the regulation of PREPs. The regulation proposed by this committee is narrowly focused on assuring that the products reduce risk of disease to the user and accumulating data that would indicate whether or not the products are harm-reducing for the population in the aggregate. Other potential regulatory approaches to tobacco control are not addressed within this report.

The recommended regulatory structure builds on the foundation of existing food and drug law, with appropriate adaptations to take into account the unique history and toxicity of tobacco products. These principles envision testing and reporting for all tobacco products, approval of claims regarding reduced exposure and reduced risk regarding tobacco or cigarette-like products, and retention of current FDA regulation of pharmaceutical PREPs. Manufacturers of tobacco products and pharmaceuticals should be encouraged to develop and introduce new products that will reduce the burden of tobacco-related disease. The regulatory system proposed in this report is not to be viewed in isolation. It is

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proposed as an essential component of a package of public health initiatives (including research, education, and surveillance) that this committee believes is necessary to realize whatever benefit tobacco and pharmaceutical product innovation can offer in reducing the nation's burden of tobacco-related illness and death. (See Box 1.)

Research Conclusions and Recommendations

Many fruitful research directions should be explored to strengthen the scientific basis for assessing harm reduction. In reviewing the range of scientific disciplines and disease areas, the committee specifically noted five general scientific issues: (1) description of the dose-response relationship between tobacco smoke and/or constituent exposure and health outcomes, (2) identification and development of surrogate markers for disease, (3) the utility of preclinical research, (4) utility of short-term clinical and epidemiological studies, and (5) the role of long-term epidemiological studies and surveillance. The committee has reviewed the evidence available regarding these points and has described a research agenda to facilitate evaluation of the harm reduction potential of these products. This section summarizes the committee's conclusions and recommendations for future research, which are elaborated in detail in Section II of this report.

1. *Currently available data allow estimation, albeit imprecise, of a dose-response relationship between exposure to whole tobacco smoke and major diseases that can be monitored for evaluation of harm reduction potential.*

There are more than 4,000 different chemicals in tobacco smoke; many of these are known to be toxic. Many of the mechanisms of pathogenesis attributed to tobacco use have been explicated, and in a few cases, causative tobacco constituents have been identified. In order to effectively evaluate the toxic effects of tobacco smoke and identify the primary causal agents, the toxic components of PREPs and comparison products must be identified and be disclosed. For the most part, the data are insufficient to accurately describe the relationship of tobacco use and disease formation at the level of detail that would establish all causal agents involved or the exact dose-response relationship. The characteristics of this relationship vary among diseases and are affected by differences in compensation and actual exposure and by interindividual or population differences. Consequently, the confidence with which the adverse effects or harm reduction potential of PREPs can be extrapolated, especially at low doses, is uncertain. Also, there is currently no evidence to support a threshold level of tobacco exposure below which no risk exists for any of the reviewed health outcomes.

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BOX 1
Regulatory Principles

Regulatory Principle 1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.

Regulatory Principle 2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various tobacco smoke constituents should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

Regulatory Principle 3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models as well as appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.

Regulatory Principle 4. Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, as compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that measurable reduction in morbidity and/or mortality (in subsequent clinical or epidemiological studies) would be anticipated, as judged by independent scientific experts.

Regulatory Principle 5. The labeling, advertising, and promotion of all tobacco-related products with exposure-reduction or risk-reduction claims must be carefully regulated under a "not false or misleading" standard with the burden of proof on the manufacturer, not the government. The agency should have the authority and resources to conduct its own surveys of consumer perceptions relating to these claims.

Regulatory Principle 6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct post-marketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

Regulatory Principle 7. In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to *increase* the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects or other adverse

continues

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BOX 1 Continued

health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

Regulatory Principle 8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and subject to a comprehensive toxicological review.

Regulatory Principle 9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of contaminants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.

Regulatory Principle 10. The regulatory agency should have enforcement powers commensurate with its mission, including power to issue subpoenas.

Regulatory Principle 11. Exposure reduction and risk reduction claims for drugs that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

In summary, current knowledge of the dose-response relationships is sufficient to support risk reduction through exposure reduction as a goal for the individual through the use of these various products. To date, these relationships are not defined well enough in terms of specific components of smoke to serve as a predictive tool for the effect a particular product will have on most health outcomes. However, a strong quantitative relationship between maternal tobacco exposure and the incidence of spontaneous abortions and intrauterine growth retardation leading to low infant birthweight has been documented extensively. This population is one in which the actual health effects of PREPs and potential for harm reduction may be most directly evaluated. Further discussion regarding dose-response can be found in the disease-specific chapters in Section II (Chapters 12–16).

2. *Although candidate disease-specific surrogate markers are currently available, further validation of these markers is needed. In addition, other biomarkers that accurately reflect mechanisms of disease must be developed to serve as intermediate indicators of disease and disease risk.*

Biomarkers are measurements of any tobacco constituent, tobacco smoke constituent, or effect of such a compound in a body fluid (including exhaled air) or organ. Although some biomarkers currently exist, these require further validation and more must be developed that have adequate sensitivity, specificity, and limited complexity and that quantitatively link biological exposure of tobacco smoke or specific constituents to disease induction or progression prior to the advent of clinically apparent

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disease. Validation and development of biomarkers will provide a stronger foundation by which to make scientific evaluations and regulatory decisions regarding PREPs.

Although no panel of markers can be utilized currently to evaluate the health effects of PREP use, potential biomarkers have been and are being developed for many of the relevant disease categories. The committee recommends further study of biomarkers for various disease categories that may potentially be determined to be intermediate indicators of disease and disease risk. For example, possible measures include markers of platelet and vascular activation, lipid peroxidation, and inflammation, which have the potential to be related to measures of cardiovascular physiology and, ultimately, reflect the risk of clinical cardiovascular disease as well as markers of inflammation in lung disease. Also, biomarkers of cancer that may indicate early carcinogenic processes and risk of cancer development include but are not limited to markers of genetic damage in blood, sputum, urine, and internal organs. Another potential marker is the measurement of bone density as a direct reflection of the severity and risk of osteoporosis.

Ideally, a set of behavioral markers is needed to monitor product use patterns, thereby enabling clinicians and researchers to measure substitution of PREP use for cessation. Although the committee realizes the difficulty of developing a set of such behavioral markers, they are needed for a comprehensive evaluation of PREPs. A further detailed research strategy regarding the development of biomarkers can be found in the disease-specific chapters (Chapters 12–16) and the chapter on exposure and biomarkers assessment (Chapter 11).

3. *The evaluation of PREPs will be facilitated by the development of appropriate animal models and in vitro assays of the pathogenesis of tobacco-attributable diseases.*

Animal models and in vitro testing can contribute to the evaluation of individual PREPs and to the development of a scientific basis for designing and evaluating harm reduction products. Such studies could include cell culture, animal studies, and molecular studies to document specific toxicants as the most likely causative agents, to better define pathogenic effects of tobacco smoke exposure, to better explain the relationship of disease risk regression and exposure regression (dose-response relationships), and to validate biomarkers of exposure and biological effect.

The new technologies of genomics and proteomics have the potential for evaluating and comparing the effects of tobacco exposure and PREP use on gene translation and expression in neoplastic and nonneoplastic disease.

The committee recommends specific applications of pre-clinical models for specific tobacco-attributable disease. For example, the committee

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recommends the utilization of genomic and proteomic technologies to investigate the effect on gene translation and expression of tobacco smoke exposure and its relevance for pulmonary, cardiovascular, and neoplastic health outcomes. Also, accurate models are needed for smoke or tobacco constituent exposure (including nicotine) and exposure to PREPs and their effects on the development of COPD, cardiovascular disease, neoplasia, and in utero injury. Again, a more detailed pre-clinical research agenda can be found in the disease-specific chapters in Section II (Chapter 12–16).

4. *Short-term clinical and epidemiological studies in humans are required for the comprehensive evaluation of PREPs.*

Some effects of PREPs in humans could be evaluated by epidemiological studies, by measurement of intermediate disease markers or, in some cases, by clinical studies of smokers who are unwilling or unable to quit but are willing to use PREPs (compared to a control group of conventional tobacco product users). The committee recommends the utilization of validated intermediate biomarkers of disease effect in these studies in order to assess potential harm reduction within a practical time frame for diseases that occur only after prolonged exposure. Examples of potential measures include the use of lung function tests or inflammatory changes, evaluated through bronchoalveolar lavage, as intermediate markers for COPD in interventional studies.

A few smoking-attributable diseases develop after relatively brief exposure (weeks to months) and provide an opportunity for strong short-term clinical and epidemiological studies. These diseases include intrauterine growth retardation leading to low infant birthweight, slowed wound or ulcer healing, and perhaps acute myocardial infarction. Human studies are also required for evaluating the relationship of individual smoking history, environment, gender, race, and other factors (e.g., diet) to disease risk and susceptibility. Further discussion regarding the utilization of clinical studies can be found in Section II (Chapters 12–16).

5. *Long-term epidemiological studies of populations and/or pilot groups of users should monitor the incidence of disease or other adverse effects.*

Most tobacco-related diseases develop clinically over many years, and the only direct and definitive way to evaluate the harm reduction value of PREPs is to monitor the health outcomes of users compared to appropriate control groups over an extended period of time. Such surveillance could be an add-on to other epidemiological studies and should include ongoing reports of smoking behavior, types of products used, and health outcomes, as well as intermittent collection of biological samples for biomarker assessment in a segment of users. Further discussion can be

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found in Chapter 6 and in the disease-specific chapters in Section II (Chapters 12–16).

Risk Assessment

A report published in 1983 by a committee of the National Research Council (NRC) outlined important steps and considerations in risk assessment (NRC, 1983). The "Red Book" identified important steps: hazard identification (Does the toxicant cause the adverse effect?), dose-response assessment (What is the relationship between dose and incidence in humans?), exposure assessment (What exposures are currently experienced or anticipated under difference circumstances?), and risk characterization (What is the estimated incidence of the adverse effect in a given population?). A risk characterization provides important information for risk management, which also includes public health, social, economic, and political considerations.

The committee did not do a formal risk assessment of PREPs. The knowledge base is inadequate to do so at this time. However, the "Red Book" framework has great utility in presenting the committee's work. Table 2 uses it to summarize material discussed in Chapters 1, 5, 6, 7 and 8. Even though the committee has concluded that harm reduction through the use of PREPs is not yet convincingly demonstrated, Table 2 illustrates how the committee's conclusions and recommendations are key to gathering important data. This new knowledge base will permit a more definitive evaluation of harm reduction as a strategy and of PREPs as tools for reducing tobacco-related morbidity and mortality.

Based on an extensive review of the scientific and medical literature, the committee concludes that although harm reduction is feasible, no currently available PREPs have been shown to be associated with biologically relevant exposure reduction or with decreased tobacco-related harm. One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Without a comprehensive program of scientific research, surveillance, and regulation, the potential benefit of harm reduction will go unrealized. Furthermore, without such a comprehensive program PREPs could, in fact, be detrimental to both individual and public health.

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TABLE 2 Use of Risk Assessment Framework in Assessing Tobacco Harm Reduction

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Information required as described in 1983 "Red Book"	Epidemiology Animal bioassay Short-term studies Comparisons of molecular structure	Epidemiology Low-dose extrapolation Animal to human extrapolation	Dose to which humans are exposed Dose of special populations Estimation of size of population potentially exposed	Estimate of the magnitude of the public health problem	A risk-assessment (qualitative or quantitative) may be one of the bases of risk management
Challenges in risk assessment of conventional tobacco products	Complex mixture Animal models are limited Constituents and additives are proprietary information	Dose changes for an individual over time Dose of individual toxicants varies over time Exposure at time of disease progression	Changes in smoking topography Complex mixture	For which disease? At which point in smoking history?	FTC regarding advertising
Additional challenges of PREP risk assessment	Tobacco-related products will change rapidly with time	Assessing effect of moving backwards on a dose-exposure curve, assuming long-time previous higher exposure	Changing exposure after long-term higher dose exposure Some toxicants could increase	Need models to consider effects on initiation, cessation, and relapse	FDA authority currently exerted only over pharmaceutical PREPs

continues

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TABLE 2 Continued

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Committee charge	1. Does product decrease exposure to the **harmful substances** in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product **decrease exposure**?	4. What are the public health implications?	4. What are the public health implications?
Disease-specific summary data (Chapter 5; Section II)	3. Utility of preclinical research to judge feasibility	1. Dose-response data for conventional tobacco products 2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	5. Long-term epidemiological studies and surveillance	
Principal conclusions	1. Risk reduction is feasible 4. Exposure reduction can be demonstrated.	3. Surrogate measures could be used to predict risk reduction	4. Exposure reduction can be demonstrated	1. Risk reduction is feasible 2. Risk reduction not yet demonstrated 6. Public health impact is unknown	5. Regulation is a necessary precondition for assuring a science base and for assuring protection of the health of the public

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Elements of surveillance system	Specific tobacco constituents of both the products and the smoke they generate	Disease outcomes	Consumption of tobacco products and of PREPs Biomarkers of exposure to tobacco products Personal tobacco product use and related behavioral patterns	Disease outcomes	Tobacco product marketing, including PREPs
Regulatory principles (all refer to tobacco-related PREPS, except for 11)	1. Ingredient disclosure 3. Preclinical testing required to support health-related claims 7. Evidence for no increased risk 8. Added ingredient review 9. Performance Standards	6. Products with claims would require post-marketing surveillance and epidemiological studies	2. Yield Assessment 4. With specific claims, no increased exposure to unclaimed compounds 9. Performance Standards 11. Exposure reduction claims for pharmaceutical PREPs	5. Labeling for products with claims cannot be false or misleading	10. Enforcement power
Recommendations	3. Develop appropriate animal models and in vitro assays of pathogenesis	1. Sufficient data to allow estimation of dose–response 2. Need to develop validated biomarkers of disease	4. Clinical and epidemiological studies in human are required	Comprehensive surveillance is recommended	Regulation is recommended

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Section I

Introduction, Background, and Conclusions

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1

Introduction

"…tobacco use, particularly among children and adolescents, poses perhaps the single most significant threat to health in the United States."

Justice Sandra Day O'Connor,
FDA v. Brown & Williamson Tobacco Corp. et al. 2000.

"…as a practical matter, it is important to appreciate that a virtually harmless cigarette smoked by only 1% of the population will have a lesser impact on the reduction of tobacco-related diseases than a somewhat more harmful cigarette smoked by 80% of the total smoking population. Research on the less harmful cigarette should therefore be directed toward developing a cigarette containing the lowest possible amount of harmful elements for all tobacco-related diseases, but one that has sufficient acceptability for the largest segment of smokers."

Ernst Wynder, Banbury Conference of Safer Cigarettes, 1979.

"…the use of tobacco, especially cigarette smoking, has been causally linked to several diseases. Such use has been associated with increased deaths from lung cancer and other disease, notably coronary artery disease, chronic bronchitis, and emphysema. These widely reported findings, which have been the cause of much public concern over the past decade have been accepted in many countries by official health agencies, medical associations, and voluntary health organizations."

Smoking and Health, Report of the Advisory Committee to the
Surgeon General of the Public Health Service, 1964.

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Knowledge of the devastating consequences of tobacco use to human health has burgeoned in the 37 years since release of the first U.S. Surgeon General's report on smoking and health (U.S. Public Health Service, 1964). As scientific evidence has steadily accumulated, policy actions and the political will to reduce this toll have waxed and waned. Tobacco-caused death, illness, personal suffering, and costs are a major scourge of our time. If the toll due to tobacco were instead due to an infectious agent for example, most societies would move vigorously to stem the losses with every resource. Public health, medical, and tobacco control professionals, however, continue their campaign against a major threat to the public health. Numerous products that make implied or explicit claims to reduce the burden of smoking while allowing continued nicotine consumption or smoking are now entering the market. This report is concerned with the evaluation of these products.

Nearly one-quarter of adult Americans—an estimated 47 million people—smoke cigarettes (CDC, 2000a). Although this is far lower than the 42% recorded in 1965, the decline in the rates of smoking among adults appears to have leveled off during much of the 1990s (PHS, 2000). A slightly higher percentage of American men (26%) than women (22%) currently smokes (CDC, 2000a). Smoking rates vary greatly among racial and ethnic groups within the United States (CDC, 2000b). American Indians or Alaskan Natives have much higher smoking rates than the national average, and Asians or Pacific Islanders have much lower rates (CDC, 2000a).

The prevalence of adolescents in the United States who report current smoking is high. In a recent survey, 12.8% of middle school children and 34.8% of high school students reported some form of tobacco use during the month prior to their being interviewed (CDC, 2000c). The vast majority of smokers begin tobacco use during adolescence (IOM, 1994). The important role of adolescent smoking in lifetime addiction and smoking-caused disease is an important justification for many tobacco control policies in the United States.

These high rates of tobacco use continue despite statistics showing that 70% of smokers say they want to quit (CDC, 1994) and 34% of smokers make an attempt to quit each year. However, 2.5% of smokers (or less than 10% of those who try) quit smoking (CDC, 1993b). Approximately half of high school seniors who smoked reported that they expect not to be smoking five years from the time of the survey (1976–1984), but 80% of those who smoked more than a half-pack per day were still smoking at follow-up (CDC, 1994). A recent study of high school students reported that almost three-fourths of those who currently smoked had tried to quit (CDC, 1998).

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The reasons for great national concern over tobacco use are well known. The harm to human health from tobacco use is well documented and has been for decades. Large-scale epidemiological studies conducted in the 1950s supported the causal relationship between cigarette smoking and lung cancer and other diseases. These studies detailed the dose-response relationship between number of cigarettes smoked and individual risk for lung cancer. The 1964 Surgeon General's report stated that cigarette smoking was causally associated with lung cancer in men. The evidence for a causal relation in women was suggestive in 1964 but not considered established until 1971. It is now known that smoking also causes cancers of the oral cavity, esophagus, and larynx and is a contributing cause of cancers of the pancreas, bladder, kidney, and cervix. Smokers are at increased risk of lung cancer (a sixteenfold increase), chronic obstructive pulmonary disease (COPD; twelvefold), and a myocardial infarction (twofold) (Fielding et al. 1998). Pregnant women who smoke have twice the risk of nonsmokers of delivering low-birthweight infants. The Surgeon General of the United States has continued to publish reports on smoking and health. Some of the most significant publications are listed in Box 1-1.

Cigarette smoking is often called the single leading preventable cause of death in the United States (U.S. DHHS, 2000). Smoking results in more deaths each year in the United States than AIDS, alcohol, cocaine, heroin, homicide, suicide, motor vehicle crashes, and fires combined. Primary causes of death from tobacco are cardiovascular disease (approximately 906,600 deaths between 1990-1994), cancer (approximately 778,700 deaths between 1990-1994), and respiratory disease (approximately 454,800 deaths between 1990-1994) (CDC, 1993a). For 1990, smoking was estimated to be the cause of 20% of deaths from ischemic heart disease, 29% of all cancer deaths, 83% of lung cancer deaths, and 79% of COPD deaths. The average reduction in life expectancy for smokers is 6.6 years (Lew and Garfinkel, 1987). Detailed descriptions of the epidemiology of tobacco health effects can be found in Chapters 12–16 of this report.

The prevalence of tobacco use varies greatly outside the United States. A recent study from the World Bank reports that 59% of males in the regions of East Asia, the Pacific, Eastern Europe, and Central Asia smoke (World Bank, 1999). The prevalence of female smoking in these regions ranges from 4 to 26%. Worldwide, tobacco use is the sixth leading cause of lost disability-adjusted life-years, a measurement that combines the effects of morbidity and mortality for comparative purposes between and across health outcomes (Murray and Lopez, 1997). The World Health Organization (WHO) estimates that by 2030, tobacco will kill 10 million people per year worldwide (WHO, 1999), making it the leading cause of

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BOX 1-1
Select Surgeon General's Reports Regarding Tobacco

1964	Report concluded that smoking causes cancer and other serious diseases.
1967	Report concluded that "cigarette smoking is the most important of the causes of chronic non-neoplastic bronchiopulmonary diseases in the United States." The report also identified measures of morbidity associated with smoking.
1969	Report made solid conclusions regarding the relationship between maternal smoking and low infant birthweight. It also identified evidence of increased incidence of prematurity, spontaneous abortion, stillbirth, and neonatal death.
1972	Report associated smoking with cancers of the oral cavity and esophagus.
1973	Report studied immunological effects of tobacco and tobacco smoke, and identified carbon monoxide, nicotine, and tar as the smoke constituents most l kely to produce health hazards from smoking.
1977-1978	Report focused on health effects of smoking on women, noting in particular the effects of oral contraceptives and smoking on the cardiovascular system.
1980	Report addressed women and smoking projecting that lung cancer in women will surpass breast cancer as the leading cause of cancer mortality.
1981	Report examined the health consequences of lower-tar and nicotine cigarettes.
1983	Report evaluated health consequences of smoking for cardiovascular disease, declaring cigarette smoking one of the three primary causes of coronary heart disease.
1984	Report examined the health effects of smoking on chronic obstructive lung disease (COLD). Smoking accounted for 80–90% of COLD deaths in the United States.
1986	Report concluded that involuntary smoking is a cause of disease in healthy nonsmokers.
1988	Report stated that nicotine is addicting.
1989	Report reported that cigarette smoking is a major cause of cerebrovascular diseases (stroke). The report addressed the future of nicotine addiction in light of new nicotine delivery systems test marketed in 1988 and associated smoking with cancer of the uterine cervix.
1990	Report presented data on the benefits of smoking cessation for most smoking-attributable diseases. Also, presented association of smoking with bladder and cervical cancers.
1994	Report looked at preventing tobacco use among young people including initiation, cessation, advertising influences, and school-based programing.
1998	Report examined tobacco use among U.S. racial and ethnic minority groups showing that patterns of use vary among these groups.
2000	Report analyzes approaches to reducing tobacco use and the future of tobacco control.

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avoidable premature death in the developing world, as it is in developed countries today. In recognition of the difficulties of cessation, the WHO Framework Convention on Tobacco Control has been reviewing scientific information on harm reduction as part of its overall strategies.

However, despite the morbidity and mortality caused by tobacco and widespread knowledge by adults and adolescents of its adverse health effects, tobacco use continues. The biologically active component in tobacco that is primarily responsible for this is nicotine. Nicotine acts on several organs, including the brain. Nicotine is pleasurable to the user, and it is addictive. Thus, many but not all tobacco users find it very difficult to break their addiction and reduce the risk to their health. The continuing toll of tobacco use has prompted the public health community to consider anew harm reduction approaches for tobacco.

Tobacco harm reduction refers simply to the goal of reducing harm to health from tobacco use, including environmental tobacco smoke (ETS). Harm avoidance is achieved by never using tobacco products or having contact with ETS. Harm is minimized by quitting tobacco use and reducing exposure to ETS. *For the purposes of this report—and as the term is commonly used in other disciplines—harm reduction refers to minimizing harms and decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use.* This definition acknowledges that a significant proportion of individuals will continue to use tobacco for the foreseeable future. Harm reduction can be accomplished by decreasing the risk of an act (e.g., tobacco use), by decreasing the intensity per user, or by decreasing the prevalence. Chapter 2 includes a detailed discussion of harm reduction in other areas of public health concern and sets forth some general principles relevant to tobacco.

A multitude of policy strategies, such as increased taxes, contribute to the goal of harm reduction. However, this report focuses on substituting conventional tobacco use with either newly developed so called less harmful tobacco products or with pharmaceutical preparations used alone or concomitantly with decreased use of conventional tobacco products. The committee uses the terms harm-reducing or risk-reducing. The term "safer cigarette" has often been used historically and colloquially. The committee avoids the term "safer" in particular in order to avoid any impression that such products are safe. They are not. The U.S. cigarette manufacturers have recently publicly echoed the public health community's assertion that that there is no safe cigarette (Philip Morris USA, 2000; R.J. Reynolds Tobacco Company, 2000). Despite any promised harm reduction, the use of tobacco harm reduction products poses greater risks than no tobacco exposure.

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HISTORY OF HARM REDUCTION

Attempts to reduce the known or suspected risks to health from tobacco use by modifying tobacco or cigarettes predate the first U.S. Surgeon General's report on smoking and health. One of the first product innovations introduced with the potential and promise of harm reduction was filters. Filters reduce the amount of toxicants that go into the smoke inhaled by a smoker. The sale of filter cigarettes went from 1% of the market in 1952 to more than half of the market by 1960 (U.S. DHHS, 1989). In 1998, 98% of cigarettes sold in the United States contained filters (FTC, 2000).

The next major product modification with safety implications was the introduction of "low-yield" cigarettes. These products emit lower tar, carbon monoxide (CO), and nicotine than other products as measured by the Federal Trade Commission (FTC) assay (the "smoking machine"). This is achieved through blending different types of tobacco, ventilation, addition of accelerants, and filtration, as discussed in Chapter 4. The utility, purpose, and inferences made of the FTC assay yields are discussed in Chapters 4 and 11.

Consumers believed, and still do, that these products pose less risk to health than other cigarettes. Typical advertising campaigns for low-yield products stressed the softer side of smoking: "For smokers who prefer the lighter taste of a low-tar cigarette" (Kluger, 1997). An advertisement in the mid-1970s for a low-yield product, True, stated, "Considering all I'd heard, I decided to either quit or smoke True. I smoke True" (Pollay and Dewhirst, 2000). The market share of products yielding 15 mg of tar or less (as measured by the FTC assay) increased from 4% in 1970 to more than 50% in 1981. These products commanded approximately 80% of the U.S. cigarette market in 1998 (FTC, 2000).

Data on the health impact of low-yield products are conflicting, in part due to a lack of systematic and comprehensive study early in the introduction of these products. Most current assessments of the epidemiological and toxicological data suggest, however, that low-yield products are associated with far less health benefit than predicted based on FTC assay-generated tar, CO, and nicotine levels. The sales-weighted average of tar and nicotine yields of cigarettes in the United States has decreased by approximately half since the 1950s (Health Canada, 1998), without a significant or proportional change in the harm or prevalence of specific smoking-related diseases. Some of this is explained by changes in smoking behavior, known as compensatory smoking. In an effort to maintain adequate exposure to nicotine, smokers who use low-yield products smoke differently (e.g, inhale more deeply) than those who smoke higher-yield products. Thus, exposure to tobacco toxicants from low-yield products is

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greater by an unknown amount than predicted by FTC assay values. In addition to the disappointing impact of low-yield products on an individual smoker's health, of concern is the health burden of smokers who might have quit smoking altogether had they not had the opportunity to switch to a product they assumed was less harmful.

DEFINITIONS

Definitions of tobacco products are important for legal and regulatory purposes. Definitions are important also as the reader considers the harm reduction strategies discussed in this report. The Food and Drug Administration (FDA), as part of its rule-making process in 1995–1996, defined a cigarette as "any product which contains nicotine, is intended to be burned under ordinary conditions of use, and consists of any roll of tobacco wrapped in paper or in any substance not containing tobacco; or any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette" (21 CFR 897.3). The Bureau of Alcohol, Tobacco and Firearms uses a very similar definition of a cigarette for purposes of taxation (27 CFR 290). Some potential harm reduction strategies involve specific modifications of conventional cigarettes, as defined above. The committee struggled with terms for other products, which currently exist or could be developed, that are similar to, but not exactly, what is commonly recognized as a cigarette. When strict adherence to the FDA definition of a cigarette (which seems to require the presence of both nicotine and tobacco and to be dependent on high-temperature burning) is not intended, the committee uses the term "cigarette-like." These products are basically paper-covered cylinders of approximately 90 mm length that, when lit, heated or burned (usually controlled in a very rigorous manner and at lower temperatures than conventional cigarettes), and puffed, allow smoke or vapors with what is recognized as the flavor of tobacco or cigarettes to be inhaled, leading to the absorption of nicotine into the body. When referring both to modifications of conventional cigarettes and to cigarette-like products, the committee uses "tobacco-related." When referring specifically to pharmaceutical preparations, it will be noted.

There is no evidence currently that use of any product, other than those that lead to cessation, can achieve harm reduction from tobacco. Many tobacco and cigarette-like products have been introduced in the distant and recent past that do, under measurement systems such as the smoking machine, result in decreased emission of some toxicants compared to conventional tobacco products. These products could, therefore,

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potentially result in reduced *exposure* to toxicants. The committee uses "potentially," because whether exposure to tobacco toxicants is reduced depends on the user's behavior, such as frequency and intensity of use. Reduced exposure, however, does not necessarily assure reduced risk to the user or reduced harm to the population. Therefore, and in order to avoid misinterpretation, the committee will use the generic phrase "potential reduced-exposure products," or PREPs, when discussing modified tobacco products, cigarette-like products (whether tobacco containing or not), or pharmaceutical products and medical devices (whether nicotine containing or not) developed for their tobacco harm reduction potential. Demonstration of exposure reduction is possible but at this time, demonstration of harm reduction is not. This conclusion is reiterated and supported in subsequent chapters.

No tobacco-based PREPs other than conventional low-yield products have been used by enough consumers to assess health impact. The recent or forthcoming expansion of the test market for several new products, which are described in Chapter 4, and public statements by tobacco company executives suggest a new and critical opportunity for assessing harm reduction. The next few years may see an explosion of available tobacco or cigarette-like products that make some claim of harm reduction based on reduced tobacco or smoke content of one or more toxicants.

Uncertainty and skepticism remains about the potential health benefits of PREPs. Key to the skepticism, in addition to the lessons learned from low-yield products, is concern that such products will discourage quitting in smokers who might otherwise have stopped using tobacco or will encourage new tobacco use. Evidence to support this concern is limited, however. Historical data suggest that people "switched down" to low-yield products due in part to health concerns, but the studies were not designed to determine whether those smokers would have quit tobacco use altogether had only high-yield products been available. Most PREPs will maintain nicotine addiction and there is little agreement in the tobacco control field that public policy should encourage products that maintain nicotine addiction. Worrisome as harm reduction might be to those who have studied the history and disappointments of low-yield cigarettes, PREPs are currently available and likely are here to stay.

NICOTINE

There is disagreement among tobacco control experts about the optimal content of nicotine in tobacco products. Whether nicotine addiction is harmful beyond supporting tobacco use and should, therefore, be the target of public health efforts is not a simple question. Nicotine has toxic properties (see Chapter 9), but they are far fewer and less serious than

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those of other tobacco constituents. Some have proposed that nicotine should be removed from tobacco products in order to prevent addiction (Henningfield et al., 1998), decrease tobacco use, and thereby decrease exposure to the most toxic constituents in tobacco. The marketability of a nonaddicting tobacco product, however, is thought to be low. Nicotine has pleasurable or rewarding effects, in addition to its addictive properties. However, societal views of addictions per se surround the controversy.

Retaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco is another general strategy for harm reduction (for a recent review of this issue, see Russell, in Ferrence et al., 2000). The tobacco industry reportedly would support some FDA regulation of cigarette products (Schwartz and Kaufman, 2000). Key to its acceptance is that there be no upper level for nicotine that is set so low as to effectively ban cigarettes (Schwartz and Kaufman, 2000). Experience with NEXT, a cigarette with extremely low nicotine levels that did not succeed in the marketplace, suggests that nicotine is one of the factors crucial to the success of a tobacco product.

PHARMACEUTICAL PRODUCTS

Modified tobacco and cigarette-like products are not the only potential strategies for harm reduction. Two classes of pharmaceutical products might provide an alternative to the less harmful cigarette for harm reduction. These two classes of drugs are nicotine products, of which there are several such as patch, gum, inhaler, and nasal spray preparations, and nonnicotine products. To date, only one product that does not contain nicotine has been approved by the FDA for tobacco cessation and is on the market—a slow-release bupropion preparation, Zyban. This has been approved by the FDA for short-term (up to six months) use for tobacco cessation and was subject to standard FDA review and approval. Chapter 4 includes a detailed description of such products and the FDA approval process.

Early speculation that these products might be used on a long-term or continuing basis to reduce exposure to tobacco toxicants was supported by the observation that some people use them far longer than indicated in the FDA labeling and continue to smoke as well. It is possible that these smokers might decrease their tobacco use to a level that is less harmful than their prior tobacco use. Some smokers might cease using tobacco but use the pharmaceutical products on a long-term basis to help ensure abstinence. Claims by the manufacturers of usefulness for harm reduction short of cessation or for long-term maintenance would require FDA review and approval for either new indications or as new products. To date,

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no drugs have been approved for use with such harm reduction claims. The health effects of pharmaceuticals used as PREPs include both the effects of the drug itself (both benefits and risks) and of any concomitant tobacco use.

REGULATORY ISSUES AND AUTHORITIES

This strong federal regulatory authority for nontobacco, pharmaceutical PREPs contrasts with that for conventional tobacco products and, possibly, tobacco-related PREPs. The FDA asserted in 1996 that conventional cigarettes and smokeless tobacco were nicotine delivery devices intended to affect the structure and function of the human body and thus fell under its jurisdiction. On March 21, 2000, the Supreme Court of the United States denied FDA jurisdiction over these products (Legal Information Institute, 2000). The Supreme Court majority opinion stated that it was never congressional intent for FDA to regulate tobacco and that the products did not fall under the Food, Drug, and Cosmetic Act or its amendments. FDA does retain the authority to regulate health claims regarding tobacco products. However, there is no precise definition of the term "health claim."

The Federal Trade Commission has regulatory authority over the advertising and marketing of tobacco products. The purpose of FTC authority, however, is to ensure consumers have opportunities to exercise informed choice. The FTC enforces a variety of federal antitrust and consumer protection laws. They seek to ensure that the nation's markets function competitively and are vigorous, efficient, and free of undue restrictions. They work to eliminate acts or practices that are unfair or deceptive (FTC, 1999). Thus, the FTC has responsibility under various federal laws to ensure the proper display of health warnings in advertising and on packaging of tobacco products sold in the United States. Further, the agency collects and reports to Congress information concerning cigarette and smokeless tobacco advertising, sales expenditures, and the tar, nicotine, and carbon monoxide content of cigarettes (FTC, 1992).

Other federal agencies have jurisdiction over tobacco (e.g., the Bureau of Alcohol, Tobacco, and Firearms and the Department of Agriculture) but not regarding health issues. No agency is responsible for ensuring that any standards are met in the manufacturing and composition of tobacco products. This disparity between strict regulation of nicotine replacement products (and Zyban) compared to tobacco products puts the safest form of nicotine administration at serious marketing disadvantage. The so-called unequal regulatory playing field has led to suggestions to raise regulatory standards for tobacco or to lower the regulatory stan-

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dards in terms of marketing, packaging, and over-the-counter availability of tobacco cessation and harm reduction pharmaceutical products.

COMMITTEE CHARGE AND PROCESS

Because of the staggering morbidity and mortality associated with tobacco use and because fewer than 10% of smokers who attempt to quit each year succeed, public health considerations suggest a need to study alternatives to cessation for some smokers. Purported harm reduction tobacco products have been introduced into the U.S. marketplace periodically over the last 50 years. There is a strong likelihood of increased marketing and more products in the near future (Philip Morris Incorporated, 2000). These products are often associated with marketing statements or claims interpreted by some as indicating less health risk than to conventional products. It is also possible that nicotine or other pharmaceutical products could be used on a long-term basis for harm reduction, either concomitant with decreased use of conventional tobacco products or by themselves for maintenance of tobacco abstinence.

In anticipation of these issues, in 1999 the FDA asked the Institute of Medicine (IOM) to convene a committee of experts to formulate scientific methods and standards by which PREPs (pharmaceutical or tobacco related) could be assessed. Specifically, the committee was asked to answer several questions about harm reduction products. Where there are not yet answers, the committee was to determine the broad strategy by which the knowledge base should be assembled. For each product or class of product, four questions were asked:

1. Does use of such a product decrease exposure to the harmful substances in tobacco?
2. Is this decreased exposure associated with decreased harm to health?
3. Are there surrogate indicators of this harm to health that could be measured in a time frame sufficient for product evaluation?
4. What are the public health implications of tobacco harm reduction products?

The first three questions are obviously necessary for regulatory review of PREPs for their ability to reduce the risk to an individual of tobacco-caused disease and for decision making by an individual about tobacco use. The fourth question is important to ensure the health of the public. That is, although a PREP might be risk-reducing for an individual's health compared to conventional tobacco products, the availability of

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PREPs might not be harm-reducing for the population. This could occur if tobacco users who might otherwise have quit do not, if former tobacco users resume use, or if some people who would not have otherwise initiated tobacco use do so because of perceptions that the risk with the "new" products is minimal and therefore acceptable. The committee was not asked to evaluate, and so did not debate, the merits of pursuing harm reduction.

The committee was drawn by its charge necessarily and inevitably into considering the regulatory framework for products purported to reduce harm from tobacco use. First, regulation is a necessary precondition for advancing scientific knowledge on the effects of using these products, especially their impact on public health. Second, whether the public health impact will be beneficial is substantially dependent on the implementation of a comprehensive and carefully designed regulatory framework for these products.

An expert committee was convened by the IOM and is the author of this report. The report is offered to the FDA, FTC, other relevant federal and state regulatory and policy bodies, Congress, scientists and health care professionals, tobacco and pharmaceutical industries, and—most importantly—the public, who will have to consider advertising and marketing information and make decisions about whether to use these products. The committee hopes the report will also be useful to similar groups in other countries, some of which are examining the harm reduction issue at present and to the global tobacco control community.

Committee expertise includes clinical medicine, epidemiology, toxicology, pharmacology, behavioral sciences, regulatory policy, and public health. The committee met five times between December 1999 and August 2000. Three of the committee meetings involved open sessions, during which invited researchers, public health advocates, clinicians, and representatives of tobacco and pharmaceutical manufacturers presented relevant data and engaged in scientific discussions. Written submissions were encouraged and reviewed by the committee (see Appendix A for a listing of these presentations and submissions to the committee). The committee in part or as a whole reviewed thousands of articles from the scientific peer-reviewed literature, including original research, review articles, and reports of advisory bodies such as the office of the U.S. Surgeon General. All materials sent to the committee and those used in support of this report are listed in a public access file maintained by the National Research Council's (NRC) Public Access and Records Office.

This report, which contains a Preface, Executive Summary, and 16 chapters including this introduction, is divided into two sections. Section I contains background material, conclusions, and recommendations on surveillance implementation and general conclusions regarding the

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committee's charge. Chapter 2 reviews general principles of harm reduction. Chapter 3 discusses the historical record of harm reduction attempts with an eye toward lessons learned for the future. Chapter 4 discusses current products and strategies for tobacco harm reduction. Chapter 5 contains a summary of the technical evidentiary base, conclusions, and recommendations regarding the first three questions of the charge. Chapter 6 reviews the public health considerations of harm reduction, including conclusions and recommendations regarding surveillance and post marketing research. Chapter 7 provides an overview of conclusions regarding the implementation of a public health approach to tobacco harm reduction, including principles for regulating PREPs. Chapter 8 sums up section one with principal conclusions. Section II contains the technical evidentiary base summarized in Chapter 5. Chapters 9 and 10 describe the pharmacology of nicotine and the toxicology of tobacco. Chapter 11 discusses principles of exposure assessment. Chapters 12—16 discuss the evidence that harm reduction strategies might impact the major diseases associated with tobacco and nicotine use.

APPLICATION OF RISK ASSESSMENT TO TOBACCO HARM REDUCTION

Predicting human health risks from toxic exposures, such as those associated with occupational and environmental toxicants, frequently involves a risk assessment process such as that outlined in "Risk Assessment in the Federal Government" (NRC, 1983), a report produced at the request of the U.S. Food and Drug Administration.

The risk assessment process outlined in the NRC report, sometimes referred to as "The Red Book," includes four basic elements:

- hazard identification (Does the agent cause an adverse health effect?),
- dose-response assessment (What is the relationship between dose and incidence in humans?),
- exposure assessment (What exposures are currently experienced or anticipated under different conditions?), and
- risk characterization (What is the estimated incidence of the adverse health effect in a given population?).

Hazard identification includes laboratory and field observations of adverse health effects resulting from exposures to specific agents. For *dose-response assessment*, if clinical or epidemiological data are not available, extrapolation from high-to-low-dose exposures and from animal to human doses in dose-response assessment is required. To determine

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exposures, research based on field measurements, estimated exposures, and characterization of populations is required. The data required for the first three elements of the risk assessment process usually include in vitro and in vivo toxicology studies in animals, including dose-response studies; mathematical modeling; toxicokinetic studies in animals and human; other clinical studies in humans; and, if available, epidemiology studies in human populations.

A synthesis of those three components leads to a risk characterization. This can be either qualitative or quantitative. Considerations that can affect the risk characterization are the statistical and biological uncertainties in estimating the health effects, the choice of dose-response or exposure assessments used, and a determination of targeted population for protection. The risk characterization is used to guide regulatory or other action for the purposes of risk management. This entails consideration of political, social, economic, and other technical (e.g. engineering) information with risk-related information. Value judgments are involved, such as the acceptability of risk and the reasonableness of the costs of control.

Risk assessment is the link between research and decision making (risk management). Complex and conflicting scientific information must be presented in an organized manner such that its meaning and limits are clear to the risk manager. The more complex the science base and the more controversial the policy implications, the more a rational and explicit framework is needed. Tobacco harm reduction presents complex technical issues and controversial policy options.

The committee has used the Red Book risk assessment paradigm in its approach to assessing the science base for tobacco harm reduction. Chapter 5 includes a discussion of the special challenges tobacco (and PREPs in particular) poses to risk assessment. Chapter 5 (and the chapters from Section II summarized in it) also contains the evidence that PREPS could affect each major tobacco-related disease. Each type of evidence is linked to the Red Book paradigm. The data gaps that currently prevent a quantitative risk characterization for PREPs are also described. Chapter 8, Conclusions, returns to the Red Book paradigm to organize the conclusions and recommendations of the report.

This organization and synthesis demonstrates that each of the four steps in risk assessment and in risk management are informed by:

- the four specific questions posed by the committee (described above) as a means to answer its charge in order to provide regulatory, scientific, and medical guidance,
- the evidence reviewed by the committee in each of the disease-

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specific chapters (contained in Section II and summarized in Chapter 5),
- the principal conclusions of the committee (found in Chapter 8) related to the questions contained within the charge,
- specific recommendations of the committee related to a comprehensive surveillance system (Chapter 6) and regulatory principles (Chapter 7), and
- the research gaps identified (Chapter 5 and Section II).

OPERATING PRECEPTS

The committee introduces the rest of the report by laying out four fundamental operating precepts. The committee reiterates and reaffirms decades of overwhelming scientific evidence and the conclusions and recommendations of advisory bodies such as those that authored the Surgeon General's reports, previous IOM and NRC committees, and international health experts such as the World Health Organization.

1. Tobacco use causes serious harm to human health.
2. Nicotine is addictive.
3. The best means to protect individual and public health from tobacco harms are to achieve cessation, prevent initiation and relapse, and eliminate ETS exposure.
4. A comprehensive and authoritative national tobacco control program, with harm reduction as one component, is necessary to minimize adverse effects of tobacco.

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2

Principles of Harm Reduction

A broadly shared goal of public policy toward cigarettes and other tobacco products is to reduce their health burden (IOM 1994, 1998). That health burden is minimized if no individual begins smoking and those who are currently smoking quit promptly (U.S. DHHS, 1988). However, quitting is difficult for most smokers and many adolescents will experiment with smoking; experimentation predictably leads a substantial fraction to become regular smokers (U.S. DHHS, 1994). Thus in addition to interventions aimed at prevention and at promoting immediate quitting, it is appropriate to consider interventions that aim to reduce the harm that the remaining population of smokers cause themselves and others by continued smoking. This is the underlying concept of harm reduction or harm minimization.

The term "harm reduction" has a variety of applications. It can refer to a policy or strategy (a set of laws and programs) or to specific interventions (e.g., an individual product innovation or dissemination effort). A harm reduction policy or intervention (a) explicitly assumes continuation of the undesired behavior as a possibility and (b) aims to lower the total adverse consequences, including those arising from continuation. In this use, the term describes an assumption and a goal rather than a result. It can also be used as a criterion for evaluating results; an intervention or policy is harm-reducing if it does in fact reduce the total adverse consequences. Finally, harm reduction can also be viewed as a framework, a way of thinking about dealing with a harmful behavior, since it requires analysis of a broader set of outcome measures than would otherwise be

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considered. One cannot usually determine in advance, on theoretical grounds, whether a particular policy or intervention is harm-reducing. For example, it may turn out that a policy which aims to minimize prevalence (i.e., addresses only abstinence) reduces total harm as compared to any other policy. But the framework allows consideration of alternatives to reduction in the number of users as a complement to abstinence.

The concept of harm reduction has application in a number of policy areas apart from tobacco, including automobile safety, sex education for children, alcohol control and policy toward illicit drugs. In some instances the harm reduction considerations are only implicit, providing an ex post rationalization of decisions already made (e.g., automobile safety, MacCoun, 1998). In others (e.g., needle exchange programs) it is a very prominent element of policy discussions. While none of the harm reduction interventions in these other policy areas are exactly analogous to those in the tobacco field, they will be used to illustrate the potential strengths and weaknesses of this approach for tobacco.

The next section elaborates the basic framework of harm reduction and briefly relates it to risk assessment. The third section also shows some of harm reduction's applications in related areas and compares these applications to some potential smoking interventions, though a much more extended discussion of those interventions is provided later in the report. The chapter concludes with some observations on the difficulties of applying the harm reduction framework, in particular the problems of developing measures to establish whether harm has in fact been reduced, and the need to give greater weight to mistaken acceptance of a product as harm-reducing than to mistakenly rejecting a harm-reducing product.

CONCEPTUAL FRAMEWORK FOR HARM REDUCTION

Basic Concepts

Harm reduction accepts that interventions focused on reducing the harmfulness of a substance or behavior, even if they increase the extent of substance use or the frequency of the targeted behavior, may be able to reduce the aggregate of adverse consequences for society, including both users and nonusers. For example, referring to the alcohol field, a prominent group of researchers stated: "Unlike 'abstinence-only' or 'zero-tolerance' approaches, the harm reduction model supports any behavior change, from moderation to abstinence, that reduces the harm of problems due to alcohol" (Marlatt et al., 1993). For illicit drugs "the central defining characteristic of harm reduction is that it focuses on the reduction of *harm* as its *primary goal* rather than reduction of *use per se*, secondly that strategies are included to reduce the harms for those who continue to

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use drugs, and thirdly that strategies are included which demonstrate that, on the balance of probabilities, it is likely to result in a net reduction in drug-related harm" (Lenton and Single, 1998). Frequently definitions assess alternatives not in aggregate health measures but in terms of the harms associated with a single act or product or with the individual user; for example, "the term harm reduction originally referred to only those policies and programmes which attempted to reduce the risk of harm *among people who continued to use drugs*" (Lenton and Single, 1998, citing Single and Rohl, 1997).

The harms consist of all the adverse consequences borne by members of society. These include increased morbidity and mortality (among both users and nonusers) from all sources; addiction itself; expenditures on regulation or enforcement, since these are costs borne by taxpayers; the increased intrusiveness of the state; and crime that might be generated by regulation or enforcement or by the behavior itself.

These adverse consequences are borne by many different groups: users themselves; intimates of the user, particularly children and spouses; nonusers directly (e.g., through crime, in the case of illicit drugs, or traffic accidents in the case of alcohol); and nonusers indirectly or society generally (e.g., through taxation). The value society gives in considering interventions to the interests of these groups may vary (MacCoun et al., 1996); typically a greater consideration is given to the welfare of children or of neonates, since they are the most vulnerable victims, with very limited capacity to undertake actions in their own interests.

Analytics

Total harm can be expressed as a function of the number of individuals engaged in the behavior and the damage each causes. In turn, the damage caused by an individual is a function of intensity of use (or frequency of behavior) and of the harmfulness of each episode of use or behavior. MacCoun and Reuter (2001) suggest that total harm can then be expressed as

$$\text{Total Harm} = \text{Harmfulness (per use)} \times \text{Intensity (per user)} \times \text{Prevalence (of use)}$$

It can be reduced through declines in any of the three components individually, including intensity.

However the three components may not be independently determined. In particular, prevalence may be affected by harmfulness through three distinct, though related, paths; initiation, nondesistance, and relapse. The lower harmfulness may reduce *perceived* harmfulness and encourage someone to begin using drugs, to drive a car too fast, or engage in sex at too early an age. Perceived dangers may be influenced both by the actual

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dangers and by information about those dangers. Where the substance or behavior is addictive or habit-forming, this may generate a long-term increase in the number of users. In addition, lower perceived harmfulness may reduce incentives to quit or desist. Relapse may also be encouraged by the perception of less dangerous means of continuing the desired behavior. Lower perceived harmfulness may also increase intensity of use.

Changing the riskiness of an act is known to alter the behavior of the population. Generally the change is in the form of compensation, i.e., higher risk will reduce the prevalence of the behavior while lower risk will increase that prevalence. Engineers tend to overestimate the benefits from safety devices, since they ignore that behavioral adaptation. On auto safety, Evans (1991) has noted: "If the safety change affects vehicle performance, it is likely to be used to increase mobility. Thus, improved braking or handling characteristics are likely to lead to increased speeds, closer following, and faster cornering. Safety may also increase, but by less than if there had been no behavioral response." In its most extreme form, this kind of risk compensation has been labeled *risk homeostasis*—a term that implies implicit or explicit efforts to maintain a constant level of risk (Wilde, 1982).

These changes are logical possibilities. How substantial they are is an empirical matter. So is the extent of generalizability across product domains and populations. The introduction of a safer automobile may, for example, have negligible effect on the driving behavior of older drivers but sharply increase speeding by younger drivers, while condom availability may increase sexual behavior of older adolescents more than it affects that of younger adolescents. The psychological mechanisms generating alcohol and cigarette dependence may be different enough that harm reduction interventions in general are more effective in one field than in the other.

This lack of generalizability raises a question as to the relevance of examples from other fields to tobacco interventions. But tobacco harm reduction involves a large variety of potential interventions. They differ in some important dimensions, just as do automobile seat belts and needle exchange programs. The examples can help identify the dimensions that influence the outcomes of harm reduction interventions.

APPLICATIONS

The harm reduction framework can be applied not only in a number of different policy areas but to a variety of forms of interventions:

(a) Lowering the inherent harmfulness of a broad class of products

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(automobile safety regulation); this is the approach used for tobacco harm reduction products that rely on removal of some toxicants from tobacco.

(b) Shift to less toxic mode of ingestion. Needle exchange programs attempt to reduce the harmfulness of the act of injecting drugs, without requiring abstinence. That is the approach embodied by products such as Eclipse, with heated tobacco or tobacco-like materials providing nicotine by a similar mechanism that allows continuation of the act of smoking but attempts to make it less harmful.

(c) Behavioral change therapies (controlled drinking); many tobacco harm reduction strategies will require behavior change as a complement to product innovation.

(d) Adding a less harmful but dependency-creating product to the available mix of dangerous products (methadone for heroin addicts); this is the rationale for nicotine replacement therapy for long-term use.

This section provides a brief description of the nature of each of the non-tobacco interventions listed and how they have fared in the harm reduction framework. It also describes the extent to which they have had the effects predicted for them when introduced. The examples presented are, by nature, imperfect analogies of tobacco harm reduction but are offered to highlight the positive and negative implications of harm reduction interventions.

Automobile Safety Regulation

Automobiles are a source of numerous injuries and fatalities; in 1998 there were 41,200 deaths in the United States associated with automobiles (National Safety Council, 1999). Some of these, but not all, are a consequence of unsafe operation of vehicles, in particular driving while intoxicated or driving at high speed. The National Highway Traffic Safety Administration (NHTSA) estimates that speeding was a contributing factor in 30% of such deaths (NHTSA, 1999a). It was also estimated that in 1994, 16,600 traffic fatalities were alcohol-related (CDC, 1995). A series of product innovations, including seat belts, anti-lock braking systems, and air bags have led to large improvements in the crash-worthiness of vehicles. Lap/shoulder safety belts, when used, reduce the risk of moderate to fatal injury to front seat passenger occupants by approximately half (NHTSA, 1999b). Federal law now requires their installation in new vehicles and all states mandate that they be used.

From the earliest days of these innovations, there has been a research interest in behavioral adjustments that might reduce the effectiveness of these innovations. Given that cars are safer, drivers may be more inclined to exceed the legal speed limit as well as exercise reduced care with respect

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to driving while alcohol impaired. This is analogous to increased intensity of smoking when given access to low tar and nicotine cigarettes.

Peltzmann (1975) found that changes in driver behavior more than offset product improvement. However, since then a substantial literature has refuted that finding. The research generally concludes that there is in fact more speeding but that the net result is a reduced burden of automobile injury and mortality. For example, Chirinko and Harper (1993) found that the introduction of air bags reduced automobile fatalities by between 13.8 and 26.1%. They also observed a shift (as did Peltzmann) in the composition of those fatalities; non-occupant fatalities (i.e., deaths of pedestrians, cyclists, etc.) increased while occupant fatalities decreased. This latter finding is consistent with the hypothesis that the technology encourages less safe driving.

Other engineering improvements on roads (stronger guard rails, brighter lights) have also reduced the frequency of accidents or severity of injuries associated with unsafe driving (Ross, 1992). Evans (1991) notes that: "When safety measures are largely invisible to the user, there is no evidence of any measurable human behavioral feedback. Likewise, when measures affect only the outcome of crashes, rather than their probability, no user responses have been measured." These are instances of pure harm reduction interventions; no behavioral response diminishes their design effect.

Seat belts can be disabled; like many harm reduction interventions they require compliance for their effect. One factor explaining the relative modest impact of mandatory seat belt laws on traffic fatalities lies in substantial rates of non-compliance (Dee, 1998). Moreover the population is not homogeneous: "unsafe drivers may be the least likely to adjust their belt use after the introduction of the law" (Dee, 1998). Thus the safety effects of automobile innovations are less than expected due to both increased speeding and selective noncompliance regarding seat belts.

Though there is strong and increasing social disapproval of unsafe driving, as expressed in congressional passage of legislation in 2000, urging states to reduce the maximum allowable Blood Alcohol Content (BAC) to 0.08%, there is no public discussion that these mandated product changes might encourage faster or less safe driving or redistribute the damage toward pedestrians and other innocent parties. This lack of debate may reflect, *inter alia*, the compelling nature of the intervention, reducing the risks associated with being the driver of a car, an almost universal experience of American adults. What is immediately discernible is the reduction for the driver, not the potential increase for other parties. Moreover, the targeted behavior (unsafe driving) is so common that, even though there is support for increasingly stringent laws and enforcement,

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there is an acceptance of its inevitability; there are no calls for a "speeding free society." Speeding, though not driving while intoxicated, also confers a benefit—namely, reduced travel time.

These benefits of reduced mortality and injury have been obtained at considerable cost. The estimated cost per life-year saved varies widely for different devices and mandates; for example, the figure for driver airbag and manual lap belts (as compared to manual lap belts alone) is $6,700 while for the same devices for passengers *and* drivers, the figure is $62,000 (Tengs et al, 1995). Some interventions are rated as essentially costless; for example, driver automatic (vs. manual) seat belts. These require investments only of government authority, not financial resources.

Automobile safety also illustrates the potential conflict among social goals that may be ignored even in a harm reduction framework. To reduce gasoline consumption and air pollution, the corporate average fuel economy standard (CAFE) has led to lighter cars; these cars are correspondingly less safe (Crandall and Graham, 1989). The trade-off between the two goals (pollution abatement and reducing injury and death from automobile accidents) has not been evaluated and is the subject of little public discussion. Indeed, the National Highway Traffic Safety Administration has been accused of obfuscating precisely this issue (Kazman, 1991). Harm reduction, despite its ostensible breadth, does not necessarily cover all potential adverse consequences.

Automobile safety represents an instance of a successful harm reduction intervention. There is indeed an increase in harmful behavior but not so much as to overcome the reduction in adverse consequences of that behavior.

Teen Sexual Behavior

Births to teenagers have been identified as a major societal health and behavioral problem (Ventura et al., 1997). For example, teenage mothers are less likely to complete their own education or provide adequate parental supervision and more likely to give birth to a low-birthweight infant. Over one third of teenage pregnancies end in abortions (Henshaw, 1999). Unwanted children are particularly at risk of neglect from teenage mothers (Federal Interagency Forum on Child and Family Statistics, 1997). There is a societal interest in reducing the number of unwanted infants born to teenage females. In addition, teen sexual activity, which frequently occurs outside of monogamous relationships, also facilitates the spread of sexually transmitted diseases (STDs), including AIDS.

The severity of problems related to premature sexual intercourse is a function of the prevalence of the acts and their average safety—mostly the probability of pregnancy and of STDs. Until recently many schools chose

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to emphasize the value of abstinence before a certain age; not only does that represent community values but abstinence, if achieved, eliminates the risky acts (Kirby, 1992). However, the rise in sexual activity among adolescents and the emergence of the AIDS epidemic have led to a concern that "abstinence only" messages may be ineffective and that the adverse consequences of unprotected sex may be greater than previously estimated. There has been exploration of the effects of harm reduction interventions which accept the high probability of sexual activity at an inappropriately young age and aim to reduce the probability of pregnancy or disease (Kirby, 1997).

Such interventions can take a number of forms. One is curricula aimed at teaching adolescents about responsible behavior, if they choose to have sexual relations. Such a curriculum may reduce the adverse consequences of early sexual activity. Opponents of these programs believe that they may encourage early sexual activity, in itself socially undesirable. However, a recent review of evaluations of a number of curricula concluded that "none of the 11 studies that examined the impact of programs on the frequency of intercourse found a significant increase" (Kirby and Coyle, 1997).

Another possible method of reducing harm is to facilitate access to adequate birth control technologies to adolescents, in particular to school children. Kirby and Brown (1996) estimate that by the mid-1990s nearly 400 schools made condoms available to students. Four recent studies found little evidence that the programs raised the percentage of high school students who engage in sexual intercourse, either by increasing teen awareness of how frequent such activity is among their peers or by reducing its perceived risks (Kirby and Coyle, 1997). On the other hand, evaluations of these programs also provide mixed support as to an effect on utilization of condoms, or any other birth control device. For example, a study of nine Philadelphia schools which provided reproductive health information, condoms, and general health referrals found that these schools showed no significant increases or decreases in condom use over time as compared to schools which did not install these programs (Furstenberg et al., 1997). A study of Seattle schools which made condoms available in vending machines or in baskets at school health clinics concluded that students use a relatively large number of condoms distributed in this fashion, but this "did not lead to increases in either sexual activity or condom use" (Kirby et al. 1999). The condoms distributed through the schools may have substituted for others obtained through other channels. There was one discrepant study: a condom distribution program that was part of a comprehensive AIDS prevention program increased rates of condom use in a sample of Chicago schools compared to a set of matched controls (Guttmacher et al., 1997).

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These interventions illustrate the effects of increasing the availability of a potentially harm-reducing product to a specific high-risk population. It appears that this one has slight impact on behavior, on either the frequency of the acts or their average safety. In the absence of a strong scientific base, the debate is largely in terms of values and impressions, a common characteristic of social policy fields in which harm reduction has been applied. Making condoms available to school students may "send the wrong signal." It involves the state in apparently facilitating acts of which society disapproves. Since the evidence to date is that these interventions have at most a modest effect on the frequency and damage of the targeted behavior, the harm reduction framework has not been explicit.

Alcohol

Alcohol policy raises many harm reduction issues, reflecting the mixed social message with respect to alcohol's health consequences. Light drinking is a socially acceptable behavior, with apparently health promoting consequences. Heavy drinking, particularly chronic heavy drinking, is the source of a huge burden of morbidity and mortality, and is acknowledged as dangerous both to the drinker and others.

Harm reduction enters alcohol control in a number of ways. Alcohol consumption is characterized, even for most light drinkers, by episodes of excessive drinking. Though each light drinker has only a small to moderate probability of an alcohol-related automobile accident or other kind of injury, their numbers are large enough that, as a group, light drinkers account almost half the damage associated with alcohol consumption (Kreitman, 1986). Duncan (1997) found that driving while intoxicated (DWI) rates across states were associated with binge drinking but not with chronic heavy drinking.

As a result, a central debate is whether alcohol policy should focus on heavy drinkers as a group, on the total amount of alcohol, consumed or primarily on intoxication as a behavior. For example, some programs in the last group emphasize how the potential harm of drinking a given amount can be reduced by consuming it over longer periods of time or eating food during the drinking session. That implies an acceptance of heavy drinking, itself an unhealthy behavior and one that is a risk factor for numerous diseases. In contrast, high alcohol taxes reduce aggregate consumption, including that which is nonharmful; these taxes can be seen as "punish[ing] the many for the sins of the few" (Stockwell et al, 1996). If all drinking is seen to generate some probability of adverse effects, as the total consumption model suggests, then measures that reduce overall drinking are likely to be harm-reducing. Single (1997) suggests that "[I]ncreased attention is likely to be given to prevention measures which

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focus on preventing problems associated with drinking rather than restricting access to alcohol." This is only partly rooted in public health; it also represents the political realities of decreasing public support for restricting alcohol availability and the dissemination of data showing that moderate levels of alcohol consumption appear to reduce all-cause mortality (Edwards, 1995; NIAAA, 2000).

Harm reduction shows up in other aspects of alcohol policy; examples include "measures to reduce nonbeverage alcohol by 'Skid Row' inebriates, measures to reduce intake of alcohol by drinkers (e.g., promotion of low-alcohol beverages, server training programs) and measures to reduce the consequences of intoxication" (Single, 1997). For example, impoverished, single men who have chronic alcohol problems are at risk of drinking various liquids that contain alcohol but are not fit for human consumption (e.g., methylated spirits). Since these men are unable (both for financial reasons and because of poor self-control) to maintain stocks of alcohol, they are likely to consume these more dangerous substances if they cannot readily obtain alcoholic beverages, as happens early in the morning when liquor stores are closed. One method of alleviating this problem is to expand opening hours for stores operating in Bowery-like areas. Early opening may reduce the extent of drinking of nonbeverage alcohol and thus alcohol-related morbidity and mortality. However, it also signals society's willingness to facilitate drinking by individuals with serious drinking problems who will remain untreated and some of whose problems may be exacerbated or ameliorated by allowing easier access to alcohol.

Some harm reduction interventions in the alcohol field are indeed aimed directly at harms and seem unlikely to induce behavioral responses that would ameliorate their effects. For example, intoxication leads to numerous violent fights in pubs and bars. In Scotland, one intervention involved serving drinks in glass which crystallized rather than shattered when it broke, thus reducing the damage caused by such fights (Plant et al., 1994). That seems highly unlikely to increase the extent of fighting (the proximate source of harm) or heavy drinking (the more distal source of the harm); indeed, if the purpose of fighting is to cause the maximum injury to others, it may actually reduce the prevalence of fighting.

Harm reduction also operates at the clinical level. A long-standing belief among treatment specialists is that any message for individuals with drinking problems other than abstinence imposes unacceptable risk of relapse to dangerous drinking behavior. Over the last quarter century, however, a number of studies have found that controlled drinking may be a better goal for at least some problem drinkers (e.g., Miller and Caddy, 1977; Sobell and Sobell, 1978), though the results have not been consistent (Foy et al., 1984; Vaillant, 1996). Its appropriateness is in part a function of

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targeting. Can one identify subpopulations of problem drinkers with higher probability of benefiting from goals other than abstinence?

Illicit Drugs

Harm reduction has been most explicitly discussed in terms of policy toward illicit drugs. A distinctive aspect of drug policy is that the policies themselves have direct adverse consequences. Toughly enforced prohibitions aimed at use reduction can lead to drug overdose deaths due to drugs of unknown purity and poor quality. That does not imply that the prohibitions should be relaxed. These current policies may in fact be harm-minimizing, since the high prices and limited accessibility reduce the use and volume of addiction- or intoxication-related harms. This presents an empirical issue that remains unexamined (Caulkins and Reuter, 1997). However the very prominence of the harms directly related to prohibition, such as the violence and disorder around drug markets has generated an interest in the possibility that society would benefit from less punitive policies, *even* if they increase prevalence of drug use.

Two important interventions have been the subject of harm reduction debates: needle exchange programs (NEPs) to reduce the spread of AIDS and the provision of methadone to ameliorate the adverse consequences of opiate dependence.

The spread of HIV among intravenous drug users (IVDUs) and their sex partners is primarily a function of needle sharing, not of the drugs consumed. NEPs aim to reduce harm caused by IV drugs by reducing the risky practice. Opponents of NEPs argue that these programs facilitate a dangerous and illegal behavior: IV drug use. The proponents of needle exchange programs argue that whatever its symbolism, both public health and considerations of humane treatment of drug addicts require NEP.

There is a base of research demonstrating the positive public health effects. As summarized by a National Research Council panel, "NEPs increase the availability of sterile injection equipment. For the participants in a (NEP) . . . this amounts to a reduction in an important risk factor for HIV transmission. . . . There is no credible evidence to date that drug use is increased among participants as a result of programs that provide legal access to sterile equipment. The available scientific literature provides evidence based on self-reports that needle exchange programs do not increase the frequency of injection among program participants and do not increase the number of new initiates to injection drug use" (Normand et al., 1995). Several recent policy reports have upheld those conclusions (IOM, 2000; U.S. DHHS, 1998). There is also strong popular support as revealed in survey research (Henry J. Kaiser Family Foundation, 1996). Congress has been unpersuaded by either the research or the

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moral arguments. The belief that it will "send the wrong signal" and thus increase drug use by undermining the abstinence message, both to current and potential users, does not seem to be responsive to empirical findings.

Perhaps more relevant to the current concerns about harm reduction in the tobacco field is the introduction of methadone as a maintenance drug for heroin addicts. Methadone is a long-acting agonist that reduces craving for other opiates; see Rettig and Yarmolinsky (1995) for a review. Provision of low-cost methadone has enabled hundreds of thousands of opiate addicts in a dozen countries (North America, Western Europe, and Australia) to lead substantially better lives; they are able to avoid the humiliation of searching for an expensive prohibited drug, achieve modest levels of workplace functioning, and mitigate major threats to their own health and the health of others. It has helped limit the spread of HIV (Longshore et al., 1993). While it is an abusable drug, addicts on methadone have a much lower mortality rate than untreated addicts (Ball and Ross, 1991).

Methadone dependence seems to be at least as difficult to end as heroin dependence. Patients who discontinue methadone use relapse to opioid dependence at a high rate (Ward et al., 1992). The perception of heightened dependence is common amongst patients. Some addicts use methadone when their heroin use has become particularly problematic, with the expectation of returning to heroin use when they are past this particular crisis.

Methadone was a major ideological battlefront in the 1970s and 1980s (Rosenbaum, 1997; White House Conference for a Drug Free America, 1988). It has been noted that "the controversies over methadone treatment stem almost entirely from philosophical differences—objections to the substitution of one drug for another—and not from doubts about the pharmacological safety and efficacy of methadone" (Newman and Peyser, 1991). Methadone is a dependency-creating opiate, as is heroin. Methadone dependence is more acceptable than heroin dependence because it improves the user's function as a member of society. That the methadone patient gets less pleasure from the substitute drug is probably not critical in itself, though the lessened intensity of pleasure may allow for greater engagement with others and less self-centeredness and thus helps generate popular acceptance.

For some policy makers, however, the reduction in the burden of disease and other social dysfunction is not enough to justify government funding and provision of an addictive drug. In this case, in contrast to the battle over NEP, the proponents have prevailed. Methadone maintenance, though inadequately funded and poorly delivered, is the mainstay of the U.S. treatment for heroin addicts (Rettig and Yarmolinsky, 1995).

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There is no evidence that methadone has increased initiation into opiate addiction where it has been made available. However, it is difficult to develop a powerful design for testing the hypothesis, particularly given the paucity of local indicators of heroin use. There has been no association between the number of persons in methadone programs and the number of reported new users in the National Household Survey on Drug Abuse, but that is at best a weak test. Assessing whether methadone prolongs a career of opiate dependence is difficult because of the very different characteristics of the methadone and heroin initiate populations. Even among addicts, many desist for long periods without treatment; for example, Anglin et al. (1986) found that 56.4% of a sample of 406 heroin addicts were able to desist for three years or more without formal assistance. However, those who initiate methadone use for addiction treatment are those who were unable to quit heroin; hence the difficulty of comparison.

Summary of Applications

Harm reduction has been controversial wherever it has been applied explicitly; moreover it often has a weak base in terms of assessed outcomes. Automobile safety is one instance for which there is good evidence of both compensatory behavior and net harm reduction. It is also the instance in which harm reduction issues have been least clearly articulated in public debate, though widely discussed in the traffic safety community.

Interventions to reduce the danger of adolescent sexual behavior have shown no adverse effect, in terms of increased sexual activity, but also little indication that the interventions have reduced the average harmfulness of the acts. For alcohol, harm reduction is gathering momentum but with only a modest scientific basis at either the population or clinical level. For heroin, research on methadone and needle exchange programs provide evidence that they do reduce total harms resulting from use by currently dependent users; there is a weaker evidentiary base for concluding that initiation is unaffected.

COMPARING OTHER HARM REDUCTION INTERVENTIONS TO THOSE FOR SMOKING

These examples are offered for the insights they may provide as to the likely consequences of tobacco-related potential reduced-exposure products (PREPs). However, harm reduction can work through a number of mechanisms and has consequences in a number of dimensions. Assessing the relevance of these harm reduction interventions to PREPs requires consideration of those mechanisms and consequences.

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Table 2-1 compares three types of tobacco-related PREPs with five other harm reduction interventions discussed above. It aims to show in what ways the various PREPs are similar to or different from the other interventions. It is intended to be illustrative rather than conclusionary; a number of entries are conjectural. The comparisons are in terms of:

(a) Theory of how the product/policy might reduce harm (Presumed Mechanism). Each intervention posits a specific mechanism as to how it might diminish adverse consequences at the individual level. For example, modified tobacco attempts to present a less toxic version of a familiar product, in contrast to nicotine replacement therapy (NRT), which involve a substitute product with a very different mode of consumption and action. Methadone is similar to NRT in that respect, while NEPs are not. This is not a judgment of actual success but simply of the theoretical basis for believing that it is possible the intervention reduces adverse consequences.

(b) Effect on prevalence of the undesired behavior. These are crude summaries of the empirical literature; where the result is particularly conjectural, this is indicated by a question mark. For modified tobacco products the entry reflects the almost certain effect of allowing their availability, with claims. The undesired behavior in the case of PREPs is smoking; for others it is fast driving, underage sex, injecting of powerful illegal opiates, and drinking by problem drinkers. This is an estimate of the effect on the number of undesired acts, not of the total harms themselves.

(c) Effect on intensity of use. As for prevalence, these are crude summaries of complex empirical literatures. Harms are a function of both prevalence and intensity of use. Low tar and filter cigarettes not only led more individuals to smoke but also on average led them to higher daily consumption. Early opening of bars on the Bowery may lead to higher alcohol consumption by chronic alcoholics, while needle exchange programs generally either reduce injecting frequency or leave it unchanged.

(d) Effects on others. Again, these are summaries of the empirical literature. In the case of mandated seat belts, the increase in speeding may have negative consequences for pedestrians, while reducing mortality of vehicle passengers or even total traffic-related mortality. Nicotine replacement products, even if they lead to more nicotine consumption, may reduce ETS sufficiently to lower harms to others.

(e) Whether the intervention conveys symbolic approval of the undesired behavior. Allowing cigarette manufacturers to market cigarettes with the claim of lower carcinogens requires the government to approve the act of smoking cigarettes, even if accompanied by warning signs, just as do condom programs for kids (underage sex) and needle exchange for addicts (injecting drug use). Other interventions have no such effect. NRT meets a physiological need through such different mechanisms that they

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TABLE 2-1 Characteristics of Eight Interventions With Harm Reduction Rationales

Product	Presumed Mechanism	Effect on Prevalence	Harms to Others	Symbolic Approval?	Effect on Intensity of Use	Potential Threats to Reducing Harm
Light & filter cigarettes	Less dangerous product	Increased cigarette consumption	Increased	No (govt. action not required)	Increase	Adaptive behavior negates technology/raises prevalence
Modified tobacco	Less dangerous product	Increased cigarette consumption	Increased	Yes (if claims allowed)	Increase	Exposure reductions not realized/ prevalence rises too much
Nicotine replacement therapy	Substitute product	Decreased smoking?	Reduced	No	Reduce	Prolongs smoking careers/ incomplete compliance
Oral methadone	Substitute product	Reduced heroin/raise opiate use	Reduced	No	Lower heroin/ possibly higher opiate	Prolongs opiate use
Needle exchange programs	Reducing danger of act	None	Reduced	Yes	Reduce/ unchanged	Incomplete compliance
Early opening of bars on the Bowery	Shifting consumption from dangerous forms	None	Unchanged	Yes	Increase	Behavioral model incorrect
Adolescent condom distribution	Reducing danger of act	Unclear	Unclear	Yes	Unclear	Increased sexual activity among kids
Mandated seat belts	Safer product	Increase	Unclear	No	Increase	Faster driving/selective compliance

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constitute no approval of smoking. Oral methadone also represents no endorsement of injecting powerful opiates, it may prolong opiate use but in a form that permits social functioning. This dimension may be important for establishing popular and professional acceptability.

(f) An assessment of why a harm reduction intervention or PREP might fail to reduce total harm. There are many paths to failure. For example, even if the mechanism of modified tobacco products is correct and they are less toxic than conventional products, the population changes may be so great as to lead not to harm reduction but to greater total adverse consequences. In the case of NEPs, it may be that compliance is so incomplete, or that the HIV epidemic is so far advanced, that needle exchange programs fail to have any detectable effect. The Skid Row intervention may underestimate the effect of early opening on other heavy drinkers.

The table indicates that no two interventions are identical in all dimensions. If one accepts the utility of distinguishing between making an existing product safer and offering a very distinctive substitute, only mandated seat belts parallel modified tobacco products. However the seat belts involve no endorsement of unsafe driving, while the modified tobacco products, if the government allows regulated claims of reduced harms, does provide endorsement of the very act of smoking tobacco. This heterogeneity complicates projections from the other harm reduction experiences to PREPs. However it indicates where one might turn for insight into likely effects.

CONCLUSIONS

Harm reduction is a viable approach to government interventions. It has informed policy debates in a number of areas, and there is a modest research base indicating that some interventions with a harm reduction focus may indeed be harm-reducing. However, the framework is not yet well developed in either theory or application and continues to encounter both popular and professional skepticism. That skepticism will form part of the backdrop to decisions about implementation of the framework in the area of reducing tobacco-related harms.

Social Values

There are well-documented health effects of tobacco exposure on the nonuser. Environmental tobacco smoke has just been included on the National Toxicology Program's list of known-carcinogens and has long been linked to respiratory diseases and cancers in nontobacco users exposed to the smoke of others. Chapter 15 includes well-documented

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evidence of effects of tobacco exposure in utero. One could argue that these involuntarily exposed people should be the touchstone for harm reduction demonstration. However it is difficult to identify other applications of the harm reduction framework in which this kind of reasoning has been used; for example, automobile safety modifications may have shifted the burden of traffic accidents to non-occupants, but this has not been given prominence.

Another important consideration in decision making about harm reduction is the social value of the product. Many judgments about regulating risks include such considerations. For example, some risks of pharmaceutical products are acceptable because the benefit outweighs the risk, with benefit measured as decreased mortality, decreased disease prevalence or severity, and in some cases as quality-of-life and social well being. As a society, we accept certain levels of air pollution and attendant harm to health because we value the right to drive a car.

Freedom of choice (to smoke or not) and the tobacco industry's right to exist are values to the American public that preclude tobacco prohibition. However, the American public overwhelmingly supports restrictions or bans on tobacco use in indoor public places (The Gallup Organization, 2000) and restriction of youth access to tobacco products (American Heart Association, 1998). Moreover, most tobacco users themselves would like to quit and there are very few health benefits associated with tobacco use (See Chapter 16). Therefore, acceptable restrictions on potential exposure or harm reduction products might be stringent, although not severe enough to put the industry out of business. However, just as social values assure the continued availability of tobacco, social values can influence the limits of harm reduction strategies. It is unclear how much actual reduction in harm should be required for approval and marketing of a harm reduction product. Should a new product be allowed and encouraged if the gain is incremental only? Because regulation of novel tobacco or cigarette-like products involves a change in philosophy about tobacco, and because this is fundamentally a value judgment absent specific scientific guidance, one gauge of how much harm reduction should be required of a novel tobacco or cigarette-like product could be an assessment of how the public values increased health or reduced harm from tobacco. Such information is obtainable in a scientific way and could guide policymakers as they set the "bar" for regulatory action.

Analytic Problems

Though conceptually simple, harm reduction is difficult to apply when assessing alternative interventions. Following MacCoun and Reuter (2001), three basic problems emerge:

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1. Aggregating harms. For illicit drugs in particular, a very heterogeneous set of adverse consequences need to be considered, such as loss of family cohesion, the spread of HIV and crime. Even if each effect can be measured, itself a major undertaking for any nonmarginal intervention (Reuter, 1999), there is little agreement about how to value them in monetary terms. The range of adverse consequences is narrower for the other cases, but even for alcohol, the range is wide enough (including crime and health) that aggregate measures in monetary terms are very approximate (e.g., Harwood et al, 1998). Some of these consequences are difficult to estimate and may consequently have been set at zero in quantitative studies because there is no systematic empirical base for an estimate. The harms derived from tobacco-related products are predominantly health related but the debate around economic interests of farmers in tobacco policy is a reminder that some other outcomes need to be taken into account.

2. Weighting the interests of different parties. The interests of users versus non-users has already been mentioned but there may also be other considerations of relative culpability and vulnerability. For example, the health burden of the poor may be given greater weight or consideration than the burden borne by the nonpoor, simply because the former can do less to ameliorate their own problems. It is also important to note that harms are not uniformly distributed; any particular option may benefit one group at the expense of another.

3. Harm reduction as a hazardous policy choice. An unsuccessful harm reduction intervention may lead to long-lasting and broadly distributed adverse consequences. For example, methadone maintenance might have turned out to increase heroin initiation and to prolong opiate addiction; it would be difficult to reverse those consequences or to be able to predict them in the early years of the intervention, let alone in advance of the decision. That suggests that harm reduction interventions may have to be held to a higher standard of proof and that government should be particularly careful, adopting one step at a time and closely monitoring the results. The fact that it will take decades to be certain about harm reduction effects of tobacco-related PREPs is a reason for particular caution in this case; this holds for none of the other applications. MacCoun (1998) summarizes the research on risk compensation: "[t]o date, research on compensatory responses to risk reduction provides little evidence that behavioral responses produce net increases in harm, or even the constant level of harm predicted by the "homeostatic" version of the theory. Instead, most studies find that when programs reduce the probability of harm given unsafe conduct, any increases in the probability of that conduct are slight, reducing, but not eliminating, the gains in safety" (Chirinko and Harper, 1993; Stetzer and Hofman, 1996). However, the

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applicability of this finding to specific tobacco interventions remains to be established.

The committee concludes with two other observations:

Harm reduction presents major problems of measurement. Harm is much more difficult to measure than is prevalence or even quantity consumed, the conventional targets of control. As Single (1997) notes with respect to illegal drugs: "[A]s a practical matter, it is very difficult to determine whether specific policies involve a net reduction in drug-related harm." It requires estimation not only of numerous disparate outcomes but also assessment of how much of their change can be attributed to the intervention. For example, vehicle fatalities are determined by many factors; it is a complex research task to identify the contribution of seat belt laws or more stringent Blood Alcohol Content laws. Harm reduction in the tobacco control field will require the development of complex surveillance programs and very difficult issues of attribution.

Public health advocates opine that tobacco is a "special case," because tobacco is the only consumer product that when used exactly as intended is lethal. Further, they posit that it is unconscionable to market an addictive product to youth who are not competent to make informed judgments about long-term risks in the face of perceived short-term benefits. Finally, an undeniable history of suppression of information about the health risks of tobacco and tobacco product design changes leads many to seriously question any assessment of harm reduction potential by the manufacturers of the products. Just as harm reduction with respect to illicit drugs has been hurt by its association with the legalization movement, so too has the tobacco companies' use of false messages about the benefits of light and filter-tipped cigarettes created suspicion in the field of tobacco control. Therefore, the burden of proof for a benefit of novel, potential exposure or harm reduction tobacco products entails special considerations beyond that required of many other scientific questions.

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3

Historical Perspective and Lessons Learned

When filtered and low-yield cigarettes were introduced into U.S. markets, they were heavily promoted and marketed with both explicit and implicit claims of reducing the risk of smoking. Even as data accumulated, albeit slowly, that these products did not result in much—if any—decrease in risk, consumers have continued to believe otherwise. The population continues to misunderstand the meaning of numbers that purport to describe yields of tar and nicotine. Consumer misunderstanding is explained in part by the ways in which these products are marketed and in part by general theories of risk perception. This chapter reviews some key evidence regarding tobacco marketing, risk perception, knowledge about toxicity, and reasons for using low-yield products in hopes of illuminating the possible effects, including the promise of benefit and the risk of increased harm, of potential reduced-exposure products (PREPs) on tobacco use and on the health of the public as harm reduction is pursued in the near future. This material provides some of the evidentiary base for several of the conclusions and recommendations found in Chapters 6 and 7 of this report.

TOBACCO MARKETING: EARLY HEALTH CLAIMS

Tobacco companies have promoted the manufactured cigarette for more than a century (Kluger, 1996). The history of cigarette marketing has been discussed in several sources (e.g., Altman et al., 1987; Cohen, 1996;

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Kluger, 1996; Kozlowski et al., 2000b; Pollay 1989, Pollay and Dewhirst, 2000; Ringold and Calfee, 1989; Swedrock et al., 1999; U.S. DHHS, 1989, 1994, 1998; Warner, 1985). As shown in Table 3-1, the tobacco companies have appealed to health concerns of smokers at least since 1927. Claims about tar and nicotine levels appeared as early as 1942.

The federal government, primarily via the Federal Trade Commission (FTC), has been involved in regulating tobacco marketing. The FTC is empowered by Congress to "prevent persons, partnerships, or corporations . . . from using unfair or deceptive acts or practices in commerce" (McAuliffe, 1988; OSH, 2000; U.S. DHHS, 1989). Using this authority, the FTC has undertaken several legal actions on health or medical claims made by tobacco companies. In 1942, for example, the FTC pressed Brown & Williamson Tobacco Corporation to stop making claims that Kool cigarettes, among other things, protected against colds and were soothing to the throat, and the company entered into a stipulation that it would refrain from doing so (FTC, 1942). As seen in Table 3-1, however, claims about Kools continued for several years after the 1942 stipulation.

The FTC also took legal action in the 1940s against claims that lower-tar cigarettes were beneficial (e.g., produced less throat irritation) (Cohen, 1996). These claims subsided. However, early in the 1950s, *Consumer Reports* published brand-specific tar and nicotine ratings. When claims increased, the FTC filed more suits against companies making claims about tar and nicotine levels. In September 1955, the FTC published "Cigarette Advertising Guides" that prohibited health claims (Cohen, 1996; Kozlowski, 2000b). Specifically, these guides prohibited claims about tar and nicotine that were not supported by "competent scientific proof" of a substantial (physiological) difference between brands (Cohen, 1996; McAuliffe, 1988).

The FTC explicitly stated that the guides would not prohibit statements about taste, flavor, aroma, or enjoyment (Kozlowski, 2000b). This led to the use of terms such as "mild," "light," and "smooth," which likely were better advertising techniques than direct health claims. The health-protecting messages brought to mind the fact that protection was needed, raising anxiety in the smoker. However, terms such as mild, light, and smooth only suggested the concept of safety and did not bring to mind the health-compromising properties of the product. The industry received counsel in the 1950s from motivational researchers who advised companies against using verbally explicit health appeals and suggested more visual images (Pollay, 1989). A comment by Martineau (1957), cited by Pollay (1989), is highly relevant. Martineau stated that direct claims "may offer some reassurance for the inveterate smokers, but they do utterly nothing to widen the market . . . to make smoking seem reasonable, justifiable, and highly desirable" (see Box 3-1).

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TABLE 3-1 Selected Advertising Text Messages for Cigarettes and PREPs-United States, 1927-2000

1927: "OLD GOLD cigarettes. Better . . . smoother . . . not a cough in a carload."

1928: "It's toasted." "No Throat Irritation—No cough." (Lucky Strike)

1929: "20,679 physicians have confirmed the fact that Lucky Strike is less irritating in the throat than other cigarettes."

"Many prominent athletes smoke Luckies all day long with no harmful effects to wind or physical condition." (Lucky Strike)

"MILD . . . and yet THEY SATISFY." (Chesterfield)

1930: "It's toasted." "Your throat protection—against irritation—against cough." (Lucky Strike)

1932: "Do you inhale? What's there to be afraid of? Seven out of 10 inhale knowingly; the other 3 do so unknowingly. Do you inhale? Lucky Strike meets the vital issue fairly and squarely . . . for it has solved the vital problem. Its famous purifying process removes certain impurities that are concealed in even the choicest, mildest tobacco leaves. Lucky's created that process. Only Lucky's have it!" "IT'S TOASTED! Your protection against irritation, against cough."

1933: "Does winter make your head feel stuffy? Steam-heated rooms parch your throat? Heavy smoking 'brown' your taste? Then you've three extra reasons for changing to KOOLS. They're mildly mentholated. Light up and feel that instant refreshment. Smoke deep; the choice Turkish-Domestic tobacco flavor is all there. Smoke long; your throat and tongue stay cool and smooth, your mouth clean and fresh. Change to KOOLS. It's a change for the better."

"Give your throat a Kool vacation! Like a week by the sea, this mild menthol is a tonic to hot, tired throats."

1935: "They don't get your wind!" (Camel)

1936: "Ask your doctor about a light smoke." (Lucky Strike)

"The truth about irritation of the nose and throat due to smoking. Philip Morris & Company do not claim that Philip Morris cigarettes cure irritation. But they do say that an ingredient—a source of irritation in other cigarettes—is not used in the manufacture of Philip Morris . . . Their [group of doctors] tests proved conclusively that changing to Philip Morris, every case of irritation due to smoking cleared completely or definitely improved."

1937: "They're so mild and never make my throat harsh or rough." (Camel)

1938: ". . . so smooth and mellow you can smoke them in any number *without cigarette hangover*." (Old Gold)

"Viceroy's filter neatly checks the throat-irritants in tobacco . . . Safer smoke for any throat. Inhale without discomfort."

1939: "Your throat will like the change. The mild menthol is definitely refreshing." (Kool)

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TABLE 3-1 Continued

1940s-1950s: "Outstanding . . . and they are mild!" (Pall Mall)

"Pall Mall's greater length of fine tobaccos travels the smoke further on the way to your throat—filters the smoke and makes it mild."

1942: "*Reader's Digest* exposes cigarette claims . . . Impartial tests find Old Gold lowest in nicotine and throat-irritating tars . . .".

1943: ". . . filtering the flavor and aroma of the world's finest tobaccos into the smoothest of blends and checking OUT resins, tar, and throat irritants that can spoil the EVENNESS for smoking enjoyment!" (Viceroy)

1944: "Try Camels as your own T-Zone. T for taste. T for throat. The true proving ground for a cigarette."

1946: "More Doctors Smoke Camels Than Any Other Cigarette."

"Pasteurized for your protection." (Philip Morris)

"HEAD STOPPED UP? GOT THE SNEEZES? SWITCH TO KOOLS. . . THE FLAVOR PLEASES!"

1947: "When you have a cold and can't taste a thing, always smoke KOOLS to get back in the swing!"

1949: "Not one single case of throat irritation due to smoking Camels."

". . . Remember: Less irritation means more pleasure. And Philip Morris is the ONE cigarette proved less irritating—definitely milder than any other leading brand."

"Got a COLD? Smoke KOOLS as your *steady* smoke for that clean, KOOL taste!"

1951: "Notice that Philip Morris is definitely less irritating, definitely milder!"

"Filtered cigarette smoke is better for your health." (Viceroy)

1952: "No other cigarette approaches such a degree of health protection and taste satisfaction." (Kent)

"Because this filter is exclusive with KENT, it is possible to say that no other cigarette offers smokers such a degree of health protection and taste satisfaction."

". . . like millions today, you are turning to filter cigarettes for pleasure plus protection . . . it's important that you know the Parliament Story."

1953: "First cigarette ever to give you black and white proof of greatest health protection . . . with full smoking pleasure!" (Kent)

"The American Medical Association voluntarily conducted in their own laboratory a series of independent tests of filters and filter cigarettes. As reported in the *Journal of the American Medical Association*, these tests proved that of all the filter cigarettes tested, one type was the **most effective** for removing tars and nicotine. This type **filter** is used by Kent . . . and only

continues

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TABLE 3-1 Continued

Kent!" "KENT. For the greatest protection of any filter cigarette with exclusive MICRONITE filter."

". . .Alpha Cellulose. Exclusive to L&M Filters, and entirely pure and harmless to health."

"Parliament filters 100% of the smoke—recessed filter keeps trapped tars and nicotine from touching lips or mouth!"

"New King-Size Viceroy gives Double-Barreled Health Protection . . . is safer for throat, safer for lungs than any other king-size cigarette."

"The nicotine and tars trapped by Viceroy's Double-Filtering action cannot reach your throat or lungs!"

"*FILTERED* CIGARETTE SMOKE IS BETTER FOR YOUR HEALTH. The nicotine and tars trapped by this Viceroy filter cannot reach your mouth, throat, or lungs!" *Reader's Digest*, January 1950.

1954: "L&M Filters are Just What the Doctor Ordered!"

"The cigarette that takes the FEAR out of smoking!" (Philip Morris)

1956: "Good news for ALL smokers . . . **Salem** filter cigarettes. THE FIRST TRULY NEW SMOKING ADVANCE IN OVER 40 YEARS! Menthol fresh. Most modern filter. Rich tobacco taste."

1958: "The *first* filter cigarette in the world that meets the standards of United States Testing Co. New Hi-Fi Filter Parliament." (note: the parenthetical phrase "high filtration" was printed, in small type, "Hi-Fi")

1966: "The truth is out: The wire services recently released a new report that revealed that, new *TRUE* Filter Cigarettes delivered less tar and nicotine than other brands tested . . . It's TRUE . . . without our knowledge or permission, these tests were conducted and TRUE Filter Cigarettes were found to be 'most effective in removing tar and nicotine.'"

1971: "You don't cop out. We don't cop out. You demand good taste, But want low 'tar' and nicotine. Only Vantage gives you both."

1976: "Considering all I'd heard, I decided to either quit or smoke True. I smoke True."

"If you are a smoker: There are many reasons to smoke Now. If you are a smoker who has been thinking about 'tar' and nicotine, these are the reasons to smoke Now: Reason. Now has the lowest 'tar' and nicotine levels available to you in a cigarette, king-size or longer. 2 mg. 'tar,' 2 mg. nicotine."

1977: "Vantage is changing a lot of my feelings about smoking. I like to smoke, and what I like is a cigarette that is not limited on taste. But I am not living in an ivory tower. I hear the things being said about high tar smoking as much as the next guy. So, I started looking for a low tar smoke that had some honest-to-goodness taste."

continues

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TABLE 3-1 Continued

1978: "*National Smoker Study*: Merit Science Works! Low tar MERIT with 'Enriched Flavor' tobacco delivers taste equal to—or better than—leading high tar brands."

"I'm realistic. I only smoke Facts. We have smoke scrubbers in our filter."

1980s-1990s: "Alive with pleasure." (Newport)

1981: "The pleasure is back. BARCLAY. 99% tar free."

1985: "Latest U.S. Gov't Laboratory test confirms, of all cigarettes: Carlton is lowest. Box King—lowest of *all* brands—*less* than 0.01 mg. tar, 0.002 mg. nic."

1987: "Ultra taste in ultra low tar. Test a pack today." (Vantage)

1997: "No Additives" (Winston)

1998: "New Marlboro ULTRA LIGHTS. Famous Marlboro flavor now in an ULTRA LIGHT."

1999: "1 mg. Isn't it time you started thinking about number one?" (Carlton)

"Discover the rewards of thinking light." (Merit Ultra Lights)

2000: "The best choice for smokers who are worried about their health is to quit. Here's the next best choice." (Eclipse™)

"…a smooth satisfying taste with less smoke around you, virtually no lingering odor, and no ashes." (Accord™)

SOURCES: Anonymous, 1946; Arnett, 1999; Caples, 1947; Chickenhead Productions, 2000; Glantz et al., 1996; Harris, 1978; Kluger, 1996; Kozlowski, 2000; Lewine, 1970; Mullen, 1979; Pollay and Dewhirst, 2000; R.J. Reynolds Tobacco Company, 2000; Sobel, 1978; Swedrock et al., 1999.

BOX 3-1
1977 British American Tobacco Company Document Describing Advertising and Communication Strategies to Reassure Consumers About Safety

"All work in this area [communications] should be directed towards providing *consumer reassurance* about cigarettes and the smoking habit . . . by claimed low deliveries, by the perception of low deliveries and by the perception of "mildness." Furthermore, advertising for low delivery or traditional brands should be constructed in ways so as not to provoke anxiety about health, but to alleviate it, and to enable the smoker to feel assured about the habit and confident in maintaining it over time" [emphasis in original].

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BOX 3-2
Summary Analysis of Cigarette Industry Advertising

"The cigarette industry has not voluntarily employed its advertising to inform consumers in a consistent and meaningful way about any of the following: (1) the technologies employed in fabricating the products, (2) the constituents added in the manufacturing processes, (3) the residues and contaminants that may be present in the combustible column, (4) the constituents of smoke that may be hazardous, (5) the addictiveness of nicotine, or (6) the health risks to which its regular customers and their families are inevitably exposed. Their advertising for low-yield products, instead, has relied on pictures of health and images of intelligence, and has misled consumers into believing filtered products in general and low tar products in specific to be safe(r) than other forms without knowing exactly why."

SOURCE: Pollay and Dewhirst, 2000.

Business Week publicly criticized the industry on the issue of direct health claims. McAuliffe (1988) cites the following quote from the December 5, 1953, issue: "Why has the industry persisted in this negative form of advertising even when, as tobacco growers and others complain, it hurts the trade by making people conscious that cigarettes can be harmful?" (Anonymous, 1953).

Advertisements using health claims in *Time* and *Life* magazines, which had increased substantially in 1952 and 1953 (after the first cancer scare), dropped to pre-1952 levels in 1954 (Swedrock et al., 1999). There has been a steady increase since the early 1960s in the percentage of magazine advertisements using visual images of bold and lively behaviors in pristine environments (Pollay, 1989; Pollay and Dewhirst, 2000; see Box 3-2).

HEALTH IMPACT OF LOW-YIELD PRODUCTS

In a recent review of epidemiologic data on the disease risks associated with the changing cigarette, Samet (1996) concluded that low-tar and nicotine cigarettes, when compared with relatively higher-tar and nicotine cigarettes, were associated with modest decreases in lung cancer risk and similar cardiovascular risk. The data on chronic obstructive pulmonary disease (COPD) were inconclusive. For all diseases, smokers of lower-tar and nicotine cigarettes experienced substantially higher disease risks than persons who did not smoke. These findings were similar to those in a 1981 report of the U.S. Surgeon General (U.S. DHHS, 1981).

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The nature of these relationships may be influenced by misclassification bias, in that smokers may not be able to accurately recall lifetime brand use patterns. In addition, selection bias may occur if symptoms or diseases cause smokers to switch to lower-yield brands and if persons who switch to lower-yield brands exhibit different lifestyle characteristics that may influence disease risk (Samet, 1996). For example, persons who switch to lower-tar products appear to be more likely to eat more fruits and vegetables (Haddock et al., 1999). Although the magnitude of such biases may eventually prove to be small, research to assess their potential impact is warranted.

In related analyses, Thun and colleagues (1997a) compared the relative risks of lung cancer and coronary heart disease in Cancer Prevention Study I (from 1959 to 1965) with those observed in Cancer Prevention Study II (from 1982 to 1988). The risks did not decrease across studies when the authors stratified for gender, duration of smoking, age, and number of cigarettes smoked daily, even though the average tar yield of cigarettes consumed decreased substantially during that time. The results of this analysis could be influenced at least in part by unmeasured differences in lifetime smoking patterns (e.g., number of cigarettes smoked daily during adolescence) and by lifestyle factors (e.g., fruit and vegetable consumption). The weight of the evidence indicates that lower-tar and nicotine yield cigarettes have not reduced the risk of disease proportional to their FTC yields, in part because smokers compensate to obtain more nicotine (Burns, 2000; Kozlowski and Pillitteri, 1996) and in part because the products themselves contain higher concentrations of selected carcinogens (Hoffman et al., 1996).

Increased prevalence of the use of lower-tar and nicotine cigarettes has been associated with an increase in the percentage of lung cancers that are adenocarcinomas and a decrease in squamous cell carcinomas (Levy et al., 1997; Thun et al., 1997b). This changing histological pattern may be influenced by increased levels, over time, of nitrosamines in cigarette smoke and by increased inhalation of lower-nicotine-yield cigarettes, as smokers attempt to compensate to reduced nicotine yields by inhaling more deeply (Hoffman et al., 1996; Kozlowski and Pillitteri, 1996).

RISK PERCEPTION

The Gallup Organization has polled Americans about their perceptions of cigarette smoking since 1949 (Moore, 1999). For example, in 1999, 95% of Americans considered smoking to be harmful, up from 60% in 1949. In 1999, 92% of Americans considered cigarette smoking to be one of the causes of lung cancer, compared to only about 40% in 1954. Additionally, about 80% of smokers considered smoking to be one of the causes of

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heart disease in 1999, compared to about 37% in 1957. For the purposes of this analysis, a focus on smokers' perceptions is crucial to understanding the possible ways in which various harm reduction approaches, including the marketing of PREPs, may be understood or interpreted and, as a result, may affect consumer behavior.

Perceptions by Smokers of the Risk of Cigarette Smoking

It is now well established that perceptions of the harmfulness of smoking affect behavior. Much might be learned about the possible consequences of introducing PREPs from analysis of studies of smokers' knowledge of the consequences of various types of tobacco products. Although Viscusi (1992, 1998) argues that smokers tend to overestimate their risks, the vast majority of research conducted to date supports the opposite conclusion. Weinstein (1999) has reviewed much of this research. In general, the work of Weinstein and others (Ayanian and Cleary, 1999; Cohn et al., 1995; Hahn and Renner, 1998; Slovic 1998, 2000) suggests the following:

- Although smokers acknowledge that smokers have higher risks for various health problems than persons who do not smoke, most smokers did not view themselves as having higher risks of heart disease or cancer compared to other adults their age.
- Smokers' estimates of the number of years of smoking that are needed to produce health consequences increase with the number of years they have been smoking.
- Many young smokers perceive themselves to be at minimal risk from each cigarette they smoke, because they intend to stop smoking before any damage to their health occurs.
- Adolescents and adults believe that they are less likely than their peers to become addicted to cigarettes.

These findings highlight the frequently observed phenomenon of "optimism bias" or "unrealistic optimism" (Weinstein, 1999). For most hazards—and regardless of how they perceive the risks for people in general—individuals tend to perceive their own risks as less than those of other people (Weinstein, 1999; see Box 3-3).

Perceptions of the Risk from Low-Yield Cigarettes

In this report, cigarettes with tar yields on the FTC method of 15 mg or less are classified as low-yield cigarettes. In 1998, 81.9% of cigarettes consumed in the United States were low yield, up from 2.0% in 1967 (FTC

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BOX 3-3
Industry Document from 1974 Reporting on a Study of Young Smokers' Health Concerns

"Health concerns exist among younger smokers. . . . One type of smoker rationalized smoking as a pleasure that outweighed the risks. Another felt that they didn't smoke enough to be dangerous. A third type rationalized his use of cigarettes by feeling he would quit before it was 'too late.' A final smoker group said that science would come to his rescue."

SOURCE: 018, K0028.

2000). Cigarette companies generally use "light" to refer to cigarettes with 6 through 15 mg tar and "ultralight" to refer to cigarettes with 1 to 5 mg of tar (Davis, 1987; Townsend, 1996). The terms are often used in surveys (e.g., Cohen, 1996), although the cut points used to classify brands may vary slightly.

The various studies described below have assessed perceptions of risks for smoking high- and low-tar cigarettes. These assessments have been conducted for smokers overall and, at various times, by tar level of the smoker's usual brand and by whether the smoker has switched to a low-yield brand.

Data on perceptions of risks from types of cigarettes from the 1966 and 1975 Adult Use of Tobacco Surveys (AUTSs) are summarized in the 1981 Surgeon General's report (U.S. DHHS, 1981). The percentage of smokers who felt that "some cigarettes [are] more hazardous than others" increased from 29.9% in 1966 to 49.1% in 1975.

Perceptions Held by Smokers of Low-Yield Products Regarding Risk

Cohen (1992) reports on the results of a 1980 industry-sponsored Roper survey that he learned about during preparation for testimony in a court case. In 1980, more than one-third (36%) of smokers of low-yield cigarettes reported that smoking their brand of cigarette did not significantly increase a person's risk of disease over that of nonsmokers; another 32% stated that they weren't sure if this was the case.

More recently, data from the 1986 AUTS and the 1987 National Health Interview Survey (NHIS) were used to assess attitudes, knowledge, and beliefs about low-yield cigarettes among adults and adolescents (Giovino et al., 1996). Both low-tar smokers and persons who've ever switched to

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lower-tar brands were (compared, respectively, to persons who smoke higher-tar brands and those who've never switched) more likely to (1) acknowledge the dangers of smoking, (2) be concerned about the health effects of smoking, (3) say that their health has been affected by smoking, and (4) believe that their cigarettes are safer. In 1987, 44% of smokers reported that they had ever switched to a low-tar brand to reduce their health risks. Among persons 10- to 20-years old in 1993 who smoked light or ultralight cigarettes, 33% said that they smoked these brands because they taste better, 20% because they are less irritating, and 21% because they thought these cigarettes were healthier than other brands.

In another study, a 1995-1996 survey of individuals who enlisted in the Air Force, which was administered during the first week of basic military training (Haddock et al., 1999), 32% of current smokers reported that they had switched during the previous 12 months to a lower-tar and nicotine cigarette brand just to reduce their health risk.

Shiffman and colleagues (In Press) analyzed 1999 national survey data to assess health perceptions, tar and nicotine delivery characteristics, and smoking sensations among cigarette smokers. Most smokers, particularly smokers of light and ultralight (L/UL) cigarettes, believed L/UL cigarettes were less harsh and that they delivered less tar and nicotine than regular cigarettes. The beliefs that L/UL cigarettes delivered less tar and nicotine and that they were less harsh than regulars each independently contributed to predicting the belief that L/UL cigarettes were safer than regulars.

Knowledge and Perceptions About Yields and Yield "Terms"

A Gallup Organization poll conducted in 1993 asked respondents the following question: Besides selling the product, what message do you think cigarette advertising is trying to get across when it uses terms like low-tar, low-nicotine, or low-yield? (Gallup Organization, 1993). Of the respondents, 56% of smokers and 60% of nonsmokers stated that the terms indicated a positive health benefit, with specific meanings that included being safer, less harmful, healthier, not as bad for you, or less cancerous.

Bolling and colleagues (2000) reported that English smokers did not find tar numbers (printed on cigarette packages) meaningful, claiming instead that the numbers were "scientific" and that they weren't sure if the numbers indicated yield per cigarette or per pack. Instead, smokers tended to rely on terms such as light, mild, and ultralight and on pack color to make assessments about various brands.

Based on results from a survey conducted in 1994, Cohen (1996) reported that 28% of smokers thought that switching from a 20-mg-tar cigarette to a 16-mg-tar cigarette would substantially reduce health risks.

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About one-quarter felt that a smoker could smoke 10 cigarettes yielding 1 mg of tar and take in the same amount of tar as smoking one cigarette yielding 10 mg of tar.

In Cohen's survey (1996), only 14% of smokers overall reported that they used the actual tar numbers to make judgments regarding the relative safety of different brands. However, 56% of smokers of cigarettes yielding 1 to 5 mg of tar reported that they used tar numbers when assessing health risks of various cigarettes. Tar numbers, which are printed on less than 10% of cigarette packages sold in the United States, are more likely to be printed on the packages of the lowest-yielding cigarettes (FTC, 2000).

Kozlowski and colleagues conducted several informative surveys on the topic of light and ultralight cigarettes (Kozlowski et al., 1996, 1998a, 1998b, 1999, 2000a, 2000b). In one study, about two-thirds of smokers either reported not having seen or heard that there were "rings of small holes on the filters of some cigarettes" or did not know that blocking these holes would increase tar yields (Kozlowski et al., 1996). Less than 20% of smokers of ventilated brands knew that their cigarettes had filter vents (Kozlowski et al., 1998b). These data show that although intense marketing by tobacco companies about low-yield products has influenced consumers' perception of product safety, a lack of marketing or communication about ventilation holes has led to less informed consumers.

Another analysis indicated that the majority of smokers in a national sample responded either "don't know" or "two" in response to the question, How many LIGHT cigarettes would someone have to smoke to get the same amount of tar as from one REGULAR cigarette? (Kozlowski et al., 1998b). Less than 10% knew that one light cigarette could give the same amount of tar as one regular cigarette.

Reasons for Switching to Low-Yield Products

Smokers of light or ultralight cigarettes were asked if they smoked for each of the following reasons (presented in random order): "as a step toward quitting smoking completely," "to reduce the risks of smoking without having to give up smoking," "to reduce the tar you get from smoking," "to reduce the nicotine you get from smoking," and "because you prefer the taste compared to Regular cigarettes" (Kozlowski et al., 1998b). This study showed that 80% of smokers of light and 69% of ultralights preferred the taste of their brands; 50% of smokers of light and 72% of ultralight endorsed less nicotine as a reason; 57% of smokers of light and 73% of ultralights endorsed less tar; 39% of smokers of light and 58% of ultralights endorsed reducing risks without having to give up smoking; and 30% of lights and 49% of ultralights endorsed smoking their brand as a step toward quitting completely.

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Knowledge Regarding Constituents, Additives, and Toxicity

Bolling and colleagues (2000) conducted a survey of 1,036 smokers in England in October 1998 to examine consumers' reactions to cigarette yield and product information. They also conducted focus groups and in-depth interviews in February 2000. While most smokers knew that tar (92%) and nicotine (98%) were present in tobacco smoke, fewer (29%) knew that carbon monoxide was present and almost none (≤5% for all chemicals) knew about the presence of toxic chemicals such as arsenic, lead, and cyanide. Bolling and colleagues also reported that smokers were shocked to learn about the presence of dangerous chemicals in their cigarettes, in part because such information undermined their beliefs that cigarettes were "natural" products.

In 1997, R.J. Reynolds Tobacco Company re-positioned the Winston brand with an advertising campaign claiming its product was made with "100% tobacco," containing "no additives" (see table 3-1, Arnett, 1999). In mall intercept interviews, 400 adolescents were surveyed about the Winston advertisements in Arizona and Washington, and 203 adults were surveyed in Washington. The two most common responses to the question, What do you think the Winston ads mean by saying that Winstons have "no additives"? were that Winston cigarettes contained only tobacco and that Winston cigarettes have no added chemicals. However, 36% of adolescents and 18% of adults also perceived them as meaning that Winston cigarettes were healthier than other cigarettes. Furthermore, 39% of adolescents and 20% of adults perceived the advertisements as claiming that Winstons were "less likely than other cigarettes to harm your health." Additionally, 42% of adolescents and 14% of adults stated that the advertisements meant that Winstons are "less likely than other cigarettes to be addictive." Overall, about two-thirds of adolescents and one-quarter of adults believed that the no additives claim meant at least one of the above implied health claims.

Evidence also suggests that consumers perceive menthol-containing cigarettes to be less harmful because they seem less harsh on the throat. Menthol cigarettes appear to be at least as dangerous as nonmenthol cigarettes (U.S. DHHS, 1998). About 26% of all cigarettes sold in the United States are mentholated (FTC, 2000). The vast majority of African-American smokers smoke menthol brands (U.S. DHHS, 1998). Epidemiological studies of mentholated cigarettes suggest that these products are at least as dangerous as nonmentholated cigarettes (Herbert and Kabat, 1989; Kabat and Herbert, 1991, 1994; Sidney et al., 1995). Additionally, the committee is aware of no evidence in support of the assertion that cigarettes without additives are less hazardous than those with additives.

Given the persistent health claims that were made about these products earlier in the century (Table 3-1), surprisingly little research has been

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conducted on people's perceptions of them. In a recent study, Hymowitz and colleagues (1995) questioned 213 adult smokers of menthol cigarettes who participated in a stop-smoking study. Among 174 African Americans, the main reasons for smoking menthols included the following: menthol cigarettes tasted better than nonmenthol cigarettes (83%); they had always smoked menthol cigarettes (63%); menthol cigarettes were less harsh on the throat than nonmenthol cigarettes (52%); inhalation was easier with menthol cigarettes (48%); and menthol cigarettes could be inhaled more deeply (33%). Among 39 white smokers of menthol cigarettes, reasons for their choice of menthols included menthol cigarettes tasted better than nonmenthol cigarettes (74%); menthol cigarettes were more soothing to the throat (51%); they had always smoked menthol cigarettes (39%); and inhalation was easier with menthol cigarettes (21%).

An industry document (Tibor Koeves Associates, 1968) reports the results of in-depth interviews (most likely conducted in 1968) of 10 African-American smokers of menthol cigarettes. The authors of the report concluded that two underlying factors "generated the great enthusiasm for menthol cigarettes." The preference for menthols seemed "based both on dynamic sensory and on psychological gratifications." The taste of menthol, which reminded many of candy, was a major attraction. The fact that the smoke wasn't hot or burning was also important. Psychologically, menthols were perceived to be modern and youthful. More relevant to this discussion, they were "considered as generally 'better for one's health.'" Most respondents viewed menthols as "less strong" than regular cigarettes, with the understanding among interviewees that cigarettes that were less strong were less dangerous to one's health.

POTENTIAL INFLUENCE OF PREPS ON TOBACCO USE BEHAVIORS

The introduction of products to reduce harm in a population can result in both intended and unintended consequences. Both Pauly and colleagues (1995) and Hughes (1998) raise the possibility that the introduction of PREPs and their promotion as less harmful ways to smoke could lead to increased initiation. Behavioral adaptation can occur in ways that diminish the possible beneficial consequences of potentially harm-reducing products. In this section, consideration is given to studies relating to the possible influence of low-yield products on initiation and quitting.

Initiation

Arnett (1999) raised concerns that adolescents' beliefs about claims made in advertisements for the no-additive products described earlier

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could influence susceptible nonsmoking adolescents by inflating whatever optimism bias they already posses. Marketing strategies for the products could influence perceptions of product safety and the overall acceptability of smoking. In addition, such information might undermine the advice of parents, teachers, and health professionals. Unfortunately, there is little evidence one way or the other on whether the introduction of filters or light cigarettes has affected rates of initiation.

Silverstein and colleagues (1980) observed that smoking prevalence increased substantially for young girls in the 1970s. Their research had indicated that high school females experienced greater societal pressure to smoke (exhibited by a higher prevalence of trying smoking than for males) but a greater physiological pressure not to smoke (exhibited by a higher sensitivity to nicotine). However, the pressures to smoke may also have been due to marketing for women's brands, which increased markedly in the late 1960s and early 1970s (Pierce et al., 1994). Silverstein and colleagues (1980) concluded that females resolve the competing pressures by smoking fewer cigarettes per day and using low-yield cigarettes. The authors argued that if low-nicotine cigarettes were less available, many females would choose not to smoke rather than experiencing the unpleasant effects of nicotine reactions.

Quitting Smoking

The introduction of PREPs into a population may increase, decrease, or have no effect on the rate of quitting smoking in that population. As with initiation, effects on quitting could be positive or negative. The direction and magnitude of these effects, if real, could influence the population impact of PREPs.

Effects on Motivation

PREPs may influence quitting by changing people's motivation to quit (Russell, 1978) in either direction. It is possible that switching to low-yield cigarettes has facilitated quitting by some people, because successful switching might increase smokers' confidence in their ability to control their smoking behavior and thereby encourage a future quit attempt (Hughes, 1995). However, switching to low-yield cigarettes could also reduce the motivation to quit. The 1980 finding that about 36% of smokers of light cigarettes reported that smoking light did not increase risk compared to not smoking provides indirect evidence that they could have decreased motivation to quit (Cohen, 1992).

Users of low-yield cigarettes are generally more interested in quitting than those who smoke regular cigarettes (Giovino et al., 1996; Jarvis et al.,

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1989), although Shiffman and colleagues (In Press) found this to be true only for smokers of light (but not ultralight) cigarettes. They may also be more confident in their ability to quit (Haddock et al., 1999; Jarvis et al., 1989). In one recent national survey, 30% of light smokers and 49% of ultralight smokers reported that they used light cigarettes as a step toward quitting (Kozlowski et al., 1998a). In another study, 5.2% of persons who tried to quit during the previous 10 years but relapsed reported using low-tar and nicotine cigarettes as a quitting strategy during their most recent quit attempt (Fiore et al., 1990). However, a similar (4.6%) percentage of persons who tried to quit within the previous 10 years and were abstinent for at least 1 year at the time of being surveyed reported using low-tar and nicotine cigarettes as a quitting strategy during their most recent quit attempt. This finding suggests that even though many people use low-yield cigarettes as a quitting strategy, the efficacy of this strategy is doubtful.

In a recent national survey, 32% of smokers of lights and 26% of ultralights reported that they would be likely to quit smoking if they learned that one light or one ultralight cigarette could provide as much tar as one regular cigarette (Kozlowski et al., 1998a). Another study (Kozlowski et al., 1999) used a simulated radio message to inform smokers that one light cigarette could provide as much tar as one regular cigarette. More than half (55%) stated that it made them think more about quitting, and nearly half (46%) said that the message increased the amount they wanted to quit. These data suggest that correcting misperceptions can motivate health-promoting intentions. Whether it can affect behavior remains unknown.

Effects on Quitting

Only a few large studies have assessed the association between tar levels or switching to lower-tar brands and actual quitting. In 1959, the American Cancer Society fielded the Cancer Prevention Study (CPS) I of approximately 1,078,000 adults. Hammond (1980) used the data to study quit rates as a function of tar levels. Persons who smoked cigarettes with ≤17.6 mg tar were classified as smoking low-tar cigarettes. Persons who smoked cigarettes with ≥25.8 mg tar were classified as smoking high-tar cigarettes. Those who smoked cigarettes with intermediate tar yields were classified as smoking medium-tar cigarettes.

Participants enrolled in 1959 were followed to 1965. Those who were still smoking in 1965 were followed until 1972. There was an inverse relationship between tar yield and the probability of quitting. Low-tar smokers at baseline and in 1965 were the most likely to be abstinent at each respective follow-up observation.

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The 1986 AUTS was used to assess quitting among a nationally representative sample of persons who had ever smoked regularly (i.e., ≥100 lifetime cigarettes) (Giovino et al., 1996). Tar levels were ≤6 mg tar, 7-15 mg tar, and ≥16 mg tar. The prevalence of cessation was higher for persons who had never switched brands to reduce their level of tar and nicotine. The relationship was observed overall and in the three age groups examined (17 through 34 years, 35 through 64 years, and ≥65 years). The prevalence of cessation was directly related to tar yield (of the current smoker's brand and the former smoker's last brand) overall and for persons age 35 through 64 and ≥65. More recent multivariate analysis of data for persons who had smoked within 15 years of the survey confirmed the direct relationship between tar level and abstinence (Giovino, 2000). Additionally, abstinence was more common among persons who had reported that they had never switched brands to reduce their tar and nicotine levels.

The differences in the direction of the finding between the CPS and the 1986 AUTS data may be due simply to methodological differences between the studies. Additionally, one must consider that the overall tar level in 1959 was substantially higher than in 1986, making comparisons unrealistic. However, the differences may also represent a real phenomenon in which patterns of quitting changed over a period of nearly three decades. Low-tar smokers of 1959 may have been more motivated to quit than higher-tar smokers. In addition, some may have switched to lower-tar brands as a step to quitting. Around the mid-1970s, various advertising campaigns were run (see Table 3-1) introducing the notion that people could switch to lower-tar brands instead of quitting. It is possible that these advertisements decreased switchers' motivations to quit (see Box 3-4).

Most recently, Haddock and colleagues (1999) conducted a study of smokers who were forced to abstain during Air Force basic training. About 32% of smokers reported upon entering basic military training, that they had switched brands during the previous 12 months to reduce health risks. At one year follow-up, the percentage of switchers who reported being abstinent was slightly higher than nonswitchers (12.5% vs. 11.1%). However, this difference was not statistically significant in a multivariate analysis that controlled for demographic and smoking history variables. Further, the intervention represents involuntary deprivation and the sample is not generalizable to the U.S. population.

SUMMARY AND RELEVANCE TO PREPS

Studies on risk perception indicate that smokers tend to underestimate their overall risks from smoking. A large proportion of smokers considers smoking low-yield cigarettes to be safer than smoking regular

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BOX 3-4
British American Tobacco Memo Describing Use of Low-Yield Products by Smokers Trying to Quit

"Smokers *needed* light brands for tangible, practical, understandable reasons" [emphasis in original]. "It is useful to consider lights more as a third alternative to quitting and cutting down—a branded hybrid of smokers' unsuccessful attempts to modify their habit on their own."

SOURCE: 081, PSC 60.

cigarettes, even though evidence does not support such a conclusion. Menthol and additive-free cigarettes, which likely pose as much risk, respectively, as nonmenthol and additive-containing cigarettes, also seem to be perceived as somewhat safer. *The committee concludes that smokers could overestimate any potential benefits of PREPs*, although it is possible that the factors that influence perceptions of traditional tobacco products might not apply to radically different products such as PREPs. In addition, PREP users might be very different from the average smoker.

The committee recommends that smokers be informed at every opportunity that all tobacco products, including modified tobacco PREPs and cigarette-like PREPs, are toxic and poisonous. Health-related statements about PREPs should be accurate and made directly, unaccompanied by terms that imply safety in an oblique manner. It is likely that strategic use of visual images and textual themes of safety would promote harm reduction. Research should be conducted to explore the optimal mix of images and text in communications. In addition, research should be conducted to determine if varying the relative attractiveness of product packaging across product types (i.e., conventional tobacco products, tobacco-related PREPs, and pharmaceutical PREPs) will influence perceptions and behaviors in a health-promoting way.

Future research in this area should be conducted to assess factors that influence perceptions of risk in order to ensure that communications about PREPs—whether made by manufacturers or by health educators—take into account a PREP user's perceptions regarding the risks of conventional tobacco and the potential benefit of using PREPs. The magnitude of misleading optimism bias for each PREP or type of PREP must be known to estimate the use of conventional tobacco and PREPs and, therefore, the possibilities for harm reduction.

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The committee recommends strong and decisive efforts to monitor and correct misperceptions that consumers may develop regarding PREPs. These efforts are described in more detail in Chapters 6 and 7.

If PREPs are used by people who otherwise would have smoked conventional products, harm reduction could occur (assuming, of course, that a given PREP actually reduces risk). However, if many people who try these products otherwise would not have experimented with nicotine and then they continue to use a PREP or later switch to cigarettes or other tobacco products, then population harm could increase. Based on data from studies of low-yield conventional cigarettes, *the committee concludes that there is a risk of decreased quitting in current tobacco users if PREPs are available*. Data regarding initiation are less clear. Research is needed to better understand the ways in which various messages might influence children's and adolescents' perceptions and behaviors regarding PREPs and initiation of tobacco use with PREPs. Chapters 6 and 7 include recommendations for research and surveillance (for both public health and regulatory purposes) to better understand and prepare to respond to unintended consequences at the population level of PREP availability.

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4

Products for Tobacco Exposure Reduction

Several tobacco-related products have been introduced recently with potential exposure reduction properties. Two classes of pharmacutical products approved for smoking cessation are also potential exposure reduction products. The chapter describes these products and concludes with a review of regulatory strategies currently in place.

TOBACCO AND TOBACCO PRODUCTS

At first glance, cigarettes seem very simple in construction and design. Typical cigarettes contain a tobacco blend, flavorings and other additives, filters, and cigarette paper. The impression of simplicity of cigarette construction wanes as each component is taken into consideration. There are various combinations of tobacco blends, filter types, and ventilation methods. Manufacturers have used various means of modifying their products to capture and shape the smokers' preference and acceptability of popular brands. Some modifications have had the potential for harm reduction. This section describes current tobacco products, including the curing and processing of tobacco, design features (both historical and contemporary) with exposure reduction potential, and currently available potential reduced-exposure products (PREPs).

Conventional Tobacco Products

There are a wide variety of tobacco products in the United States including cigarettes, cigars, cigarillos, bidis, kreteks, and different types

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of smokeless tobacco. The most common form of a tobacco product in the United States is the manufactured cigarette. A cigarette is considered to be any roll of tobacco wrapped in paper or in any substance not containing tobacco. Cigarettes can be either manufactured or individually constructed. Cigarettes are lit, and the burning process allows smoke to be inhaled at the other end. Cigarettes are approximately 8 mm in diameter and 70 mm to 100 mm in length.

A cigar is a roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco. There are four main types of cigars: little cigars, small cigars (sometimes called cigarillos), regular cigars, and premium cigars. Little cigars contain air-cured and fermented tobaccos. Little cigars 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 cigars are available in various shapes and sizes and rolled to a tip at one end. The dimensions vary from 110 to 150 mm in length and up to 17 mm in diameter. Regular cigars weigh between 5 and 17 grams. Premium cigars vary in size, ranging from 12 to 23 mm in diameter and 12.7 to 21.4 cm in length.

Bidis are made by rolling dried leaf into a conical shape around approximately 0.2 grams of sun-dried, flaked tobacco and securing the roll with a thread. Bidis are used extensively in India, the rural areas of several countries in Southeast Asia, and some parts of the United States. There have been no scientific studies or assessments of the physical characteristics and pharmacologic properties of Indian bidis. In comparison, American versions of bidis were shown to have higher percentages of tobacco by weight (94% vs. 42.5% respectively) and lower levels of nicotine (16.6 mg/g vs. 21.2 mg/g) than Indian bidis. Kreteks are a type of small cigar containing tobacco, cloves, and cocoa, which gives a characteristic flavor and 'honey' taste to the smoke. Kreteks are indigenous to Indonesia but are also available in the United States.

Smokeless tobacco includes tobacco that is sniffed, dipped, or chewed according to the type and constitution of the tobacco. Smokeless tobacco products are made from dark or burley-leaved tobacco. Smokeless tobacco is often referred to as oral tobacco or spit tobacco.

Snuff is a cured, finely ground, flavored tobacco product that is sold in tins or cans and is available in two main types: dry and moist. Dry snuff is fire-cured powdered tobacco and is sniffed. After initial curing, the tobacco is fermented further and processed into a dry powdered form. It has a moisture content of less than 10%. Moist snuff is a granulated tobacco product that is made from both air-cured and fire-cured tobacco and multiple additives. Moist snuff is used by placing a pinch (or "dip")

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between the lip or cheek and gum. Moist snuff consists of tobacco stems and leaves that are processed into fine particles or strips. It has a moisture content of up to 50%. It is sold in both loose form and ready-to-use pouches (also called packets or sachets) that contain about 0.5 grams tobacco. Moist snuff is available in two varieties, according to the size and consistency of the tobacco: long cut and fine cut. Moist snuff is by far the more prevalent form of snuff used in the United States.

Chewing tobacco is a coarsely shredded, flavored tobacco that is sold in pouches of tobacco leaves or in "plug" or "twist" form. Chewing tobacco is chewed or held in the cheek or lower lip.

Curing, Blending, and Processing

The genus *Nicotiana* is indigenous to the Americas. A member of the family Solanaceae, *Nicotiana* contains more than 64 species. In the United States, the tobacco used in cigarettes, cigars, and smokeless products comes from the species *N. tabacum* and can be categorized by the three traditional methods used in curing or by the geographic region in which it is grown. These are distinguished by important differences in sugar, nicotine, and nitrogen content (Browne, 1990).

Flue curing uses high heat to speed the curing process and control humidity. The principal chemical change is conversion of starch to sugars. During the aging of cured tobacco, enzymatic oxidation of amino acids and carbohydrates takes place. The water content, acidity, and concentration of malic and citric acids increase. There are other, undefined chemical changes that occur, resulting in increased aroma and a less bitter taste. Flue-cured tobacco is also called Bright (also known as Virginia) tobacco. These plants are grown in sandy soils from Virginia to Florida, but their agriculture is centered in North Carolina. These tobaccos generally have low-nitrogen, high-sugar content. The smoke from Bright is acidic with a light aroma. Bright tobacco has medium nicotine content.

Air curing uses heat only to maintain temperature and humidity, not to speed the curing process. The primary chemical changes that occur during air curing are protein degradation, polyphenol formation, and a change in the composition of organic acids. Air-cured tobacco consists of Burley and Maryland tobacco. These plants are grown in silt loams in Kentucky, Tennessee, and western North Carolina and in sandy loam soils in southern Maryland. These tobaccos have very low-sugar content and are more heavily fertilized with manure and artificial fertilizer than the flue-cured products. Air-cured tobaccos have an alkaline smoke, fuller aroma, and high nicotine content. Maryland tobacco also has the quality of continuing to burn on its own, making it less likely to self-extinguish.

Sun-cured or oriental tobaccos (Oriental) require a Mediterranean

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climate and come mostly from Turkey, Greece, Yugoslavia, Bulgaria, and Russia. They are cultivated with little fertilizer. Oriental tobaccos have mild, aromatic smoke and low nicotine content.

Cigarettes, cigars, and smokeless products use blended tobaccos. The largest component of most cigarette blends in the United States is Bright tobacco (Browne, 1990). Blends are made to achieve specific pH, taste, burning characteristics, and nicotine content. The type of tobacco blend found in cigarettes significantly affects the pH, nicotine content, and toxicity of the smoke produced. The blend can be manipulated by a choice of 60 species and 100 varieties of tobacco. Almost all commercial tobacco products, however, use *N. tabacum* species and a small amount of *N. rustica* in some specialized tobacco products. Cured tobacco lines can contain between 0.2 and 4.75% nicotine (depending on plant genetics, growing conditions, and place of harvest from the stalk; NIH, 1996).

In addition to tobacco leaf, reconstituted sheet tobacco is also used in most commercial products. Cigarettes primarily made with reconstituted tobacco deliver lower smoke yields of tar, phenols, and benzo [a] pyrene (NIH, 1996). Reconstituted tobacco sheet is also used for economic reasons and for the introduction of additives that change various characteristics of the cigarette. Reconstituted tobacco results from a process that combines stems, leaves, and tobacco scrap into a slurry or from making a tobacco "paper," which is cut (Browne, 1990).

Another alternative to leaf tobacco is puffed, expanded, or freeze-dried tobacco (Hoffman and Hoffman, 1997; NIH, 1996). Less tobacco is therefore needed to fill a cigarette while still providing a sensation of fullness and substance in the smoke. While tobacco is being cured, it loses some of its integrity through water loss. Expanding tobacco increases its filling capacity in the final tobacco column of the cigarette by primarily restoring the original cellular structure. This process is performed by expanding the cells with water, steam, and various organic or inorganic fluids depending on the manufacturers patent (David and Nielsen, 1999; NIH, 1996).

The pH strongly influences the concentration of free nicotine in tobacco smoke. The pH is influenced by the type of tobacco used, as well as by the addition of ammonia to the manufacturing process. Free nicotine has a greater effect on the sensory nerves in the mouth and throat than protonated nicotine, which contributes to the impact or strength of the cigarette. Free nicotine is absorbed more rapidly than protonated nicotine across mucous membranes. The phenomenon of more rapid absorption of nicotine at higher pH has been documented in people using different brands of smokeless tobacco. Free nicotine is absorbed through the mouth from alkaline pipe, cigar, and dark cigarette smoke, but not from acidic smoke of blonde tobacco cigarettes. Free nicotine may be absorbed more

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quickly from the lungs of cigarette smokers as well, although this has not yet been demonstrated experimentally in smokers.

The nitrate content influences the carcinogenic potential of smoke. Nitrogen oxides formed during pyrolysis are free-radical precursors of the polycyclic aromatic hydrocarbons (PAHs). As nitrate concentration in tobacco increases, the synthesis of benzo[a]pyrene (BaP), a carcinogen, is inhibited. Air-cured tobaccos have higher content of nitrates than sun-cured or flue-cured tobaccos and, therefore, lower BaP content. However, the higher the nitrate concentration, the higher are the levels of tobacco specific-nitrosamines (TSNAs), also a known carcinogen.

Hundreds of additives are used in the manufacturing of cigarettes. Several additives are known to have toxic properties. For example, glycerol is a humectant used in cigarettes. Glycerol may lead to the formation of acrolein, a ciliotoxic agent, and diethylene glycol can be converted to ethylene oxide, a carcinogenic compound (Hoffmann and Hoffmann, 1997). Eclipse, that heats but does not burn tobacco, uses glycerol particles as the carrier for nicotine. The glycerol level in smoke from this product is much higher than in conventional low-yield products. As described above, some additives can influence other tobacco constituents (e.g., the role of ammonia in nicotine protonation and TSNA formation).

Although some additives have toxic potential, the concentration of these compounds is low (other than those listed above) and their relative contribution to overall toxicity compared to compounds such as TSNA, BaP, and carbon monoxide (CO) is not definitively known. The toxicity of individual ingredients is sometimes well described, but little is known about how toxicants affect the body when smoked in combination (U.S. DHHS, 2000). The current emphasis on additive disclosure focuses on the consumer's right to know and on understanding better which additives are used to increase the acceptability (e.g., by improving taste and smoothness) of the product to the consumer.

Menthol is a common additive used for flavor and customer acceptability. Early advertisements for menthol products claimed a "soothing" effect on irritated throats. Menthol can be added to cigarettes in several ways including addition to the tobacco shred through an ethanol spray and addition to the filter or packaging. Approximately 3 mg of menthol is added per cigarette. The rest is lost through the filter, sidestream smoke, and in packaging (Browne, 1990). Because menthol is an anesthetizing agent, it has been hypothesized that it may be easier to inhale deeper when smoking a mentholated cigarette. This might also help explain why there are higher rates of lung cancer among blacks despite their lower daily cigarette consumption than whites, who tend to not smoke mentholated cigarettes. Various studies, however, have produced mixed results on the subject (Carpenter et al., 1999; Clark et al., 1996; Gaworski et al.,

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1997; Kabat and Hebert, 1991; McCarthy et al., 1995; Sidney et al., 1995; Women who smoke menthol cigarettes have greater nicotine exposure, 1999).

Cigarette paper is second to tobacco as the most variable component in producing cigarettes. The degree of ventilation allowed by the paper can be manipulated in the production process. More porous cigarette paper has been shown to reduce smoke yields of CO and tar as well as volatile nitrosamines, TSNAs, and BaP through dilution. Increased permeability does not reduce the low-molecular-weight gas-phase components in smoke however (NIH, 1996). For a more detailed discussion of the toxicology of smoke, see Chapter 10.

A new paper has been introduced for Merit cigarettes, which claimed to decrease the smoldering of cigarettes when dropped onto fabric. The new technology consists of a modified wrapping paper that reduces the amount of oxygen entering the cigarette, therefore slowing the rate at which it burns. This could decrease the 25% of fatal residential fires started by smoldering cigarettes (Meier, 2000). New York became the first state to pass legislation imposing fire safety standards on cigarettes (Cigarettes-fire bill, 2000).

Smoke Yields

The procedure for measuring the tar and nicotine yields of mainstream smoke (i.e., the "smoking machine") is standardized for consistency between laboratories and from product to product. There are two methods in widespread use: the Federal Trade Commission (FTC) method and the International Standards Organization (ISO) method. Differences between these two are minor, and puff volume, duration, and interval are common to both standards. Particulate matter is collected on Cambridge filter pads as what is called "wet total particulate matter" (Davis and Nielson, 1999). Tar is a generic term for the total particulate matter minus the nicotine and water. The material that passes through the filter is called the vapor phase. This is described in more detail in Chapters 10 and 11.

Tar yields are influenced primarily through filtration, ventilation (tip ventilation holes and paper porosity), and the choice of tobacco processing and blend. As with any agricultural product, there is natural variation from year to year. In the interest of manufacturing a consistent product, prepared tobacco is blended with stock of crops from previous years to maintain a uniform product line. Finally, the burn rate of cigarettes has been proven to influence smoke yields. The faster the burn rate, the lower the tar yields will be, according to FTC measurements. Shredded tobacco can facilitate a faster burn rate (Davis and Nielsen, 1999), as can the use of accelerants.

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The FTC test does not account for the wide range of smoking behaviors and compensation that occurs naturally among smokers, thus, the standardization has come under great criticism. Human smoking behavior can greatly influence the tar, nicotine, and CO levels to which smokers are exposed. The yields of so-called light and ultralight cigarettes have changed over the years but have produced similar nicotine levels across yields. These terms are not official government designates and are often part of the trademarked name of a product. In general, however, ultralights have less than 6 mg of tar, light cigarettes have between 6 and 15 mg of tar, and "regular or full-flavored" cigarettes have more than 15 mg (NIH, 1996; Sweeney et al., 1999). Although there is not a standard nicotine classification, a study by Byrd et al. (1995) comparing measured and FTC-predicted nicotine uptake in smokers described nicotine levels in products they categorized as 1 mg tar, ultralow-tar, full-flavor low-tar, and full-flavor cigarettes. The mean FTC nicotine yields were 0.14, 0.49, 0.67, and 1.13 mg per cigarette, respectively. FTC measures, particularly for low-tar cigarettes or for cigarettes with filter ventilation holes, do not, however, reflect true exposures in humans. Cigarettes are positioned in the smoking machines in a manner that allows air to enter the perforated filters. These holes are often covered by the lips or fingers of smokers (Hoffman and Hoffman, 1997). In addition, smokers of low-yield products compensate by inhaling more deeply, holding a puff in the lungs for longer periods, or puffing more frequently.

Conventional and Historical PREP Technology

Two cigarette design features that reduce toxin yields as measured by the FTC are dilution and filtration. Dilution is achieved primarily with ventilation, although paper porosity can also increase smoke dilution. Cigarette holders popular in the 1930s provided ventilation. Ventilation is achieved today with small holes around the filter. The primary means of toxin reduction however is the addition of a filter component on the mouth end of the cigarette to trap certain components before they are released from the cigarette in the form of smoke.

The majority of cigarettes sold in the United States today have cellulose acetate filters. Most cellulose acetate filters reduce tar and nicotine yields by 40–50% compared to nonfiltered cigarettes (Davis and Neilson, 1999). Because filter materials influence tar and nicotine smoke yields as well as taste to differing degrees, filter preference has become regionalized. Filters that contain charcoal provide selective removal of a range of vapor-phase smoke constituents and are more popular in Japan than in the United States. Although Japanese and American smokers smoke a

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comparable numbers of cigarettes per day there is a lower incidence of lung cancer in Japan (NIH, 1996). Many factors play a role in the differences in cancer rates between countries. It is speculated that along with diet, genetics, epidemic patterns, and other life-style factors, charcoal filters and tobacco processing may contribute as well (Hoffmann and Hoffmann, 1997).

Traditional cellulose acetate filters treated with certain plasticizers can reduce some additional volatile and semivolatile compounds in smoke. The addition of charcoal particles in the filters reduces volatile smoke constituents such as ciliotoxic hydrogen cyanide, acetaldehyde, and acrolein. It can also reduce some volatile aromatic hydrocarbons, such as benzene and toluene, in the first puffs of a cigarette but becomes less effective in later puffs (NIH, 1996). Segmented filter systems, like charcoal-containing filters, provide a multitude of options. Charcoal, for instance, is available in a variety of activities depending on its surface area and pore volume. The amounts of material used in filters, filter length, and particulate removal efficiency can be adjusted (Davis and Nielsen, 1999).

Since about 1968, many filter tips have been perforated with one or more lines of ventilation holes placed around the middle of the filter. Ventilation holes act slightly differently than the permeability ventilation provided by the cigarette paper. Filter tip ventilation is engineered to dilute the smoke as it travels through the cigarette and the filter. The result is an overall reduction in smoke and tar yields at standard smoking conditions to levels that filters, permeable papers, or processed tobaccos alone could not achieve. Approximately 80% of U.S. cigarettes have tar yields of 15 mg or less (FTC, 2000); most of these cigarettes have filter tip ventilations (Davis and Nielsen, 1999). The ventilation holes are inserted where smokers are likely to place their fingers or lips, which inhibits the intended use of the vents. Machine-generated smoke yield tests, however, position cigarettes so that the ventilation holes are exposed. Jenkins and colleagues conducted a study in 1982 comparing smoke yields between open and blocked tip ventilation. Their abbreviated results can be found in Table 4-1. The results showed that blocking the ventilated filters (VF) increased the tar, nicotine, and carbon monoxide to levels similar to that of regular filter cigarettes (F).

There have been a few notable historic developments regarding novel cigarette filters of unproven efficacy. The Kent cigarette line produced cigarettes with a novel filter of coiled crepe paper with cotton fibers and crocidolite fibers in the 1950s. Crocidolite is a form of asbestos with fibers so thin that they could be arranged and used to trap particles as small as 1 μ (Longo et al., 1995). The so-called Micronite filter eliminated nearly

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TABLE 4-1 Effect of Smoking Conditions (Blocked Tip Ventilation) on Smoke Yield (mg per cigarette ± one standard deviation)

Brand	FTC (35 ml, 2 sec, 1 puff per minute)	FTC+ (tip taped 35 ml, 2 sec, 1 puff per minute)
Tar Yield		
VF-A	3.8±0.5	9.4±0.9
VF-C	2.9±0.6	7.6±0.9
VF-D	1.6±0.2	9.7±0.8
F-A	18.5±1.2	ND
F-C	16.4±1.4	13.2±0.6
F-D	9.9±0.8	11.7±1.3
NF-A	22.5±1.0	21.3±1.5
NF-C	19.4±1.1	21.3±1.0
Nicotine Yield		
VF-A	0.40±0.05	0.72±0.05
VF-C	0.25±0.04	0.45±0.03
VF-D	0.19±0.05	0.62±0.07
F-A	1.09±0.07	ND
F-C	0.94±0.02	0.71±0.06
F-D	0.61±0.02	0.68±0.10
NF-A	1.14±0.05	1.37±0.07
NF-C	1.13±0.13	1.6±0.23
Carbon Monoxide Yield		
VF-A	4.1±0.7	12.3±1.5
VF-C	2.1±0.2	8.7±1.2
VF-D	1.0±0.1	10.7±0.4
F-A	15.7±1.8	ND
F-C	13.4±1.2	17.9±1.2
F-D	8.5±0.3	11.5±0.7
NF-A	11.3±1.0	12.8±2.7
NF-C	11.3±1.2	12.9±0.8

NOTE: F=filter; ND=not determined; NF=nonfilter; VF=ventilated filter; A,C,D=different brands.
SOURCE: Modified from Jenkins et al., 1982 in NIH, 1996.

twice as much tar and nicotine delivered to the smoker as any other standard brand of its time. Yet it failed in the marketplace due to the flavorless smoke and difficulty in drawing on it (Kluger, 1997).

Ligget tobacco company experimented with adding palladium and magnesium nitrate to tobacco in efforts to decrease cancer rates in smokers. Preliminary tests on mice resulted in a 95% reduction in tumors compared to other brands. Little else is known about this innovation, because

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research ended, reportedly due to litigation, in 1988 (Was a safer cigarette research snuffed, 1994).

A new filter treatment called the "Wellstone Filter" has been developed. The cellulose acetate filter has been treated with a nonbiological compound that supposedly removes nearly 90% of tar and carcinogenic compounds while maintaining taste (Fisher, 2000). Patents are still pending.

R.J. Reynolds also experimented with its own variation on filters. Reynolds created an extra corrugated carbon paper filter for the Winston Select EW brand. It was intended to reduce compounds linked to heart problems. The product was test marketed in Oklahoma City in 1996 (Feder, 1996). (This filter was known more commonly as the "carbon scrubber filter" to reduce free radicals linked to cardiovascular disease.)

Other product modifications of interest for historical reasons include the Favor Smokeless Cigarette and Masterpiece Tobacs. The Favor Smokeless Cigarette was introduced in 1985 and was evaluated soon afterwards by the Food and Drug Administration (FDA), which determined the product to actually be a type of drug delivery device also known as a nicotine inhaler. The FDA removed it from the market. Masterpiece Tobacs is a chewing gum containing shreds of tobacco. Pinkerton Tobacco Company introduced it in 1987. This too was withdrawn from the market when the FDA determined the gum to be a food product with an unapproved food additive, tobacco (Fielding et al., 1998).

Philip Morris also experimented with a modified cigarette with denicotinized tobacco called NEXT. NEXT had a tar yield of 9.3 mg but a nicotine yield of only 0.08 mg. Lacking the addictive component, this product was not successful on the market (Ferrence et al., 2000).

Currently Available and Novel PREPs

Modifications of Conventional Tobacco Products (See Table 4-2)

A new curing process is being used for the production of tobacco with substantially reduced tobacco-specific nitrosamines (Star Scientific, 1999). The StarCure technology of Star Scientific (formally called Star Tobacco and Pharmaceutical Co.) has a modified and controlled curing process that has used microwaves to kill the bacteria that convert nitrogen-containing compounds into TSNAs. Star has recently stopped using this method and now uses curing barns that decrease microbial activity (Blackwell, 2000). Star Scientific has been using Virginia flue-cured Kentucky burley tobacco in its process. Star expected to bring to market products with only StarCure tobacco in late-2000. Other tobacco companies are reportedly working on methods for reducing or eliminating TSNAs from tobacco

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TABLE 4-2 Tobacco Products

Product	Company	Year	Key Characteristics
Kent	Lorillard Co.	1950s	Micronite filters
Spectra	Kinney	1980s	Contained N bloctin, designed to block nitrosamine absorption in the lungs
Favor Smokeless Cigarette		1985	Nicotine inhaler
Premier Cigarette	R.J. Reynolds	1987	Less combustion than conventional
Masterpiece Tobacs	Pinkerton	1987	Chewing gum with tobacco shreds
NEXT	Philip Morris	1989	Low-nicotine cigarette
Eclipse Cigarette	R.J. Reynolds	1996	Less combustion than conventional
Winston Select	R.J. Reynolds	1996	Extra corrugated carbon paper filter
Accord	Philip Morris	1998	Lower operating temperature than conventional cigarette and heat produced from electrical resistance
Advance	Star Scientific	2000	Low-nitrosamine cigarette

(Fairclough, 2000). Brown and Williamson purchased two million pounds of low-nitrosamine tobacco from Star in 1999 and contracted for millions of additional pounds in 2000 (Fairclough, 2000; Star Scientific, 2000). Nitrosamines are still formed from these tobaccos upon combustion, but the noncombusted product contains very little or no TSNAs.

Star Scientific has used this modified tobacco along with activated charcoal filters in a new line of cigarettes called Advance. Star hopes that by replacing traditional filters with the activated charcoal filter, it will reduce the levels of vapor-phase toxins (Star Scientific, 2000; Fairclough, 2000). Star Scientific gives smoking yields on its Web site and claims to have substantially lower TSNA, CO, and tar levels and similar nicotine levels compared to the average of three leading light brands (Star Scientific, 2000). A package insert for Advance cigarettes lists these findings as reported independently by the FTC and the Massachusetts Department of Public Health.

Smokeless Tobacco Products

Currently, most smokeless tobacco users in the United States use moist snuff. The 1999 National Household Survey on Drug Abuse reported that among the 66.8 million Americans who report current use of

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tobacco products, 3.4% use smokeless tobacco (SAMHSA, 2000). The highest prevalence of smokeless tobacco use was found in males between 18 and 25 years of age (SAMHSA, 2000). The manufacturing of fine-cut tobacco for the production of moist snuff increased in the 1970s. An active advertising campaign is thought to have led to increased prevalence of smokeless tobacco among 18- to 24-year-old males. From 1970 to 1991, the use of smokeless tobacco in this population increased from 2.2% to 8.9% (U.S. DHHS, 2000). For most of the 1990s, the Centers for Disease Control and Prevention's (CDC's) Youth Risk Behavior Survey has shown a consistent use of smokeless tobacco among male high school students at about 20% (U.S. DHHS, 2000).

Sweden has a high prevalence rate of smokeless tobacco use: 18% of Swedish men and just under 2% of women aged 15-75 dipped snuff in 1995, compared to 3.3% of American adults (less than 1% of American smokers were women) (Ahlborn, 1997; SAMHSA, 1996). In 1996, only 18% of Swedish adults were daily smokers (primary reference: Ramstrom, personal communication in Jimenez-Ruiz, 1998), whereas in the United States in 1998 the smoking prevalence was 24.1% of adults (18 years and older) (CDC, 2000). In fact, Sweden has the largest per capita consumption of moist snuff. In 1990, Swedish citizens consumed 0.68 kg per person per year, or 4,846 tons annually (Ahlborn, 1997). Swedish snuff differs from snuff in the United States in that it has been shown to contain fewer TSNAs. The difference in recent years has become smaller due to a decrease in TSNAs in U.S. products (Ahlborn, 1997). For the health effects and toxicity of smokeless tobacco, see Chapter 10 of this report. There is debate in the tobacco control field whether smokeless tobacco has a role as a PREP and whether controlling factors such as marketing will prevent its use as a "gateway" to cigarette use.

Cigarette-like Products

Aside from modifications of traditional tobacco products, there has been a recent introduction of cigarette-like products. R.J. Reynolds (RJR) was the first of the tobacco companies to develop such a PREP in 1988, called Premier.

An RJR monograph about the development of Premier describes the prototype product as "similar to other cigarettes in that it requires tobacco for taste and enjoyment" (R.J. Reynolds Tobacco Company, 1988). Premier is a cigarette-like product that delivers nicotine with less combustion. This controlled burning reportedly releases volatile, flavorful components, but does not decompose the tobacco. Similar to traditional cigarettes, the smoker inhales an aerosol. The four components of Premier include tobacco and tobacco flavor beads, a volatile liquid to form the

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aerosol or smoke, a heat source to warm tobacco and vaporize the liquid, and finally a system that condenses the vapor into an aerosol delivered to the user (R.J. Reynolds Tobacco Company, 1988).

The RJR monograph of this cigarette prototype details the "tar," nicotine, and CO levels using a modified FTC rating. The rating is modified to a version that is not based on the butt length. The prototype ranked lower in tar and nicotine levels compared to all the traditional cigarettes to which it was compared: tar=6 mg per cigarette (nicotine-free dry particulate matter); nicotine=0.3 mg per cigarette; CO=12 mg per cigarette.

This prototype has developed into a new product Eclipse, which is being sold over-the-counter in Dallas, TX and other test markets and over the telephone and Internet. Eclipse has recently been marketed as "a better way to smoke. A Cigarette that responds to concerns about certain smoking-related illnesses. Including Cancer" (R.J. Reynolds Tobacco Company, 2000). The advertisements for Eclipse also address social acceptance because it produces no ash and substantially less visible environmental tobacco smoke (ETS).

Eclipse resembles an ordinary cigarette in shape and size just as Premier did. The carbon tip is ignited and heats the mixture of tobacco and glycerin before passing through a charcoal filter. The heating unit consists of a carbon fuel element surrounded by a fiberglass insulator. Glycerin contributes to 50-60% of the composition of the light reconstituted tobacco filling of the product. Research has shown that the glycerin has been treated to prevent it from sweating out of the tobacco blend, yet little else is known regarding what additives have been used or how else the tobacco may have been treated. Eclipse is different from Premier in that it does not have flavor beads or an aluminum cylinder or the alumna beads (Ferrence et al., 2000; Slade, 1996). These changes are likely to enhance the smoke aerosol so that it more closely resembles that of traditional cigarette products. Tests conducted under FTC-like conditions resulted in 3.2 mg tar, 0.18 mg nicotine, and 7.5 mg CO (R.J. Reynolds Eclipse web site, 2000).

In a study conducted by Fagerström et al. (2000) measuring nicotine and CO exposure using Eclipse, nicotine oral inhaler, and traditional cigarettes, it was discovered that there is little difference in nicotine blood concentrations in subjects smoking only Eclipse or their usual brand of cigarettes. Eclipse, however, did produce increased carbon monoxide levels. A recent study commissioned by the Massachusetts Department of Public Health compared Eclipse to two conventional low-yield products. Eclipse produced higher yields of tar and CO than the comparison products. Under more intensive conditions, the Eclipse yields of nicotine were also higher than comparison products, as were specific toxicants, BaP, acroline, and nicotine-derived nitroketone (NNK) (Labstat, 2000). A sci-

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entific panel convened by RJR has also studied the toxicity of Eclipse compared to a reference cigarette. Among its many conclusions, this panel reported elevated acrolein, furfural, formaldehyde, and CO in the smoke from Eclipse when compared to a ultralow-tar reference cigarette (Eclipse Expert Panel, 2000). The panel went on to report a significant reduction in evidence of lower respiratory tract inflammation and tumorigenic activity in dermal studies.

Philip Morris Tobacco Company has developed and marketed a PREP with some similarities to Eclipse. It differs significantly in other ways. Preliminary technical information on Accord was publicly presented by Philip Morris scientists in a poster presentation at the Society of Toxicology in 1998. They began consumer testing in the fall of 1997 (Jones, 1998). Like Eclipse, Accord uses the lower temperature and controlled burn of the cigarette to dramatically alter the composition of smoke produced. Accord burns at 950°F, or 700°F lower than the traditional cigarette. The burning device in the Accord cigarette is powered by rechargeable batteries in a beeper-sized unit called a Puff Activated Lighter (Holzman, 1999). This unit fits special Accord cigarettes and powers a microchip that senses when the cigarettes are being drawn on. When signaled, it produces a controlled two-second burn from one of eight heating blades around the cigarette and thus delivers smoke to the user.

The company reports that Accord delivers 3 mg of tar and 0.2 mg of nicotine, similar to other Philip Morris ultralight products (Jones, 1998). Philip Morris scientists report that Accord smoke contains marked reductions in 35 of 53 potentially hazardous compounds and that Accord produces 83-98% less carbon monoxide, benzene, and nitrogen-based compounds than the cigarette smoke of comparison products (Jones, 1998). The data was stated without specifying the nature of the comparison products. Like Eclipse, Accord does not produce ash and produces little ETS (ASH, 1997). A recent study indicates that smokers who switch to Accord under experimental conditions are exposed to minimal CO and less nicotine compared to their usual brand (Buchhalter and Eissenberg, 2000).

PHARMACEUTICAL PRODUCTS

Unlike tobacco products, medications developed to aid smoking cessation have undergone rigorous scientific and regulatory examination. Medications for the treatment of tobacco dependence came into existence in the 1970s in Europe and 1980s in the United States. The first effective medications for the treatment of nicotine dependence were nicotine replacement therapies. Currently, there are four different nicotine replacement products that have been approved by the Food and Drug Administration.

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These products include nicotine gum, transdermal nicotine, nicotine inhaler, and nicotine nasal spray. The only nonnicotine medication for smoking cessation that is approved by the FDA is bupropion sustained release (SR), or Zyban. This product, originally marketed as an antidepressant, was initially observed to reduce smoking among depressed patients (Ferry et al., 1992). Subsequent clinical trials among smokers showed that this agent is an effective smoking cessation aid.

In the United States, the FDA has approved these medications only as cigarette smoking cessation aids. Currently, these pharmaceuticals are not recommended solely for the purposes of reducing the number of cigarettes or as a step toward achieving abstinence, to treat withdrawal symptoms or craving in situations when smoking is not allowed, or for quitting tobacco products other than cigarettes. In addition, the safety and efficacy of these medications in pregnant smokers have not been determined, and the use of medications to aid smoking cessation in this population has been delegated to the discretion of the physician.

It is important to note that the pharmaceutical industry was required to provide ancillary behavioral treatments along with the medications to assist the smoker in quitting. These behavioral treatments range from general self-help materials, to tailored self-help materials, to telephone counseling. The FDA imposed this requirement because cigarette smoking not only is considered a physical addiction to nicotine but also is associated with behavioral components. Research results indeed show that behavioral treatment will augment the success rates of medications alone, and the more intensive the treatment is, the greater is the rate of abstinence (Fiore et al., 2000). However, the use of medications with minimal or no behavioral treatments still outperforms placebo treatment, as demonstrated by the efficacy of over-the-counter nicotine medications (Fiore et al., 2000). Therefore, harm reduction approaches with medications may have to be considered in the context of ancillary behavioral treatments.

Nicotine Replacement Products

The concept of the use of nicotine replacements was first fully described by Ferno (1973). The principles behind nicotine replacements are to (1) provide cigarette smokers a sufficient amount of nicotine to allay some of the withdrawal symptoms experienced shortly after tobacco abstinence; (2) to permit progressive reduction of the level of nicotine exposure, leading to eventual ease of totally withdrawing from nicotine products; and (3) to reduce the abuse potential of nicotine due to the slower rate of nicotine absorption. The validity of these principles and mechanisms has been demonstrated by a number of studies (see Henningfield

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and Keenan, 1993; Hughes et al., 1989). Other potential mechanisms accounting for product efficacy could be the reinforcing effects derived from nicotine or, on the other hand, blocking the reinforcing effects of nicotine from cigarettes. Chronic exposure to nicotine could result in desensitization of nicotinic cholinergic receptors, thereby blocking potentiation of the nerve. In addition to these beneficial effects, the administration of nicotine medications is associated with significantly lower toxicity than cigarettes since the main ingredient in these replacement products is nicotine with no other toxic elements. The toxicity associated with nicotine alone is confined primarily to reproductive disorders and enhancement of cardiovascular risk factors (Benowitz, 1998), although nicotine's contribution to cardiovascular disorders is minimal compared to that of cigarettes.

Nicotine polacrilex, or nicotine gum (Nicorette), manufactured by Pharmacia Upjohn, was introduced first in Europe and approved for marketing in the United States in 1984. Nicotine gum was initially a prescription medication in the United States but, in 1996, became an over-the-counter medication. In 1998, a mint-flavored nicotine gum was approved in the United States and it was marketed in 1999. An orange flavored version has recently been introduced. Two doses of nicotine gum are currently available, 2 and 4 mg. In 1991 and 1992, the United States was introduced to nicotine patches distributed by four different pharmaceutical companies. The first patch introduced in the U.S. market was Habitrol (marketed and manufactured by Ciba-Geigy, and now by Novartis); then Nicoderm (manufactured by Alza Corporation, marketed by Marion Merrell Dow, then Hoescht Marion Rousel, followed by SmithKline Beecham, now GlaxoSmithKline); Nicotrol (manufactured and marketed by Pharmacia Upjohn); and finally Prostep (manufactured by Elan and initially marketed by Lederle as a prescription medication; currently generic patches using a different patch technology are being manufactured by Perrigo). Nicotine patches were initially prescription only, but both Nicoderm CQ and Nicotrol were approved to go over the counter in 1996. Habitrol and a modified Prostep are now sold as generic products through major drugstore chains. Nicotine patches are available in three different doses for Habitrol and Nicoderm CQ (21, 14, and 7 mg). Nicotrol was available in three different doses (15, 10, and 5 mg) by prescription, but only in one dose (15 mg) over-the-counter. Perrigo's patches are available in 22-mg and 11-mg doses. The nicotine inhaler was introduced on the market in 1998 and is regulated as a prescription drug. This product is a tube-shaped device that contains a porous plug saturated with nicotine enclosed in a replaceable plastic cartridge. The nicotine inhaler is puffed upon like a cigarette, but absorption occurs primarily buccally and from the upper airway and not in the lungs because its design does not provide

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an aerosol that could be substantially inhaled in the lung. Each cartridge contains 10 mg of nicotine, with 13 µg delivered with each puff (compared to 100 µg delivered with cigarettes), which is about one-tenth the nicotine dose from puffing on a cigarette. The nicotine nasal spray was introduced to the U.S. market around 1997 and is also regulated as a prescription drug. The dosing for nicotine nasal spray is one spray in each nostril, delivering 0.5 mg of nicotine per spray for a total dose of 1 mg.

Each product has a different route of administration, instructions for use, amount of nicotine absorbed, and speed of nicotine delivery. Nicotine patches are used once a day, with a patch being placed on the skin in the morning and taken off prior to bedtime or the next morning. For nicotine gum, a fixed schedule of use (e.g., at least one piece every 1-2 hours, with a maximum of 24 pieces per day) is recommended to achieve sufficient levels of nicotine. The nicotine inhaler is puffed on, not inhaled like a cigarette, and used ad libitum. The recommended number of cartridges is 6-16, with each cartridge used in three smoking periods. For the nicotine nasal spray, the recommended initial dosing is 1-2 sprays per hour, with a minimum recommended treatment of 8 doses per day and a maximum of 40 doses per day. The recommended duration of treatment for all these products ranges from 3 to 6 months.

The route of administration will contribute to the side-effect profile and contraindications (see Table 4-3). Contraindications include smokers in the immediate postmyocardial infarction period with serious arrhythmias

TABLE 4-3 Side Effects and Contraindications of Nicotine Replacement Products

Product	Most Frequent Side Effects	Contraindications
Nicotine Gum	Jaw ache, mouth soreness, dyspepsia, hiccups	TMD, Dentures
Nicotine Inhaler	Local irritation of mouth and throat, coughing, rhinitis	Allergy to menthol
Nicotine Patch	Local skin reaction, sleep disruption	Skin disorders
Nicotine Spray	Nasal and airway irritation	Reactive airway disease, sinusitis
Bupropion	Insomnia and dry mouth	Seizures, concurrent use of MAO inhibitors, history of eating disorders

NOTE: MAO=Monoamine Oxidose; TMD=temporomandibulor joint disfunction.
SOURCE: Information gathered from Fiore et al., 2000.

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and with serious or worsening angina pectoris. Studies in individuals with stable cardiovascular disease have shown that smokers who used nicotine patches were not at greater risk for cardiovascular events than those assigned a placebo (Joseph et al., 1996), even when used while smoking a cigarette (Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease, 1994). For pregnant or lactating female smokers, nicotine replacements are recommended only when the use of psychosocial treatment has failed and the benefits of abstinence achieved from using the nicotine replacements outweigh the risk of nicotine replacement and potential concomitant smoking (Fiore et al., 2000). In general, the contraindications and side effects are minimal with these products.

The bioavailability (see Table 4-4) and amount of nicotine absorbed per unit dose (see Figure 4-1) varies across products. The mean nicotine peak concentrations attained from tobacco products are higher than those of all nicotine replacement products. Furthermore, for cigarettes, high arterial plasma nicotine concentrations are achieved that are not reached by nicotine replacement products (Henningfield et al., 1993). The daily dose of nicotine from medications used ad libitum will depend on the frequency of use. Typically, these products are underutilized in terms of both frequency and duration. Rarely does the daily level of nicotine concentration attained by the use of these products exceed three-fourths the level attained with cigarettes and typically ranges from one-fourth to two-thirds of the cigarette level (Benowitz et al., 1988; Hjalmarson et al., 1997; Leischow et al., 1996; Schneider et al., 1995, 1996; Sutherland et al., 1992; Tonnesen et al., 1993).

The time to reach peak blood nicotine concentrations (T_{max}) also varies across products. The nicotine replacement product that has the shortest T_{max} is nicotine nasal spray followed by nicotine inhaler, nicotine gum, and finally the nicotine patch (see Figure 4-1 and Table 4-5). It should be

TABLE 4-4 Bioavailability of Nicotine

Product	Bioavailability per Dose
Cigarette	1-2 mg
Smokeless tobacco	3.6-4.5 mg
Nicotine gum (2 or 4 mg)	1 or 2 mg
Nicotine inhaler	2 mg per cartridge
Nicotine patch	15-22 mg (over 16-24 hr)
Nicotine spray	0.5 mg

SOURCE: Data from Benowitz, 1988; Fagerström, 2000; Fant et al., 1999.

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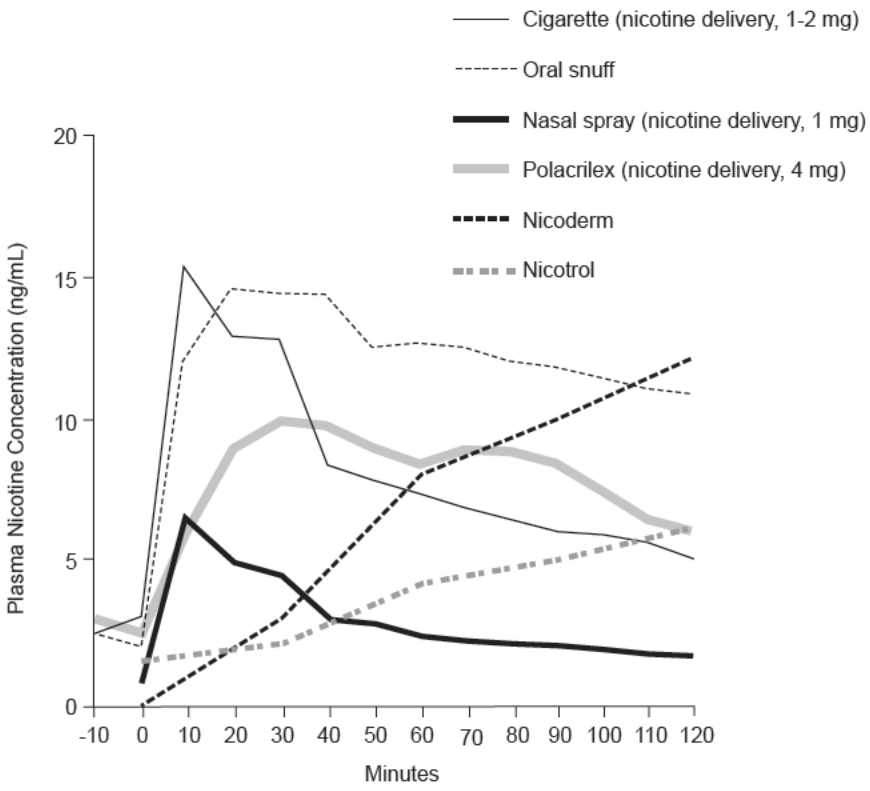


FIGURE 4-1 Venous blood concentrations.

NOTE: Venous blood concentrations in nanograms of nicotine per millimeter (ng/ml) of blood as a function of time for various nicotine delivery systems.
SOURCE: Reprinted with permission from Fant et al., 1999. Copyright 1999 Lippincott, Williams and Wilkins.

noted that a faster T_{max} for nicotine nasal spray was observed with arterial than with venous blood (mean value, 5 vs. 25 minutes, respectively) as well as a higher maximum nicotine concentration (mean value, 10 vs. 5 ng/ml; Gourlay and Benowitz, 1995).

The faster the speed of nicotine delivery, rate of absorption, and attainment of peak level, the greater is the likelihood of continued use or abuse (deWit and Zacny, 1995). The fastest time for maximum nicotine concentration occurs with cigarettes, followed by nicotine nasal spray, smokeless tobacco, then other nicotine replacement agents. Smokeless tobacco appears to take longer or seems equal in time to reach maximum

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TABLE 4-5 Pharmacokinetics

Product	Time to Maximum (T_{max}) for Venous Blood
Cigarettes	Within 5 min.
Smokeless tobacco	20-30 min.
Nicotine nasal spray	10 min.
Nicotine gum (2-4 mg)	30 min.
Nicotine inhaler	20-30 min.
Nicotine patch	4-9 hr.

SOURCE: PDR, 2000; Benowitz et al., 1988.

concentrations compared to some nicotine replacement products such as nicotine gum and inhaler. However, the abuse potential is likely to be greater for smokeless tobacco not only because of the amount of nicotine delivered, but also because a nicotine boost of 10 ng/ml has been observed within the first 10 minutes of use (Holm et al., 1992). This venous level is higher than the maximum venous concentration observed with other nicotine products including from nicotine nasal spray.

Although few studies have examined the abuse potential across various nicotine replacement products, it remains significantly lower than that of cigarettes. Of the few nicotine replacements studied, withdrawal symptoms and the rate of use beyond the recommended period for the nicotine patch appear to be minimal and the abuse potential appears to be low (see deWit and Zacny, 1995; Hughes, 1998). In clinical trials, prolonged use of nicotine gum (e.g., 12 months) is around 22% among abstinent smokers, but about 9% of those who have been randomly assigned to the gum (Hughes, 1998). Similar rates of prolonged use are observed for nicotine inhaler (Schneider et al., 1996; Tonnesen et al., 1993). For nicotine nasal spray, about 29-43% of individuals who have quit smoking reported use of the active spray at 12 months compared to 0% in the placebo spray group, even though the recommended period of use was 3 months (Hjalmarson et al., 1994; Sutherland et al., 1992). Of smokers assigned to the active nasal spray, about 10% continued to use it at 12 months (Hjalmarson et al., 1994). This finding would indicate that continued use of this product might be greater than that of other nicotine products. It is important to note that the continued use of nicotine products may be motivated by the desire not to relapse to smoking rather than addiction to the product. Furthermore, the cost of the product plays a role in continued use as well, with higher cost deterring longer use. All of the aforementioned studies provided the nicotine products for free, and therefore the rate of continued use may be highly exaggerated. In a nonresearch setting, the unit dose costs of cigarettes and smokeless tobacco are

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typically less than or equivalent to those of the medication (see Table 4-6). However, medications must be bought in larger quantities, resulting in yet higher costs per purchase.

Based on a report issued by the Public Health Services (Fiore et al., 2000), the nicotine replacement products have comparable rates of treatment success. The PHS undertook an extensive meta-analysis of studies to determine the efficacy of various medications for smoking cessation. Only published, peer-reviewed and randomized controlled studies with a follow-up time of at least five months post-quit were included in the analyses. The primary outcome variable was point prevalence abstinence (not smoking in the past week), unless only data for continuous abstinence (or of an unknown nature) were available. Data for the efficacy of various medications are presented in Table 4-7. The estimated odds ratios range from 1.5 to 2.7 for active nicotine replacements versus the controls, and the estimated rates of abstinence range from 18 to 31% for active nicotine replacements versus 10 to 17% for the controls. Several trials have been conducted with nicotine patches that simulate over-the-counter use. The estimated rates of abstinence observed in these studies are about 11.8% with active nicotine patch and 6.7% with placebo patch with an estimated odds ratio (OR) of 1.8 (Fiore et al., 2000).

Similar meta-analyses have been conducted by the Cochrane Tobacco Addiction Group (Lancaster et al., 2000). Randomized controlled trials (published and unpublished) with at least six months' follow-up were included in the analyses. Sustained abstinence was the primary outcome examined, rather than point prevalence, although point prevalence rates

TABLE 4-6 Costs for Tobacco Products and FDA-Approved Medications[a]

Product	Cost per Day
Cigarettes (20 per day)	$1.70-$4.85 per pack
Smokeless tobacco[b]	$1.88-$2.00
Nicotine gum	$4.26-$6.87 (10 2–4 mg pieces)
Nicotine inhaler	$10.81-$10.94 for 10 cartridges
Nicotine patch	$2.36-$4.50
Nicotine spray	$4.50-$9.20 for 10-20 doses
Bupropion	$3.33-$3.40

[a]Prices are from U.S. PHS guidelines and based on the retail price of the medication purchased at a national chain pharmacy located in Madison, Wisconsin, and Minneapolis, Minnesota.

[b]Cost per day is based on a mean use of 3.5 tins per week (Hatsukami and Severson, 1999) at $3.75 to $4.00 per tin.

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TABLE 4-7 Efficacy of Nicotine Replacement Products

Medication	Abstinence Rate: Active (95% CI)	Abstinence Rate: Placebo	Odds Ratio (95% CI) PHS (Cochrane)
Gum (*N*=13 studies)	24 (21, 27)	17	1.5 (1.3, 1.8) (1.6 [1.5, 1.8][a])
Inhaler (*N*=4 studies)	23 (16, 29)	11	2.5 (1.7, 3.6) (2.1 [1.4, 3.0][b])
Nasal spray (*N*=3 studies)	31 (22, 39)	14	2.7 (1.8, 4.1) (2.3 [1.6, 3.2][c])
Patch (*N*=27 studies)	18 (16, 20)	10	1.9 (1.7, 2.2) (1.8 [1.6, 1.9][d])

NOTE: CI=Confidence Interval.

[a]*N*=48 studies
[b]*N*=4 studies
[c]*N*=4 studies
[d]*N*=31 studies

SOURCE: Abstracted from Fiore et al., 2000; Lancaster et al., 2000.

were used when sustained abstinence rates were unavailable. The results are very similar to PHS results. The odds ratio across the nicotine products ranged from 1.7 to 2.3 for active nicotine replacement versus control, and efficacy was similar across products (see Table 4-7).

Other Nicotine Replacement Agents and Nonapproved Methods of Use

Several other nicotine replacement products have been tested, but are not currently on the market. These products include a sublingual nicotine tablet (Molander et al., 2000), the oral nicotine transmucosal (Leischow et al., 1996), and the nicotine lozenge (Foulds et al., 1998). Other nicotine replacement products are likely to be developed in the future. It is likely that nicotine replacements with a faster speed of delivery that mimic the effects of cigarettes will be explored, with the hopes that such delivery devices would be safer than nicotine-containing tobacco products. In addition, fast nicotine delivery devices may lead to greater treatment success or provide a bridge toward using slower nicotine absorption products. Future replacement medications are also likely to become more sophisticated, targeting specific nicotinic receptor subtypes that are associated with specific functions.

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Many researchers also believe that combinations of different types of nicotine replacements might be more effective than single agents alone (Fiore et al., 2000). Combination products would result in higher levels of nicotine replacement, which may lead to less desire to smoke and less reinforcement from a cigarette when smoked due to the development of tolerance. Interestingly, doses greater than 21 mg of nicotine generally show minimal increases in long-term abstinence rates (Hughes et al., 1999a,b), although the Cochrane Group found that high-dose nicotine patches were marginally more effective than a standard dose (1.2, 95% CI=1.0 to 1.4; $N = 6$ trials). However, combinations of nicotine patch with nicotine products that can be used ad libitum have resulted in better treatment success. The use of the nicotine patch would result in a steady-state trough level of nicotine to prevent withdrawal symptoms, whereas the ad libitum product could be used during periods when an urge to smoke is experienced. Treatment studies have been conducted that examine a combination of nicotine gum and patch (Kornitzer et al., 1995); nicotine spray and patch (Blondal et al., 1999); and nicotine inhaler and patch (Westman et al., 2000). Results from the meta-analyses conducted with some of these studies showed that a combination treatment approach was more effective than a single treatment approach (OR=1.9, 28.6% vs. 17.4%, respectively) (Fiore et al., 2000). Furthermore, two studies showed that a combination approach led to greater reductions in withdrawal symptoms compared to a single treatment approach (Fagerström, 1994; Fagerström et al., 1993).

Antidepressants

To date, the antidepressants that have been successful in treating smokers are bupropion SR and nortriptyline. Bupropion SR, or Zyban, which is approved by the FDA, is recommended as a first-line pharmacotherapy similar to other nicotine replacement therapies (Fiore et al., 2000). Nortriptyline, which is not approved for this indication by the FDA, is recommended as a second-line treatment for smokers who were unresponsive to the first-line treatment. The mechanism of action of various antidepressants is unknown. Understanding these mechanisms is important in order to refine and develop drugs that are targeted to specific population of smokers or essential neurotransmitter systems. As one mechanism, it is possible that since a higher incidence of depression is observed among smokers than nonsmokers (Breslau et al., 1991; Glassman et al., 1990; Kendler et al., 1993) and smokers with a history of depression are more likely to relapse (e.g., Anda et al., 1990; Covey et al., 1990; Glassman et al., 1990; Hall et al., 1993) and experience depressive symptoms or mood after cessation (Borrelli et al, 1996; Glassman et al., 1990),

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antidepressants may be effective in enhancing treatment efficacy among this population. However, clinical studies show that antidepressants are effective for smoking cessation in both nondepressed and depressed populations (Fiore et al., 2000). Another mechanism is the use of antidepressants to reduce withdrawal symptoms. Tobacco withdrawal symptoms overlap with symptoms associated with major depression—depressed mood, irritability, low energy, and problems with sleep. A third possible mechanism may be that antidepressants and nicotine release similar neurotransmitters. For example, since bupropion is a weak dopamine uptake inhibitor (Ascher et al., 1995), the efficacy of this product has been attributed to an increase in dopamine levels. Dopamine levels are increased by nicotine and constituents in tobacco smoke, and this increase is thought to be responsible for some of the positive reinforcing effects of cigarette smoking. Bupropion also weakly blocks the neuronal reuptake of noradrenaline (Ascher et al., 1995; Ferris and Cooper, 1993; Perumal et al., 1986), and increased noradrenaline levels may also serve a reinforcing function. Nortriptyline is a tricyclic antidepressant drug that is also known to enhance levels of noradrenaline and to have some serotonergic activity. Interestingly, both medications also decrease firing of the locus ceruleus. The beneficial effects from inhibiting firing in the locus ceruleus may be derived from blocking the pathways of acute nicotine stimulation or resembling the desensitized state seen with continuous nicotine exposure (Benowitz and Peng, 2000). Finally, a preliminary study suggests that bupropion may act as a noncompetitive antagonist of nicotinic acetylcholine receptors, an action that is independent of its antidepressant mechanisms of action (Fryar and Lucas, 1999).

Fluoxetine and sertraline target primarily the serotonin system and are serotonin reuptake inhibitors. Antidepressants that target the serotonin system do not show enhanced efficacy over placebo, although some preliminary evidence exists that fluoxetine may be effective as a smoking cessation aid in smokers experiencing symptoms of depression at baseline (Niaura et al., 1995). In a very small trial, doxepin, a tricyclic antidepressant, reduced the number of cigarettes smoked and increased short-term success compared to placebo (Edwards et al., 1988), but no larger clinical trials with long-term follow-up have been conducted at this time. Other antidepressants, such as moclobemide, a monoamine oxidase (MAO) inhibitor, have shown equivocal success (Berlin et al., 1995).

Bupropion was approved as a prescription medication for smoking cessation in 1997. At a constant daily dose, it takes about eight days for bupropion blood levels to reach steady state. There is an active metabolite that takes even longer to reach steady state. Consequently, the dosing procedure involves taking bupropion one to two weeks prior to the quit date. Smokers are instructed to take 150 mg per day during the first three

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days and 300 mg per day thereafter for seven to twelve weeks. Side effects include primarily dry mouth and insomnia.

In general, dose-related effects are observed with bupropion. At one year, point prevalence smoking cessation rates are significantly different between placebo and 150- or 300-mg bupropion per day, but not between placebo and 100 mg per day (Hurt et al., 1997). For the 150-mg and 300-mg doses, the OR was approximately 2.0, with abstinence rates of around 23% at 12-month follow-up versus 12% with placebo (Hurt et al., 1997). Continuous abstinence rates (biochemically confirmed not smoking at each visit) were highest among the 300-mg (24.4%) and 150-mg (18.3%) groups versus placebo (10.5%). In another study, bupropion and bupropion plus nicotine patch were observed to be more effective than placebo or nicotine patch alone, although in this study the efficacy of the patch was unusually poor (Jorenby et al., 1999). Based on the PHS meta-analyses of these two studies, the OR was 2.1 (95% CI=1.5, 3.0) for bupropion compared to placebo, and the estimated abstinence rate was 30.5% versus 17.3% (Fiore et al., 2000). The Cochrane review (Lancaster et al., 2000) also found a similar OR of 2.7 (95% CI=1.90, 3.9) based on the two published studies and two unpublished smaller studies. The efficacy of bupropion is unrelated to a history of major depression (Hayford et al., 1999).

Nortriptyline also involves a dosing procedure that is initiated 10-28 days prior to quitting to achieve steady-state levels. Dose initiation begins at 25 mg per day and escalates to 75-100 mg per day. The duration of treatment in published trials has been about 12 weeks. Two studies have shown that nortriptyline is more effective than placebo (Hall et al., 1998; Prochazka et al., 1998) with an OR of 3.2 (95% CI=1.8, 5.7) for nortriptyline compared to placebo and estimated abstinence rates of 30.1% and 11.7% respectively, (Fiore et al., 2000). These results were similar to those observed in the Cochrane review (OR 2.8, 95% CI=1.6, 5.0; Lancaster et al., 2000). This rate of success again is independent of a history of depression. Although this medication costs less than bupropion, there is concern about side effects, particularly overdose. Side effects include sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and shaky hands.

Other Medications

Antagonists

Other medications to aid cessation have an antagonist effect, that is, they prevent the drug from acting on the receptor site. This antagonist action would reduce the reinforcing effects from smoking and thereby decrease some of the satisfying aspects of smoking and the desire to

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smoke. Mecamylamine is a nonspecific nicotinic receptor antagonist that was originally used as an antihypertensive agent. Mecamylamine has been shown to block many of the physiological, behavioral, and reinforcing effects of nicotine (Collins et al., 1986; Corrigall and Coen, 1989; Levin and Rose, 1991; Martin et al., 1989; Stolerman, 1986). Mecamylamine also decreases craving for cigarettes and reduces nicotine preference (Rose et al., 1989). Clinical trials have focused on the use of a combination of mecamylamine and the nicotine patch. The rationale behind this antagonist–agonist combination is that both mecamylamine and nicotine from the patch would block the reinforcing effects of nicotine by occupying the nicotinic receptor sites. In addition, the nicotine patch would reduce the experience of withdrawal and minimize adverse side effects from the peripheral ganglionic blockade produced by mecamylamine. One of the major problems with the use of mecamylamine is constipation as a side effect, although at lower doses this side effect is not as much of a problem. An early smoking cessation trial with a small sample size showed that a combination of mecamylamine and the nicotine patch demonstrated greater success than the patch alone (Rose et al., 1994). In a later trial, precessation treatment with mecamylamine with or without the nicotine patch compared to no-mecamylamine conditions (nicotine patch alone or no drug) led to significantly higher continuous abstinence throughout treatment in smokers, who later all received both the nicotine patch and mecamylamine after the quit date (Rose et al., 1998). The six-month continuous abstinence rates were high only in the nicotine-mecamylamine precessation condition compared to pooled data from the other groups. These trials also showed greater reductions in craving, satisfaction from smoking, and smoking rates during the pre-quit period when mecamylamine and the nicotine patch were administered together compared to any drug alone. A subsequent larger clinical trial showed a higher abstinence rate at seven weeks posttreatment with the combination approach compared to the patch alone, but only in females (Rose et al., 1999).

Another type of antagonist treatment that has been examined only in animal models is immunization to produce nicotine-specific antibodies. Such antibodies would reduce drug entry into the central nervous system by binding to circulating nicotine and thereby decreasing the concentration of unbound nicotine. In animal studies, the nicotine vaccine has been found to reduce nicotine in the brain in a dose-dependent manner (Hieda et al., 1997; Pentel et al., 2000); to block the relief of withdrawal symptoms from nicotine administration in rats undergoing abstinence; and to block behavioral (locomotion), physiological (blood pressure), and neurochemical adrenocorticotropic hormone (ACTH) release effects from nicotine administration (Pentel et al., 2000). Studies are under way to examine the effects of this vaccine on nicotine self-administration. This approach is an

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attractive intervention because of its specificity and lack of direct impact on the central nervous system, although one concern may be attempts to surmount the effects of the vaccine by intensive compensatory smoking.

Nicotine has been shown to release endogenous opioids, which may be responsible for some of the reinforcing effects from smoking (Pomerleau and Pomerleau, 1984; Taylor and Gold, 1990; Watkins et al., 2000). An opioid antagonist may therefore reduce smoking by blocking the endogenous opioid-induced reinforcing effects. The effect of naloxone and naltrexone on smoking behavior has been variable, with some studies showing that naloxone reduces smoking compared to placebo in a laboratory session (Gorelick et al., 1989; Karras and Kane, 1980), while other studies showed no effect of naloxone (Nemeth-Coslett and Griffiths, 1986) or naltrexone (Sutherland et al., 1995) on smoking rate. Naltrexone has been successfully used for the treatment of opioid and alcohol abuse and dependence. Although, earlier studies showed some promise for naltrexone as a smoking cessation aid, long-treatment outcome success has not been enhanced by naltrexone over placebo, even in combination with the nicotine patch (Wong et al., 1999).

Medications That Target Other Systems

Clonidine is another antihypertensive that has been used to promote smoking cessation. Its mechanism of action is likely through stimulation of the α_2 adrenergic autoreceptors in the brain stem, which results in decreased noradrenergic activity and inhibits firing in the locus ceruleus. In a study conducted about 15 years ago, clonidine was observed to alleviate withdrawal symptoms from opiates, alcohol, and cigarettes (Glassman et al., 1984). Because of the observed reductions of nicotine withdrawal symptoms, several clinical trials have been undertaken to determine the effects of clonidine in the treatment of smokers. The PHS performed a meta-analyses on five randomized, placebo-controlled trials with at least five months follow-up post-quit (Fiore et al., 2000). This analysis found that clonidine, administered either orally or transdermally, is effective as a smoking cessation aid, resulting in a twofold increase in cessation compared to placebo (estimated abstinence rates of 25.6% vs. 13.9%, respectively; OR=2.1 [95% CI=1.4, 3.2]). A Cochrane review (Lancaster et al., 2000) of six trials showed evidence of similar efficacy (OR=1.9, 95% CI=1.3, –2.7). When examining individual studies, some studies showed greater efficacy among women than men (Gourlay and Benowitz, 1995). One study found greater treatment effect in women who are heavily dependent and/or who experience recurrent episodes of depression (Glassman et al., 1993). In another study, more dependent smokers (classified with a Fagerström score of ≥7) experienced greater efficacy

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with higher compared to lower concentrations of clonidine, whereas efficacy was independent of clonidine concentrations in smokers with low dependence scores (Niaura et al., 1996). Because of the proven efficacy of clonidine, the PHS has recommended using clonidine as a second-line pharmacological treatment. However, the main drawback to using clonidine is the profile of side effects, which include dry mouth, drowsiness, dizziness, sedation, and constipation as well as lowering of blood pressure. In addition, rebound hypertension may occur when the medication is discontinued.

Medications other than antidepressants that target the serotonin system, such as buspirone, a partial serotonin (5-hydroxytryptamine) agonist having anxiolytic effects that may also increase firing of dopaminergic and noradrenergic neurons (Benowitz and Peng, 2000), have produced equivocal results with regards to short-term treatment outcome. One study showed positive results with buspirone (West et al., 1991), and two studies showed negative results (Robinson et al., 1992; Schneider et al., 1996). One other study showed enhanced rates of abstinence at the end of treatment, but not at long-term follow-up, for those individuals with high levels of anxiety but not for those with low anxiety levels (Cincirpini et al., 1995). Effects on withdrawal symptoms have also been equivocal, with some studies showing positive effects of this medication in reducing withdrawal symptoms (Gawin et al., 1989; Hilleman et al., 1992) and other studies showing no effect (Cincirpini et al., 1995; Robinson et al., 1992; Schneider et al., 1996; West et al., 1991).

One innovative proposal for treating cigarette smokers is to change the rate of nicotine metabolism. Nicotine is metabolized primarily by the hepatic CYP2A6 (cytochrome P-450) enzyme. Several studies have examined the effects of having normal homozygous CYP2A6*1 (wild-type) alleles compared to inactive or mutated CYP2A6 alleles on nicotine metabolism and smoking behavior in humans. A prior study with a small sample size showed that smokers homozygous for the CYP2A6 deletion (and therefore having impaired enzyme function) showed lower cumulated urinary cotinine excretion compared to individuals who were homozygous CYP2A6*1 (Kitagawa et al., 1999). In another study, tobacco-dependent smokers who are carriers of null or inactive alleles (CYP2A6*2 or CYP2A6*3) were observed to smoke fewer cigarettes per week than smokers with two active CYP2A6 alleles (Pianezza et al., 1998). Results from both of these studies were duplicated by another study showing that smokers with defective alleles (*4 and *2) smoked fewer cigarettes and demonstrated lower expired CO levels than smokers with homozygous wild-type alleles. Cotinine levels were lower in the group with the defective alleles, and the nicotine-cotinine ratios were higher in this group (Tyndale et al., 2000). One clinical laboratory study examined the effects

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of methoxsalen, a CYP2A6 inhibitor, on cigarette smoking and found that methoxsalen in combination with oral nicotine decreases carbon monoxide exposure, smoking rate, latency between lighting the first and second cigarettes, and number of puffs taken (Sellars et al., 2000) compared to a placebo-placebo condition. No differences in cigarette consumption or CO exposure were observed with oral nicotine or methoxsalen alone. To date, these results are suggestive of the role of nicotine metabolism in smoking behavior.

Summary and Recommendations:

In summary, many different types of medications have demonstrated efficacy: nicotine replacement therapies, antidepressants, and other medications that target the dopaminergic and noradrenergic systems. These medications have also been shown to be safe and to produce minimal dependence and misuse. New antagonist medications, such as the nicotine vaccine or medications that may alter the metabolism of nicotine, are being evaluated for their effort on smoking cessation. Furthermore, with increasing knowledge of the function of various nicotinic receptor subtypes, medications that target the specific receptor subtypes responsible for the reinforcing effects of nicotine are likely to be developed. Unfortunately, although current smoking cessation aids are effective and relatively safe, the use of these medications by smokers to facilitate cessation attempts is not widespread. New prescription rates represent only a 10% share of the approximately 24 million quit attempts made per year (Shiffman et al., 1998), or 15% of the 16 million who attempt to stop smoking cigarettes for at least 24 hours (CDC, 2000). Obstacles to the use of these medications include cost, consumer concern, and misperception regarding the health effects of nicotine and the limitations presented by prescription status (Shiffman et al., 1998).

Medications that are now available over-the-counter (OTC) have had a significant impact on the number of quit attempts. With the introduction of OTC nicotine patch and nicotine gum, the estimated number of pharmacological quit attempts increased from two million to three million in 1993-1995 to six million in 1996 with numbers increasing in 1997 and remaining stable in 1998 (CDC, 2000). Successful quitting has been estimated to increase by 6%-20% when OTC products are made available compared to when only prescription products are available (Lawrence et al., 1998; Shiffman et al., 1998). If significant reduction in harm is to be achieved, easier access to and reduced costs of these products are necessary.

Another area that requires attention is misinformation regarding the safety of nicotine. In a 1996 survey by Ketchum and Harris, the majority of

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smokers (86%) perceived nicotine as harmful. Of further concern is the fact that despite the proven efficacy of existing pharmacological agents, relapse rates still remain high at around 60-75%, with even higher rates (exceeding 95%) among those who quit on their own. Furthermore, tobacco cessation treatment targets only a small percentage of smokers who want to quit. Among cigarette smokers, at any one time, only 10% are prepared to take action toward quitting (i.e., they intend to quit in the next 30 days; Prochaska and Goldstein, 1991) and only 20% of tobacco users are willing to quit in the next six months (Etter et al., 1997). For individuals who are unwilling or unable to quit, alternative methods of treatments or tobacco-like nicotine delivery devices must be considered and tested. Although total abstinence should be the ultimate goal in treatment, for those who are unwilling or unable to quit, reduction may be an important alternative to further decrease the mortality and morbidity associated with smoking (Henningfield and Slade, 1998; Hughes, 1995). The importance of this alternative strategy is highlighted by the dose-response relationship that has been observed between the amount of tobacco consumption and morbidity and mortality (Jimenez-Ruiz et al., 1998; Thun et al., 1995). Similarly, models have been developed showing that reduced smoking may lead to reduced of risk premature death (Burns, 1997), although longitudinal studies have not been conducted to date to confirm the results from these models. Therefore, methods to reduce tobacco use or long-term use of products to sustain abstinence require serious consideration.

Harm Reduction Indications for Pharmacological Treatments

The use of medications for harm reduction can be considered in various ways. First, medications can be used to reduce the rate of smoking either as a means toward eventual abstinence or as an end goal. Second, medications can also be used in situations in which the smoker cannot smoke cigarettes and chooses to use a medication, most likely nicotine replacement, to abate craving or withdrawal symptoms. This situational use of nicotine replacement may indirectly lead to reduced smoking, as well. Third, harm reduction may also include long-term maintenance on a medication as a relapse prevention aid and not merely a smoking cessation aid.

Several concerns exist when considering these approaches, particularly when advocating for reduced smoking if smokers are unwilling or unable to quit. One concern that has been raised is the potential for exposure to increased amounts of nicotine beyond those that the smoker normally experiences solely from smoking and the adverse effects that may be experienced when combining smoking with a nicotine replacement. This increased nicotine exposure may have associated toxicity, although

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the risk depends on the toxicity specific to nicotine, which tends to be confined primarily to reproductive and cardiovascular disorders. Prior studies have examined the use of nicotine replacements with concurrent smoking. These studies have found no major adverse effect even at a very high dose of nicotine patch (Benowitz et al., 1998) or in smokers who have experienced cardiovascular disease (Joseph et al., 1996; Murray et al., 1996; Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease, 1994).

A second concern is the reduced desire for abstinence as a result of a reduced perception of risk associated with decreased levels of smoking. Individuals who would normally have quit may choose continuing to smoke at lower amounts. Similarly, the desire to quit may also be decreased if the use of nicotine products is encouraged in areas that restrict tobacco use, so that the individual no longer needs to contend with withdrawal symptoms in these situations. A third and related concern is the reduced perception of risk among adolescents and younger adults. If the option of smoking a few cigarettes with reduced health consequences is available, then perhaps a greater number will be more willing to initiate smoking. A fourth concern, which is related to the long-term use of medications, is the potential toxicity that may be associated with chronic use, even though the toxicity is lower than that of tobacco products. An important principle that underlies all of these concerns is that no increase in harm occurs as a result of using a tobacco exposure reduction approach and that a significant and meaningful decrease in actual harm be the outcome.

Several advantages related to the availability of exposure reduction approaches include potentially increasing recruitment into treatment. That is, smokers who are not ready to quit can perhaps be persuaded to begin to reduce their tobacco consumption as a step toward cessation or as a method to reduce harm. This reduction may then reduce mortality and morbidity among individuals who want to continue smoking, and may also reduce environmental tobacco smoke exposure, and eventually facilitate abstinence. Furthermore, the use of medications in situations where smoking may not be allowed (e.g., work environment) may reduce work-related accidents, which have been observed to increase during periods of tobacco withdrawal (Waters et al., 1998).

Use of Pharmacological Agents for Tobacco Exposure Reduction

The use of nicotine replacements for tobacco exposure reduction has been suggested to minimize compensatory smoking behavior when reducing the number of cigarettes smoked (Shiffman et al., 1998). In addition, nicotine replacements are likely to induce minimal harm since it is

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the cigarette constituents and pyrolysis products other than nicotine that are primarily responsible for the morbidity and mortality associated with smoking (Benowitz, 1998; Henningfield, 1995). Use of nicotine to reduce smoking is not a new concept. One study observed that half of the smokers prescribed gum at a nonresearch routine outpatient setting reported using gum to help them cut down rather than quit smoking (Johnson et al., 1992). Furthermore, nicotine replacement treatment studies have shown that smokers continue to smoke at a reduced rate in conjunction with using nicotine products (e.g., Bjornson-Benson et al., 1993; Transdermal Nicotine Study Group, 1991).

The effects of administering nicotine intravenously or orally on reducing cigarette consumption were observed in the late 1960s and 1970s (e.g., Jarvik, 1970; Lucchesi et al., 1967). Subsequent short-term, laboratory research studies have demonstrated that nicotine administered intravenously (e.g., Benowitz and Jacob, 1990), by nicotine gum (e.g., Herning et al., 1985; Nemeth-Coslett and Henningfield, 1986; Nemeth-Coslett et al., 1987; Russell et al., 1976), and by patch (e.g., Foulds et al., 1992; Pickworth et al., 1994) reduced smoking behavior, although modestly. This modest reduction may be due to the insufficient doses of nicotine that were administered, short-term treatment, and/or enrolling subjects who were not interested in reducing the number of cigarettes smoked. In a recent study, Benowitz et al. (1998) examined the use of high-dose transdermal nicotine (TN) on smoking suppression. In a double-blind, crossover design among smokers with no desire to quit, they observed that TN reduced nicotine intake from cigarette smoking by 3, 10, and 40% on average under the 21, 42, and 63-mg/day conditions, respectively. Peak plasma nicotine concentrations were approximately 40, 60, and 70 ng/ml, respectively, versus 28 ng/ml attained with the placebo patch. They concluded by saying that high-dose nicotine has the potential to substantially reduce smoking and thereby harm.

Current studies, which have examined the use of nicotine replacements for the primary purpose of cigarette use reduction, have shown substantial decreases in the number of cigarettes smoked and levels of carbon monoxide (Fagerström et al., 1997; Rennard et al., 1990). Rennard et al. (1990) studied the effects of treating smokers with at least ten pieces of 2-mg gum per day on lower respiratory tract inflammation in heavy smokers. He observed that cigarette consumption decreased by more than one-half (from 51 to 19 cigarettes per day) and carbon monoxide was similarly reduced (from 49 to 27 parts per million [ppm] after a two-month period). Furthermore, lower respiratory tract inflammation in these heavy smokers was significantly improved.

Fagerström et al. (1997) conducted a crossover study in which dependent smokers had a choice of either 2-mg nicotine gum, a nicotine

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patch, nasal spray, and 2-mg oral tablet or were assigned to a product for two weeks. This study showed that compared to baseline, there were a 54% reduction in smoking, 35% reduction of CO, and 32% reduction of withdrawal symptoms. About 59% reduced smoking by more than 50%, and 5% smoked no cigarettes at the end of the four-week intervention period. The highest mean cotinine concentration attained during treatment was 373 ng/ml compared to 360 ng/ml obtained during the screening period. Fagerström and associates concluded that a "smoking reduction procedure may help the very recalcitrant smoker gain confidence and increase the control of his/her smoking behavior."

Bolliger et al. (2000) examined the effects of the nicotine inhaler in reducing smoking among smokers who were unwilling or unable to stop smoking immediately (N=400) in a double-blind, placebo-controlled four month trial with a two year follow-up. Participants were allowed access to the inhalers for up to 18 months. At the end of the four-month trial, significantly greater numbers of participants assigned to the active group (26%) were able to sustain reduction (reduced smoking by at least 50% from week six) compared to the placebo condition (9%). This significant difference continued to be observed at 24 months (9.5% vs. 3.0%, active vs. placebo). Significant differences in reduction in carbon monoxide were observed between active and placebo inhaler conditions at six weeks (68.4% vs. 84.1% of baseline, respectively) and four months (58.3% versus 71.1% of baseline, respectively). About 10% of the population was abstinent at the two-year follow-up. No serious adverse events related to treatment occurred during the study. The authors concluded that sustained reduction in smoking can be achieved using the nicotine inhaler. Recent studies have examined the effects of short-term use of the nicotine patch on reducing cigarette consumption among psychiatric patients who are not interested in quitting. These studies have observed reductions in cigarette consumption ranging from 20 to 42% (Dalack and Meador-Woodruff, 1999; Hartman et al., 1989, 1991), with the greatest reductions observed among the heaviest smokers (Dalack and Meador-Woodruff, 1999). Reduction approaches with psychiatric populations may be beneficial.

Other Harm Reduction Strategies Associated with Medication Use

Nicotine replacement agents, used on an ad libitum basis, can be used under circumstances in which smoking is not permitted (e.g., restaurants, airplanes, smoke-free workplaces). Nicotine replacements have been shown to reduce craving as well as withdrawal symptoms (Hughes et al., 1989) and therefore may be beneficial in situations where a smoker cannot smoke. Long-term maintenance of medications may also be considered a harm reduction strategy, similar to methadone use among individuals

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addicted to opiates. Few studies have examined the long-term use of nicotine replacement products to sustain long-term abstinence.

One study was the Lung Health study in which nicotine gum was available up to six months, but approved for longer use if deemed necessary. Nicotine gum was dispensed in the context of 12 weeks of cognitive behavioral smoking cessation treatment. The results showed a five-year sustained smoking cessation rate of 22% in this intervention group versus 5% in the usual care group (Kanner et al., 1999). An ancillary examination of the data focused on long-term gum use in this population (Bjornson-Benson et al., 1993). Among participants enrolled in the study, 28.9% were using gum at 12 months since study entry. About one-third of the sustained nonsmokers, over one-half of intermittent smokers, and one-fifth of continuing smokers were using gum at 12 months. This rate of long-term gum use among nonsmokers is consistent with other studies that showed rates of use around 22% at one year (Hughes, 1998). As an added note, in the Lung Health Study, continuing smokers using nicotine gum were smoking less than continuing smokers not using nicotine gum (12.4 vs. 23.5 cigarettes per day). No adverse effects were observed, although among sustained nonsmokers, continuous gum users reported more mild side effects than intermittent gum users.

Recently, a trial has been conducted examining the use of bupropion for at least one year as a relapse prevention agent (Hays et al., 2000). All smokers enrolled in the trial were assigned to bupropion SR for a period of seven weeks. Those smokers who were abstinent at the end of seven weeks were randomly assigned to bupropion SR or placebo for 48 weeks. Subjects assigned to the bupropion group had greater success in maintaining abstinence compared to those assigned to the placebo at the end of the 78-week follow-up (47.4% vs. 37.7%, respectively).

Summary and Recommendations

In summary, the results show that nicotine replacements are effective in reducing smoking on a short-term as well as a long-term basis in some smokers. The availability of a reduction or controlled smoking approach does not seem to deter individuals from becoming abstinent. Furthermore, high doses of nicotine do not seem to cause acute adverse events even among smokers who have experienced cardiovascular disease. Long-term use of nicotine replacements may also be effective in sustaining abstinence and is less toxic than a relapse to smoking. There is a great need for large and long-term clinical trials to determine whether different pharmacological agents, including products other than nicotine replacements, can lead to prolonged and significant reductions in smoking and less harm to individuals. Included in potential medications to be exam-

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ined are some antidepressants, antagonists and medications that alter the metabolism of nicotine. Finally, these treatment methods must be considered carefully for special populations of smokers, including adolescents, individuals with comorbid conditions or medically compromised individuals, and pregnant women.

OTHER POTENTIAL HARM REDUCTION METHODS: BEHAVIORAL STRATEGIES AND TOBACCO CONTROL POLICIES

Altering tobacco products and using pharmacological agents to reduce smoking are not the only methods of harm reduction. Behavioral methods and tobacco control policies have also led to reduced smoking. These approaches have to be considered so that the pharmacological approaches aimed at reducing an individual's smoking behavior can be complemented or augmented by behavioral and public policy approaches. Furthermore, changes in tobacco products aimed at reducing toxicity must be marketed only in the context of a comprehensive tobacco control policy whose primary goals are prevention of smoking initiation and total cessation of smoking. The normative belief that any tobacco use is harmful must be maintained (IOM, 2000).

Harm Reduction Using Behavioral Methods

Even as early as the 1970s, researchers observed that a significant "number of habitual smokers reported that they wanted to give up smoking but found it extremely difficult to reduce their rate of smoking or quit entirely" (Shapiro et al., 1971). This observation led to a number of studies using behavioral interventions aimed at reducing smoking. The behavioral means for achieving a reduction in smoking included smoking at fixed intervals and increasing the intervals between cigarettes; smoking a cigarette only when signaled to smoke (e.g., Levinson et al., 1971; Shapiro et al., 1971); changing smoking behavior, such as taking shorter puffs, reducing the number of puffs, and reducing the percentage of the cigarette smoked (e.g., Frederiksen and Simon, 1978; Glasgow et al., 1983); contingency contracting (Frederiksen and Peterson, 1976); and eliminating smoking in specific situations (e.g., Foxx and Axelroth, 1983; Glasgow, 1978). In addition, although they represent more of a pharmacological than a behavioral approach, gradually lowering the nicotine content in cigarettes (e.g., Foxx and Brown, 1979; Prue et al., 1981) and graduated filters (McGovern and Lando, 1991) have also been used as methods for reducing nicotine. All of these methods have shown some degree of success in reducing the number of cigarettes smoked, with concomitant reductions in extent of nicotine exposure. Two studies have compared the

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effects of a behavioral intervention of cigarette reduction versus a waiting list control. Each study had a goal of reducing cigarettes by 50% of baseline using a variety of behavioral techniques. In one study, although only 60% of the original sample remained in the program, these smokers achieved a median reduction of 75% compared to a 2% reduction in the waiting list control group at the end of the eight-week treatment period (Shapiro et al., 1971). Furthermore, six weeks after the termination of treatment, the median reduction was 43%. In the other study, a combination of treatment techniques, with and without feedback on carbon monoxide levels, was used sequentially over five weeks: changing brands to machine-measured low-tar and nicotine cigarette, reducing the number of cigarettes, and reducing the percentage of the cigarette smoked (Glasgow et al., 1983). Significant treatment effects were observed at the end of treatment when comparing the waiting list control with controlled smoking treatment groups. In general the results showed a mean reduction of 56% in the nicotine content of cigarettes, 28% in the number of cigarettes, and 19% in the percentage of cigarette smoked in the controlled smoking conditions.

Studies have also been conducted to determine long-term maintenance of reduced smoking and the rate of cessation attempts among these individuals. Hughes et al. (1999a) examined whether cigarette smokers can significantly reduce and sustain reduction by analyzing longitudinal data from subjects involved in the Community Intervention Trial for smoking cessation. He observed that at the two-year follow-up, 17% had decreased smoking by 5-25%, 15% by 24-49%, and 8% by 50% or more. Among smokers who reduced their smoking (≥ 5%) at two years, 52% reported maintaining this reduction at four years. In addition, these investigators found that decreased smoking did not predict an increase or decrease in quit attempts or abstinence, indicating that reduction does not seem to promote or deter cessation.

One study indirectly assessed maintenance of reduction and rate of cessation by conducting a three- to four-year follow-up among smokers who had enrolled in a smoking cessation program (Colletti et al., 1982). About one-third of the smokers who were unable to achieve abstinence, but smoked less than or equal to 50% of baseline smoking at posttreatment, maintained this rate at one-year follow-up. This maintenance rate declined to about 13-18% at three- to four-year follow-up. However, 18-20% of the smokers achieved abstinence. Therefore, among those who had reduced smoking at posttreatment, about 33-36% were able to quit or sustain the reduction for three- to four-years. These results would suggest that a lower smoking rate can be sustained and does not necessarily discourage cessation attempts.

Glasgow et al. (1985) directly examined these issues by conducting a 2½-year follow-up in 48 subjects enrolled in a controlled smoking program

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rather than a cessation study. The results indicated that 9% became abstinent and 9-36% showed some improvement on various reduced smoking behavior parameters from posttest to follow-up. These results would suggest that further tobacco exposure reduction can occur in about a third or more of the population. In addition, the smoking cessation rate is no lower than that observed among a general population of smokers or general practice intervention with smokers. In a later study, Glasgow et al. (1989) explored how an abstinence-based program, in which smoking was not condoned after the quit date, compared to a program in which participants had the option of complete smoking cessation or controlled smoking. No significant differences in smoking cessation rates were observed between the two conditions at either posttest or six months. This result would indicate that allowing controlled smoking among those who want to quit does not necessarily lead to either less interest in abstinence or a promotion of abstinence. In a review article (Hughes, 2000) also concluded that smokers can sustain reductions in smoking, and reductions in smoking do not undermine cessation.

More recent exploration of reduced smoking has used computerized devices to gradually wean smokers from cigarettes as a means to achieve cessation. One computerized program, Lifesign Computer Assisted Smoking Program, involves a scheduled reduction by increasing the interval between cigarettes and informing individuals when to smoke. The scheduled time-interval approach seems the most promising of the behavioral treatment methods based on studies by Cinciripini and colleagues (Cinciripini et al., 1995 and 1997) compared to abrupt cessation or nonscheduled reduction of cigarettes. This behavioral method systematically reduces the level of nicotine exposure, disrupts habitual smoking patterns, and gives smokers the opportunity to develop new behaviors or skills in response to cues associated with smoking.

Summary and Recommendations

In summary, the results from these studies show that smokers can reduce their smoking rate using behavioral methods, that this rate can be sustained over time, and that reduced smoking does not necessarily compromise cessation efforts. However, more systematic studies focused directly on these issues should be conducted. Furthermore, tobacco addiction involves more than a physical addiction to nicotine, but also behavioral and psychological aspects that also need to be targeted in exposure reduction as well as cessation. Rigorous studies combining behavioral and pharmacological methods for reduced smoking have yet to be conducted. For example, the use of pharmacological agents may have

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to be embedded in effective behavioral treatment methods to maximize tobacco use reduction and maintain this reduction.

Harm Reduction Using Environmental Methods

Although not directly considered a harm reduction approach, comprehensive tobacco control policies have clearly lead to a reduction in the overall consumption of cigarettes, including smoking intensity (e.g., IOM, 2000; Pierce et al., 1998). Increasing taxes or the price of cigarettes has uniformly reduced their overall consumption (IOM, 2000), with a 10% increase in price resulting in a 4% decrease in total consumption of tobacco. Price elasticity, that is, the degree of responsiveness of demand to price change, may be greater among youth than among older adults. Increased cigarette prices lead to significant reductions in the quantity smoked by youthful smokers as well as a reduction in participation in smoking (Chait, 1994; Chaloupka and Wechsler, 1995; Lewit et al., 1981; Tauras and Chaloupka, 1999). Increased taxes on smokeless tobacco also result in a reduction in the amount used as well as the frequency of use (Chaloupka et al., 1996).

Workplace smoking restrictions have also significantly reduced the consumption of cigarettes (IOM, 2000). This reduction includes the intensity of smoking among employees as well as increased quit rates (e.g., Brownson et al., 1997; Evans et al., 1996; Glantz, 1997; Glasgow et al., 1997; Tauras and Chaloupka, 1999). In one study, the number of cigarettes smoked per day was not significantly different between work sites with restrictive versus unrestrictive smoking policy in a cross-sectional analysis. However, in a longitudinal analysis, work sites that initially had unrestrictive smoking policies but changed to restrictive policies showed reduced smoking compared to those that continued unrestrictive smoking policies (Jeffery et al., 1994). A 10% decrease in smoking was observed in this study, which is similar to if not lower than the reduction in number of cigarettes reported in other studies (Evans et al., 1996; Farrelly et al., 1999).

In another study, smokers who worked in places where the smoking ban was total or partial smoked five fewer cigarettes during the work days than leisure days. No differences were observed in the consumption of cigarettes between work days and leisure days in smokers who were employed in places with no smoking bans (Wakefield et al., 1992). These results were found across all occupational status groups. Reduced work day smoking, 18 months after the initiation of a total ban on smoking in the workplace, was found among 32.3% of smokers, and generalization to nonworkdays occurred in some smokers (Borland et al., 1991).

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Another study showed that a greater number of daily smokers were light smokers (<15 cigarettes per day) if they worked in a smoke-free environment and if they lived in a home in which there was a partial or total ban on smoking (Farkas et al., 1999). Among young smokers, limits on smoking in schools and restrictions in public places led to a reduced number of cigarettes consumed (Chaloupka and Grossman, 1996; Chaloupka and Wechsler, 1995). Furthermore, schools that have comprehensive policies, including a high emphasis on prevention education, resulted in lower amounts of smoking by smokers than schools that had less comprehensive policies (Pentz et al., 1989).

Other tobacco control policies include tobacco advertisement bans and limiting access of adolescents to tobacco products. While a limited set of tobacco advertising restrictions have no effect on tobacco consumption, comprehensive tobacco advertising bans have reduced tobacco consumption by more than 6% and counter advertising by 2% (Saffer and Chaloupka, 1999). Whether these bans have any effect on the number of cigarettes smoked is unclear. Limits on the availability of tobacco products to underage youths have no impact on college students (Chaloupka and Wechsler, 1995) and adolescents or youth, which may be a function of poor enforcement of these restrictions (Chaloupka and Grossman, 1996; Rigotti et al., 1997). Other studies show that enforcement of youth access restrictions does reduce tobacco consumption (IOM, 2000). Strong limits on youth access to smokeless tobacco, however, have been observed to reduce the frequency of use of this product (Chaloupka and Grossman, 1996).

Summary and Recommendations

In summary, individual harm reduction strategies must occur in the context of public policy of tobacco control if a significant reduction in death and disease is the primary goal. These policies would set the normative standard that tobacco use is highly discouraged. Other issues that require careful consideration are the cost and availability of products. The costs of pharmacological agents that have less associated toxicity are much higher per unit of purchase than those of the more highly toxic tobacco products. Furthermore, tobacco products are more readily available at a number of outlets than pharmaceutical products. The impact of availability, even within the area of pharmaceuticals, is highlighted by a study showing increased quit attempts among smokers when the nicotine patch was released and when nicotine gum and the patch went over-the-counter (CDC, 2000). The rate of these quit attempts was sustained with the advent of OTC products rather than the introduction of new products. Therefore, if a significant impact is to be made on the negative consequences

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associated with tobacco use, then the safer nontobacco products must be made more available to consumers who are already addicted to nicotine, whereas the more toxic tobacco products must be made less available.

General Conclusive Statements

Harm reduction is not a new concept, but it is a controversial one, in part because of the previous history with low-tar and nicotine cigarettes. Evidence exists showing that "light" cigarettes may have lead to compensatory smoking behavior and therefore no reduction in harm. Furthermore, many smokers of these light cigarettes believed that they were reducing harm, and this perception may have undermined cessation attempts (Cohen, 1996; Kozlowski et al., 1998). These observations led to recommendations for principles that should be followed to determine the feasibility and effectiveness of tobacco exposure reduction approaches (Henningfield and Slade, 1998). Some of the these principles that should be considered include the following: (1) reduction of exposure to toxins with verification based on biomarkers; (2) no reduction in cessation attempts; and (3) no increased safety risk.

Various methods to reduce harm have been proposed. These include changing tobacco products themselves by adding filters, reducing tar and nicotine, via ventilation, or maintaining nicotine but reducing tar (e.g., reducing tobacco nitrosamines, controlled tobacco burning). Other approaches include reducing tobacco consumption, by use of either pharmacotherapies, behavioral strategies, or polices that restrict access to tobacco products. In addition, long-term use of pharmacotherapies to substitute for tobacco use has also been advocated. Examination of harm reduction products and approaches will present a number of issues such as (1) the extent to which reduction of exposure to tobacco toxins must occur before beneficial effects are observed and treatment can be considered a success, that is, how to define a successful treatment outcome; (2) the length of the follow-up or type of surveillance necessary to monitor for any adverse effects; (3) valid and reliable indices for reduction of tobacco toxins; (4) methods to market and position this approach without compromising the message of abstinence as the primary goal and without increasing the initiation of using tobacco products; (5) the cost-effectiveness of this approach; (6) the willingness of health care providers to advise and assist patients who are reluctant to quit in using this technique if reduction in risk is observed as a result of reduction in toxic tobacco exposure; (7) whether nicotine-containing tobacco products should ever be touted by the tobacco industry as a way to quit smoking or reduce its health consequences; and (8) the industry's positioning of pharmaceutical products and tobacco-containing products with less toxins, especially when

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the differences between them tend to become blurred. In clinical trials, the issue may arise as to how to identify individuals who are unwilling or unable to quit, that is, the criteria to be used to make this determination as well as how and when to intervene with smokers, who use PREPs, to help them eventually achieve abstinence. Finally, a number of regulatory issues will have to be addressed.

REGULATION OF EXPOSURE REDUCTION PRODUCTS

Drugs

The regulatory system in the United States for therapeutic drugs, administered by the Food and Drug Administration, is the most stringent regulatory system in our society for new products. The scientific, legal, and administrative features of this system have been described in many publications, but a particularly good review for the purposes of this report is that of Page (Page, 1998).

The Food, Drug and Cosmetic Act requires affirmative approval of all new drugs by the FDA before marketing. The scientific information required to support such approval includes proof of the identity and structure of the active ingredient(s); detailed information on the composition of the formulation (e.g., tablet, capsule, solution); reports of toxicology studies in animals, including carcinogenicity and reproductive toxicology when necessary; clinical pharmacology studies in humans to show the pharmacokinetic (blood-level) profile and potential for interactions with other drugs; and most importantly, at least two controlled clinical trials in humans demonstrating the effectiveness of the drug for the claimed indication and an acceptable side-effect profile (21 CFR 314). This information is summarized in the product labeling for the physician in a leaflet popularly known as a package insert. This labeling also serves as the basis for regulating promotion and advertising after marketing.

In addition, all clinical studies in humans sponsored by drug manufacturers are subject to regulatory oversight under the Investigational New Drug (IND) regulations (21 CFR 312). This oversight includes review of each protocol by the FDA and by an institutional review board, submission of periodic reports, and prompt submission of serious adverse events that occur during clinical studies.

After marketing, the manufacturer must continue to submit to the FDA reports on new and unexpected adverse events, changes in manufacturing or formulation, changes in labeling (e.g., new warnings), and new advertising materials. Manufacturing plants are also subject to periodic inspection to ensure compliance with good manufacturing practices.

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This regulatory system serves to promote public trust in the quality, effectiveness, and truthful labeling of medicinal products and also makes the pharmaceutical and biotechnology industries among the most heavily regulated businesses in our society.

Essentially all new drugs are first approved as prescription drugs. In time, however, some may be switched to over-the-counter status and be sold directly to consumers. OTC drugs are subject to the same regulatory requirements as prescription drugs except that the regulation of their advertising is under the authority of the FTC rather than the FDA. The tests for determining whether a drug can be sold OTC are (1) whether it can be labeled for use by the consumer without the need for a physician and (2) whether it is safe and effective for OTC use. The FDA has historically limited the use of OTC products to symptomatic conditions such as colds, heartburn, and headaches that can be diagnosed without the need for a physician. Furthermore, to promote safe use, the FDA has typically approved for OTC use only drugs of low inherent risk such as antacids and sunscreens or, in the case of drugs that are potentially toxic such as nonsteroidal anti-inflammatory agents and antihistaminics, lower doses than are available by prescription. Drugs with sufficient abuse potential to be scheduled under the Controlled Substances Act cannot be offered OTC.

The only nicotine-containing products currently approved by the FDA for OTC use are Nicorette gum, Nicoderm CQ patch, and Nicotrol patch. The FDA decision to permit these products to switch from prescription to OTC status required discussion at two meetings of the Non-Prescription Drug Advisory Committee before action was taken. A later decision to permit mint-flavored Nicorette gum also required considerable time and discussion. The concerns raised in these discussions were whether these products would actually be effective in an OTC setting without accompanying professional intervention and whether increased abuse and/or cardiovascular risk might develop. Subsequent experience has been reassuring on all counts (Hughes et al., 1999a).

Nicotine-containing drugs are currently approved by the FDA only to reduce withdrawal symptoms as an aid in smoking cessation. Their labeling clearly states that the goal of treatment is cessation of smoking and subsequent withdrawal from the nicotine-containing tobacco product. The labeling of the prescription products advises against chronic use beyond six months and over-the-counter labeling advises against long-term use while continuing to smoke or use other nicotine-containing products. Although use as part of a comprehensive behavioral smoking cessation program is encouraged, there is no information in the labeling of nicotine-containing products about their effectiveness in combination with other programs or Zyban (bupropion SR). In contrast, the labeling for Zyban

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the only other drug approved as an aid for smoking cessation, notes an additive effect in combination with the nicotine patch and advises that Zyban may be continued indefinitely in successfully treated patients. Long-term use of these products with cigarettes, which might occur in a harm reduction strategy, is discouraged by the approved labeling.

The other prescription drugs reported to be useful for smoking cessation—clonidine, nortriptyline, and mecamylamine—are not approved by the FDA for this indication. That does not limit the ability of physicians to prescribe them for this use, but it does prohibit manufacturers from promoting them for this use.

Medical Devices

The modern regulatory framework for medical devices derives from the Medical Device Amendments of 1976 to the Food, Drug and Cosmetic Act. This legislation defines a medical device as an "instrument, contrivance or similar article intended to affect the structure or any function of the body" and requires the FDA to classify all medical devices according to their degree of risk (Page, 1998). Class I devices are those of low risk such as crutches and bandages that need meet only general standards. Class II devices are envisioned in the law as devices of intermediate risk that need specific performance standards to ensure their safety and effectiveness. Because performance standards can be established only by regulation and the process is time-consuming and burdensome, this provision of the law has seldom been used. Class III devices are those of highest risk, such as heart valves and pacemakers, and require preclearance by the FDA before marketing.

The device laws have never been applied by the FDA to any therapeutic product intended for smoking cessation. Although the containers for the Nicotrol Inhaler and Nicotrol Nasal Spray may look like devices, they are regulated by FDA as the packaging for a drug and not as medical devices.

In 1996, the FDA claimed regulatory authority over cigarettes and smokeless tobacco products on the grounds that a cigarette is a medical device intended to deliver the drug nicotine. This resulted in extensive litigation between the FDA and the tobacco industry, the details of which are included in the next section.

Tobacco Products

The effort to regulate tobacco has a long history (Jacobson and Wasserman, 1997; Kluger, 1997). By the beginning of the twentieth century, there was an important antitobacco movement in the United States

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based on the conviction that tobacco use was immoral, uncouth, and corrupting. Many states passed laws prohibiting the production, sale, or use of cigarettes. Smoking, especially by women, was discouraged, and female smoking was equated with low moral character. A few states also banned the sale of tobacco to minors in an effort to combat the "demoralizing" effect of tobacco on children. These state laws, however, were poorly enforced and were eventually overturned as smoking became much more popular during the Great Depression and World War II.

Beginning in the 1930s, the scientific community began linking smoking directly to disease. This evidence mounted in the 1940s and 1950s, culminating in 1964 in the landmark Surgeon General's report (PHS, 1964) outlining the adverse health effects of smoking in terms of cancer, heart disease, and lung disease. Later Surgeon General's reports considered such topics as the adverse health effects of environmental tobacco smoke (U.S. DHHS, 1986), the problem of adolescent smoking (U.S. DHHS, 1994), and tobacco use by minorities (U.S. DHHS, 1998). In response to the 1964 Surgeon General's report, Congress passed the Cigarette Labeling and Advertising Act of 1965, which forced cigarette manufacturers to place the warning, "Caution: Cigarette smoking may be hazardous to your health," on all packaging. This act, however, prevented the states and the FTC from enacting their own rules requiring more explicit warnings on packaging.

In 1969, Congress enacted the Public Health Cigarette Smoking Act, which banned all cigarette advertising on television and radio and modified the warning labels to read, "Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health". This law negated a decision by the Federal Communications Commission that would have required, under the "Fairness Doctrine", stations broadcasting tobacco ads to provide equal air time to antitobacco public messages because it also prohibited broadcast advertising of cigarettes after January 1, 1971. In 1972, the FTC began requiring cigarette manufacturers to display a warning label on all cigarette advertising. Further changes in the health warnings came in 1984 and 1986 through the Comprehensive Smoking Health Education Act and the Comprehensive Smokeless Tobacco Health Education Act, respectively, which required the rotation of four specific warnings on cigarette and three rotating warnings on smokeless tobacco packaging and advertising (Jacobson and Wasserman, 1997)

Comprehensive federal tobacco regulation has been limited by the exemption of tobacco from numerous federal acts designed to protect the public from harmful products, including the Controlled Substances Act of 1970, the Consumer Product Safety Act of 1972, and the Toxic Substances Control Act of 1970. The Food, Drug and Cosmetic Act (FDCA), however, is silent with respect to tobacco products and thus stands as a potential

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regulatory tool for any product, tobacco containing or not, that makes an explicit health claim and also meets the definition of a drug or device. In the 1950s the FDA exerted jurisdiction in two cases in which tobacco companies made explicit claims regarding the health benefits of their products. In 1953, the FDA classified Fairfax cigarettes as drugs when the manufacturer enclosed leaflets with language that implied effectiveness in preventing an array of diseases, and in 1959 (*United States v. 354 Bulk Cartons Trim Reducing-Aid Cigarettes*), the FDA successfully prohibited explicit claims of weight reduction by a cigarette. During the late 1970s, however, when Action on Smoking and Health (ASH) and others petitioned the FDA to assert jurisdiction over cigarettes as drugs and devices, the FDA denied the petition on the grounds that cigarettes did not fall under the statutory definition of a drug. The FDA asserted that evidence of consumer intent to use the product predominantly for the health effects or the effects on the structure or function of the body was not sufficient to infer a similar intent by the manufacturers. Tobacco manufacturers appeared to be free from more comprehensive regulation as long as they did not make explicit claims about health benefits or effects on body structure or function and if they complied with advertising and labeling restrictions enacted by Congress (Slade and Ballin, 1993; U.S. DHHS, 2000).

In 1988, the Coalition on Smoking or Health (CSH) and others petitioned the FDA to classify low-tar and nicotine products as drugs and to classify the new smokeless cigarette product by RJR, "Premier", as an alternative nicotine delivery system and, hence, subject to regulation as a drug. CSH cited indirect claims made through advertising and marketing as evidence of the manufacturer's intent to have the product used for the mitigation or prevention of disease (Slade and Ballin, 1993). Again in 1994, the FDA was petitioned by CSH to classify all cigarette products as drugs as defined in the FDCA. Later that year, the FDA Commissioner announced in a letter to CSH and later in congressional testimony that the FDA, in light of new evidence, would revisit the FDA's authority to regulate tobacco products as drugs and devices as defined in the statute.

Following this investigation, the FDA asserted its jurisdiction and proposed regulation of certain tobacco products in the *Federal Register* in August 1995. The authority for such regulation was based on new evidence showing that cigarettes and smokeless tobacco products are nicotine-containing (i.e., drug-containing) devices as defined by the FDCA of 1938. The FDA determined that nicotine could be classified as drug based on the facts that (1) nicotine causes and sustains addiction, (2) nicotine produces other psychoactive (mood-altering) effects, and (3) nicotine controls weight. The definition of nicotine as a drug as defined by the FDCA includes an intent by the manufacturer for the product to be used as a drug in the bodies of their customers.

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The FDA's assertion that cigarettes and smokeless tobacco products may be defined as nicotine delivery devices was based on findings that (1) the effects of nicotine are so widely known that it is foreseeable to a reasonable manufacturer that these products will cause addiction and other pharmacological effects and will be used by the consumers for these effects and to sustain the addiction; (2) consumers use tobacco products mainly to sustain addiction, for the mood-altering effects, and for weight loss; (3) manufacturers of tobacco products know that nicotine has pharmacological effects and that consumers use their products primarily to obtain the pharmacological effects of nicotine; (4) manufacturers design their products to provide consumers with a pharmacologically active dose of nicotine; and (5) as a consequence, consumers keep using cigarettes and smokeless tobacco to sustain their addiction to nicotine (U.S. DHHS, 1995). The agency disclosed new evidence from industry documents of product engineering, nicotine delivery manipulation, and industry research in support of its contention that tobacco products are intended to change the structure or function of the body. This provided the rationale for the FDA's proposed new rules on the advertising, marketing, and sale of tobacco. Many of the proposed actions were directed toward limiting the access of minors to tobacco products and stopping cigarette advertising and promotion targeted at adolescents.

Specifically, the new regulations imposed a ban on the sale of tobacco products to minors; required vendors to check for proof of age; banned cigarette vending machines, banned billboard or other advertisements easily accessible to youth; restricted all advertising to black and white text (except in publications read primarily by adults); banned tobacco manufacturer sponsorship of sporting and entertainment events; banned promotional items displaying a brand name, logo, or free samples; and required tobacco industry financial support for antitobacco education for children (U.S. DHHS, 2000).

On August 28, 1996, after soliciting public comment, the FDA published its final rule, modified only in that adult-only businesses were exempted from certain restrictions. The FDA was met by legal action from the tobacco industry, advertising industry, and tobacco vendors to block implementation of these rules. The case was initially heard by the federal district court in Greensboro, North Carolina (April 1997), which upheld the FDA's regulatory authority over tobacco products and supported the FDA definition of tobacco products as combination drug and drug delivery devices. The court, however, ruled that the FDA had no statutory authority to regulate tobacco advertising or promotion.

The decision was appealed by both sides in August 1997, and in August 1998, the Fourth Circuit overturned the district court decision and revoked FDA's proposed authority to regulate tobacco products. The

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court found that if cigarettes and smokeless tobacco were under FDA jurisdiction as outlined by the proposed regulations, the agency's only choice would be to ban the products in light of their known dangers to health. Any other consideration would not be within the scope of FDA's regulatory powers. The court concluded that Congress did not intend the FDCA to be used for the regulation of tobacco products and that Congress has never equipped the FDA with the power to regulate tobacco products. This decision was upheld by the Supreme Court on March 21, 2000. The majority opinion stated that the FDA's regulatory actions were incongruous with what was intended by Congress and that Congress has historically denied FDA the authority to regulate traditional tobacco products.

It is important to recognize that this recent Supreme Court decision in no way limited the authority of FDA to regulate any product, tobacco containing or not, that makes an explicit health claim that would bring the product under the definition of a drug or device. For example, an exposure-reducing claim for a smokeless tobacco product, to the effect that it (like nicotine patches) promotes cessation of smoking, could be judged by the FDA as a drug claim requiring approval under a new drug application. Similarly, the newly emerging set of smoked nicotine-containing products is not necessarily excluded from FDA regulatory authority by the recent Supreme Court decision. An interesting consequence of the current regulatory situation is that a tobacco manufacturer may not be able to make a legitimate exposure-reducing or reduced-risk claim for a new product, even if truthful, without bringing the product under the jurisdiction of the FDA.

It is also important to note that as a result of the Supreme Court's decision overturning FDA jurisdiction, all current regulatory provisions over tobacco relate only to labeling, promotion and advertising, and taxation. None relate to the technical or scientific standards required of new products or to product safety. Unlike pharmaceutical or device manufacturers, cigarette manufacturers may introduce new curing, blending, and manufacturing techniques into tobacco products without regulatory oversight of any kind. Similarly, new additives, new filters, new aeration mechanisms, new papers, and new constituents may be introduced without regulatory scrutiny. Neither the extent nor the results of toxicology testing of new ingredients in animals are known outside the manufacturer. The effects of new product design and of changes in constituents on the composition of inhaled smoke are not reported to any health authority. Clinical studies on new products are conducted without regulatory oversight over protocols (except for institutional review board review) or review of the results. Once research and development on a new product has been completed, the product is marketed based on the manufacturer's

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responsibility, again without regulatory review. Manufacturers are under no regulatory obligation to conduct postmarketing epidemiological studies or to collect and report adverse events.

The contrast between the regulatory systems for drugs or devices and for tobacco has been discussed by a number of authors (Henningfield, and Slade, 1998; O'Reilly, 1989; Page, 1998; Slade and Henningfield, 1998; Warner et al., 1997), who point out the paradox of a stringent regulatory system for exposure reduction products developed by the pharmaceutical industry and a weak regulatory system for exposure reduction products developed by tobacco manufacturers. Table 4-8 illustrates the problem.

TABLE 4-8 Comparison of Two Nicotine Inhalers

Feature	Eclipse (tobacco company)	Nicotrol Inhaler (pharmaceutical company)
Operation	Heat source volatizes nicotine and glycerol, and scorches tobacco	Ambient air passing through nicotine reservoir volatizes nicotine
Dose	Mimics cigarettes (lung delivery of nicotine)	Similar to low Nicorette dose (buccal delivery of nicotine)
Projected abuse liability	High	Low
Contaminants	High CO, acrolein, "soot," and other contaminants	Not allowed
Claims or indications	Reduced delivery (unproven to FDA)	Smoking cessation (FDA-approved studies)
Intent	Cause and sustain dependence	Treat dependence
Cost	More than $3.00 per pack of 20 ($0.15 each)	$55.00 per pack of 42 ($1.30 each)
Modification oversight	Modified to be more palatable (and more toxic) without approval	Any modification requires FDA approval
Premarketing approval data	None submitted to FDA	Conventional new drug application submission and FDA approval
Availability	Over-the-counter	Prescription only

SOURCE: Slade and Henningfield, 1998. Reprinted with permission of the Food and Drug Law Institute.

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Chapter 7 of this report discusses the principles of a science-based regulatory system for tobacco products, including those with exposure reduction or risk reduction claims.

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5

The Scientific Basis for PREP Assessment

Assessing health risks from conventional tobacco products is similar to that for many environmental and occupational exposures. Tobacco risks, however, are among the more complicated to assess for several reasons. The general components of risk assessment (hazard identification, dose-response assessment, exposure assessment, and risk characterization) described in Chapter 1 are still useful to consider (see Table 5-1).

Hazard identification is challenging because tobacco and the smoke generated upon its combustion are complex mixtures. Some of the hundreds (or thousands) of known or suspected toxicants are fairly well understood; however, the relative contribution to overall toxicity of most of the individual compounds is not. In addition, tobacco products contain added constituents or ingredients, but the identity and concentration of these compounds within a specific tobacco product is unknown, due to proprietary concerns. Animal models of tobacco toxicity are limited, posing additional barriers to complete hazard identification.

Dose-response assessment is complicated. Because the exposure is a complex mixture, the diseases associated with tobacco exposure are many and the dose-response relationships vary significantly. Assessing the dose in epidemiological studies is complicated in part by the factors described for hazard identification. In addition, the dose a tobacco user is exposed to can change often over a long and variable smoking history. Finally, the responses are most often diseases with long periods of disease progression until diagnosis and from time point of dose estimation.

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TABLE 5-1 Tobacco and PREP Risk Assessment

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
1983 "Red Book"	Epidemiology Animal bioassay Short-term Studies Comparisons of molecular structure	Epidemiology Low-dose extrapolation Animal to human extrapolation	Dose to which humans are exposed Dose of special populations Estimation of size of population potentially exposed	Estimate of the magnitude of the public health problem	A risk-assessment (qualitative or quantitative) may be one of the bases of risk management
Challenges in risk assessment of tobacco	Complex mixture Animal models are limited Constituents and additives are proprietary information	Dose changes for an individual over time Dose of individual toxicants varies over time Exposure at time of disease progression	Changes in smoking topography Complex mixture	For which disease? At which point in smoking history?	FTC regarding advertising
Additional challenges of PREP risk assessment	Products will change rapidly with time	Assessing effect of moving backwards on a dose-exposure curve, assuming long-time previous higher exposure	Changing exposure after long-term higher dose exposure Some toxicants could increase	Need models to consider effects on initiation, cessation, and relapse	FDA authority currently exerted only over pharmaceutical PREPs

continues

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TABLE 5-1 Continued

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Committee charge	1. Does product decrease exposure to the harmful substances in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product decrease exposure?	4. What are the public health implications?	4. What are the public health implications?
Disease-specific summary data (Chapter 5; Section II)	3. Utility of preclinical research to judge feasibility	1. Dose-response data for conventional tobacco products 2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	5. Long-term epidemiological studies and surveillance	

NOTE: Numbers correspond to research recommendations listed in the Executive Summary.

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Exposure assessment is difficult for some of the same reasons. There is a multiplicity of tobacco products on the market. The specific exposures associated with any one "branded" product could change throughout time because the product can change. Changes in exposure throughout time are not documented. In addition, smokers of "low-yield" products often compensate (change smoking behavior to increase nicotine exposure), so their exposures to nicotine and tobacco/smoke toxicants are often higher than predicted by a common form of exposure assessment, self-report.

The objective of a potential reduced-exposure product (PREP) risk assessment is to determine if the risk of harm from the use of the PREP is less than the risk of harm in the absence of the PREP (see Table 5-1). The risk management objective considered by the committee is not to ban or control the exposure per se, as is the case for environmental and occupational exposures. The risk management objective, as will be made clear in Chapter 7, is primarily to verify whether or not a product is associated with either exposure reduction or harm reduction.

A PREP risk assessment involves lowering the dose of a complex mixture in a person (or population) with varying degrees of pre-existing pathology or cellular damage caused by a complex mixture exposure (that of conventional products) and trying to reverse early damage or to stop disease progression. This is problematic at this point, as there are no adequate human or animal studies that replicate this scenario. While some studies report risks in persons who switch from nonfiltered cigarettes to filtered cigarettes, or from high- to low-tar cigarettes, this "switching" did not reduce exposure (due to compensation) significantly in many people. The reduction in risk, if any, would occur only in persons who do not compensate for lower nicotine levels by smoking more or smoking differently. The basic elements of risk assessment can, however, be still considered. The questions become slightly different, and the data required or the study designs might be different from that required for a tobacco risk assessment.

For *hazard identification*, the questions include:

- Does the PREP contain (or produce during use) toxicants known to cause adverse health effects?
- To what extent are the compounds targeted for reduced exposure causally linked to a tobacco-related disease?
- How does its content compare with the toxicants in the conventional tobacco product to which it is compared?
- Are there unique toxicants in a PREP compared to conventional tobacco products?

For hazard identification, it is essential to know the composition of the material to which people will be exposed from the PREP compared to

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the standard product. Any new material, such as flavors, added to standard products must be included in the analyses. It is important to analyze the product that actually enters the body (for example, the combustion products that are inhaled) rather than the composition of the product as sold.

The approach to testing the toxicity of the material to which people are exposed in the tobacco-related PREP compared to standard tobacco products is discussed in Chapter 10. The objectives of the toxicity tests are to determine what toxic effects can be induced by the test materials (the tobacco-related PREP compared to the standard product) and how much of the test materials is required to cause the adverse effect, i.e., the dose-response characteristics in animals of the test materials. Data from animal studies can be used to eliminate new products that are much more toxic than existing ones.

A series of comparative potency tests is appropriate. In vitro studies in cultured cells from both animals and humans can be used to determine the ability of the test materials (from the tobacco-related PREP and the standard product) to induce cellular damage, an inflammatory response, or cell death. Assays of the mutagenic or clastogenic activity of the test materials can be done in bacterial or mammalian cell systems.

In animal studies, tests for tobacco-related toxicity should include evaluation of the ability to induce adverse health effects or cancer in the respiratory tract, the nervous system, the cardiovascular system, the reproductive and developmental systems, and other organs. Toxicokinetic studies should be used to determine dosimetry to different organs and to suggest biomarkers of internal dose that can be used in humans. Short-term clinical tests in humans should be done to compare the potencies of the test materials to induce acute adverse health effects (such as reduced pulmonary function) and to determine the toxicokinetics of the tobacco-related PREP compared to the standard product.

For *dose-response assessment*, the questions include:

- What are the dose-response characteristics of the PREP compared to the conventional tobacco product?
- Do smokers use PREPs at a time in their individual smoking history (and therefore of disease progression) that induce different dose-response effects?
- Are the patterns of adverse health effects different from PREPs compared to conventional tobacco products?
- What is the evidence that reduction in exposure to the targeted compounds in the complex mixture or other hazardous material in the PREP will decrease or reverse the development of disease?
- What is the dose-response relationship between the targeted compounds and the disease outcome?

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- What quantitatively happens to disease induction if exposures are reduced?
- How much exposure needs to be reduced to result in a measurable benefit?
- Are there individual susceptibilities (age, gender, genetic makeup, and prior use of tobacco products) that change this dose-response relationship?

Some dose-response information can be obtained from standard preclinical animal studies. However, there will be uncertainties in extrapolating from animal data to humans. Additionally, it will be difficult, even in animals, to determine the response to a reduction in dose after a period of higher exposure.

For *exposure assessment*, the questions include:

- Do PREP users compensate differently than users of more conventional "low-yield" products?
- Do PREP users exclusively use PREPs or do they switch back and forth between PREPs and conventional products?
- How does the PREP change the exposure pattern for the population?
- Does the introduction of the PREPs increase the number of people initiating use of tobacco products or decrease cessation attempts?
- What is the overall balance in exposures (directly and as environmental tobacco smoke) with or without the PREP?

Past experiences with "low-yield" cigarettes containing less tar and nicotine than other products underscore the need to determine internal dosimetry of toxic material entering the body during use of tobacco-related PREPs. The internal dosimetry of the new products can be compared to that of standard products in short term toxicokinetic studies in humans. Biological markers of internal dosimetry of key ingredients can be used when available.

The risk assessment process will need to rely on the use of animal preclinical and human clinical studies, in which biomarkers of exposure and potential harm can be measured. Biomarkers of exposure to tobacco products have been validated and are in current use. Unfortunately, few specific early indicators of biomarkers have been validated as predictive of later disease development. It is recognized that today, biomarkers of exposure are better validated compared to biomarkers of potential harm, and that it is more feasible to consider exposure reduction in contrast to risk reduction. However, while an assessment of risk reduction through biomarkers will have more uncertainty, these will need to be included in the PREP risk assessment process in order to enhance confidence that there is no worsening risk, in the least.

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For *risk characterization*, the questions include:

- Can the exposure levels of the PREP, given its dose-response characteristics, be expected to result in reduced risk of one or more tobacco-related diseases than the standard tobacco product to which it is compared?
- What is the magnitude of any reduction in risk?
- What are the limits in understanding of the risk reduction?
- Do fewer tobacco users quit and use PREPs instead?
- Do former tobacco users relapse to PREPs?
- Do nonusers initiate tobacco use through PREPs?

In order to achieve a level of confidence that a PREP will provide meaningful reductions in risk, especially compared to the real possibility of others using this product to initiate or resume smoking, prospective epidemiological studies are required. This could be done in a timely manner for some disease endpoints, such as birth outcomes or recurrence of myocardial infarction. For many other diseases associated with tobacco use, however, definitive demonstration of reduced harm will require studies of a long duration. Moreover, it is reasonable to anticipate that the design of PREPs would change rapidly in the coming years so that assessing PREP use will be difficult.

The claim that a PREP will result in a reduction of the risk for harm requires scientific evidence for the validity of that claim. A discussion of the information relevant to hazard identification and dose-response information (the first two elements of risk assessment) is given in Chapter 10. Information on the best means of evaluating exposures is given in Chapter 11. In the case of tobacco products, animal models of adverse health effects have been problematic in the past, but new animal models show promise for being useful (see Chapter 10). There currently are no population risk assessment models that mimic the types of predictions hoped for tobacco users who switch to PREPS and how the public health will be effected by the initiation of PREP use by never and former smokers.

The committee has evaluated the science base regarding the toxic effects of tobacco on the major diseases known to be caused by tobacco exposure (i.e., cancer and diseases of the cardiovascular, pulmonary, reproductive systems). The committee has done so to arrive at summary conclusions regarding the evidence base that would directly feed into a risk assessment paradigm, such as that described above (see Table 5-1). Specifically, the committee has elaborated in each of the major disease-oriented chapters of Section II and summarized later in this chapter the evidence regarding:

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1) the dose-response relationship between tobacco smoke and/or constituent exposure and health outcomes,
2) identification and development of surrogate markers for disease,
3) the utility of preclinical research in understanding the potential of PREPs to be harm reducing for the disease under review,
4) utility of short-term clinical and epidemiological studies, and
5) the role of long-term epidemiological studies and surveillance.

The review of preclinical research and the material in Chapter 10 (Toxicology) provide information on hazard identification and, in part, dose-response assessment. The material on surrogate markers for disease is informative for both dose-response assessment and exposure assessment. The review of the short-term clinical studies, epidemiology, and surveillance data provide the proof of reduced harm.

In conclusion, the PREP risk assessment process will be challenging because no single definitive study, either human or experimental animal study, would stand up to rigorous scientific scrutiny to be used in such a process. Therefore, today, several types of data will be needed that includes both experimental animal studies and human clinical data, with a definitive plan to conduct epidemiological and surveillance studies. The clinical data is needed because animal studies cannot predict interindividual differences in human behavior that would affect how the PREP is used or cause damage, and because there are too many uncertainties about the use of animal data. During this interim time, and with more research, the regulatory process might be able to identify key types of data needed for the risk assessment process. At this point in time, however, it can only be concluded that both experimental animal and clinical human studies would be needed, and that this would include both the consideration of exposure to individual PREP constituents and as a complex mixture. It is conceivable that the PREP risk assessment process can be simplified, for example by comparing only experimental data for one PREP to another, but this will require substantial experience and characterizing the data for existing PREPs. Sufficient data for streamlining this process in not available today.

The remainder of this chapter provides a summary of the major conclusions and recommendations, arranged by chapter, reached by the committee in Section II of this report.

TOBACCO SMOKE AND TOXICOLOGY (SEE SECTION II, CHAPTER 10)

Mainstream tobacco smoke and environmental tobacco smoke each is a complex mixture of toxicants composed of carcinogens and other chemi-

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cals with health effects that alone or in combination are only partially known (see Table 5-2) (Davis and Nielson, 1999). The evaluation of conventional tobacco products and tobacco-related PREPs is complicated by a lack of adequate in vivo models of tobacco-related morbidities in man.

Toxicology studies, both in vitro and in vivo, provide the opportunity to evaluate the potential harm reduction offered by potential reduced-exposure products. The comparative potency of the PREP can be determined in a series of preclinical studies that include both the PREP and the standard tobacco product that can be replaced by the PREP. The preclinical tests should include in vitro tests in both animal and human cells

TABLE 5-2 List of Selected Tobacco Mutagens and Carcinogens[a]

Constituent Class	Phase	IARC Evaluation[b]	Examples
N-Nitrosamines	Particulate	Sufficient in animals	Tobacco-specific nitrosamines (NNK, NNN), dimethylnitrosamine, diethylnitrosamine
Polycyclic aromatic hydrocarbons	Particulate	Probable in humans	Benzo[*a*]pyrene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, 5-methylchrysene
Aryl aromatic amines	Particulate	Sufficient in humans	4-Aminobiphenyl, 2-toluidine, 2-naphthylamine
Heterocyclic amines	Particulate	Probable in humans	2-Amino-3-methylimidazo[*4,5-b*]-quinolone (IQ)
Organic solvents	Vapor	Sufficient in humans	Benzene, methanol, toluene, styrene
Aldehydes	Vapor	Limited in humans	Acetaldehyde, formaldehyde
Volatile organic compounds	Vapor	Probable	1,3-Butadiene, isoprene
Inorganic compounds	Particulate	Sufficient in humans	Arsenic, nickel, chromium, polonium-210

NOTE: NNK=nicotine-derived nitroketone; NNN=N-nitrosonornicotine.

[a]This list is intended to provide a conceptual overview of the complexity of tobacco product exposures. It is not all-inclusive but is presented to allow the reader to understand the number of considerations that must be made in assessing harm reduction strategies.

[b]International Agency for Research on Cancer: The classifications here refer to evaluations of the compound from any exposure, not just tobacco. Not all chemicals within the class are considered carcinogenic in humans. There is no consideration in this table to delivered dose or route of exposure (IARC, 1986).

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to determine the cytotoxicity and the genotoxicity of the tobacco product to which humans will be exposed. Such tests have recently been reported for a new tobacco-related PREP (Eclipse Expert Panel, 2000). Such a test must include dose-response studies to determine the amount of the exposure material required to cause toxicity. Next, studies should be conducted in vivo in the best animal models available to determine the comparative potency of the PREP versus the standard product in producing: (1) pulmonary inflammation, (2) COPD, (3) cardiovascular disease, (4) reproductive toxicology, and (5) pulmonary neoplasms.

In vitro studies and in vivo animal studies are useful but limited tools in evaluating the toxicity of products that claim to reduce exposure to tobacco toxicants and potentially reduce tobacco-related harm. In vitro studies may allow rapid, low-cost screening for the toxic properties of conventional tobacco products and tobacco-related PREPs, although the relationship between in vitro toxicity and in vivo human response has not been established for most compounds. These assays include cytotoxicity and genotoxicity assays, which are possible screens for the carcinogenic or inflammatory potential of products. In vivo toxicity testing can be developed to supplement in vitro and clinical studies.

Such animal models, if developed, may be useful as a screening assessment of the efficacy of PREPs for reduction of various tobacco-attributable diseases (see Chapters 12-16). The committee concludes that animal models should be used to test for the potential adverse health effects of tobacco smoke or any proposed additives. The A/J mouse model, which is sensitive to induction of lung adenomas, shows promise as an animal model for screening the potential of tobacco products to induce lung tumors (Witschi et al., 2000; Witschi et al., 1999; Witschi et al., 1997a,b). Future studies should validate the model. These studies (Witschi et al., 2000) indicated that removal of single classes of carcinogens, such as nitrosamine or polycyclic aromatic hydrocarbons (PAHs) may not be protective against induction of lung tumors by smoke. Studies also indicate that some animal models show promise for use in studying the development of symptoms similar to those of chronic obstructive pulmonary disease (COPD), the development of cardiovascular disease, adverse effects on the immune system, intrauterine growth retardation, and poor fetal lung maturation from the inhalation of new or existing tobacco products (see Chapter 10).

Testing the general toxicity of smokeless tobacco and evaluating of the potential harm reduction properties of smokeless tobacco (e.g., Swedish snus) use in smokers may greatly benefit from assays for genotoxic and cytotoxic potential and the animal models discussed above.

Details to be considered in determining the specific set of toxicity tests include species and strain of test animal, duration of test, end points of interest, dose-response considerations, biomarkers of dosimetry and

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response, and standard comparison products to be tested as positive and negative controls.

EXPOSURE AND BIOMARKER ASSESSMENT IN HUMANS (SEE SECTION II, CHAPTER 11)

Accurate measures of exposure and the development of biomarkers of adequate specificity and sensitivity are needed to evaluate the toxicity and harm reduction potential of PREPs. Biomarkers can be defined as measurements of tobacco constituents, tobacco smoke constituents, or changes in body fluids (including exhaled air) and organs. The assessment of a PREP will have to include markers of external exposure and biomarkers indicative of internal exposure, biologically effective dose (Perera, 1987), and potential harm. The definitions of each are provided in Table 5-3. There have been different definitions of types of exposure assessments used previously, but more recent understandings of biomarker uses and limitations, as well as different approaches needed for PREP evaluation lead to a need for clarification and redefinition.

The latter three measurements in Table 5-3 improve upon the first by quantifying exposure at the cellular level to characterize low-dose exposures or low-risk populations, provide a relative contribution of individual

TABLE 5-3 Exposure and Biomarker Assessment Definitions

Exposure or Biomarker Assessment[a]	Definition
External exposure marker	A tobacco constituent or product that may reach or is at the portal of entry to the body
Biomarker of exposure	A tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose
Biologically effective dose (BED)	The amount that a tobacco constituent or metabolite binds to or alters a macromolecule; estimates of the BED might be performed in surrogate tissues
Biomarker of potential harm	A measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes "preclinical changes"

[a]Categories and definitions reflect concept that the critical exposure is at the level of a biological macromolecule, so that exposure for this discussion is not limited to a measurement at the portal of entry to the body.

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chemical carcinogens from complex mixtures (e.g., tobacco-specific *N*-nitrosamines in cigarette smoke), and estimate total burden of a particular exposure where there are many sources (e.g., benzo[*a*]pyrene [BaP] from air, tobacco, diet, and occupation) (Vineis and Porta, 1996). In assessing PREPs through biomarkers, understanding the biological effects of a wide range of exposures will be important. Within the context of this discussion, exposure at the level of the cell and critical macromolecules is considered with greater weight, rather than the traditional view of exposure at the portal of entry into a person.

Markers of external exposure attempt to measure the dose of tobacco or tobacco smoke constituents that may enter the body and usually involve machine testing of products and user questionnaires. Internal exposure markers assess the amount of tobacco or tobacco smoke constituents or their metabolites in body fluids or organs. Biomarkers estimating the biologically effective dose measure the internal dose that interacts with cells and macromolecules and may be mechanistically related to disease outcome. Finally, biomarkers of potential harm reflect changes in cells and macromolecules that may lead to disease (see Table 5-4).

Measuring the number of cigarettes per day and smoking duration, estimating lifetime exposure, smoking topography, and so forth can provide an effective indicator of exposure that has been associated with harm. However, these measures may be insensitive to changes in risk, are difficult to assess accurately over time, and have not been tested in the context of harm reduction. Also, because there is interindividual variation in the way the body responds to these exposures, such measures might not be sufficiently accurate for new products intended to decrease exposure. Thus, for new products, the relationship of external exposure markers to disease risk might be less predictable. Currently, there is sufficient evidence to show that biomarkers can provide better estimates of risk in the context of exposure, and therefore they will likely be able to provide improved assessments for harm reduction products. However, no single biomarker has been sufficiently validated and related to disease risk that it can be recommended as an intermediate biomarker of cancer risk. Thus, different types of biomarkers along the pathway from internal exposure, biologically effective dose, and potential harm are needed, and additional research is necessary to identify the best combination of markers to be used. Experimental toxicity testing (in vitro and animal models) are not sufficient to support a PREP claim because only validated biomarkers can show that the PREP reduces exposure adequately enough to imply risk reduction. The use of intermediate biomarkers as surrogate risk factors for disease may possibly overestimate the number of people who actually develop disease, because not all early changes in morphology or function progress to disease. On the other hand, it may underestimate if, as

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TABLE 5-4 Biomarkers of Potential Harmful Effects[a,b]

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
Enzymatic induction	Aryl hydrocarbon hydroxylase	No	>30 d	Yes	Yes	No
	CYP1A2	No	NDA	Yes	Yes	No
	DNA repair enzymes	NDA	Yes	Yes	NA	No
	Microarray assays for mRNA expression and proteomics	NDA	NDA	Yes	NA	No
Chromosomal alterations	Chromosomal aberrations	Yes	Yes	Yes	No	No
	Micronuclei	Yes	Yes	Yes	No	No
	Sister chromatid exchanges	Yes	Yes	No	No	No
	Loss of heterozygosity	Yes	Yes	Yes	No	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA-adduct levels	Technically difficult to assess in large epidemiological studies
Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA-adduct levels	Technically difficult to assess in large epidemiological studies
NA	No	NDA	Indicates acquired changes in susceptibility; provides analysis of what is likely to be critical part of carcinogenesis	Technically difficult
NA	No	NDA	Reflects integrated measure of multiple genotypes, provides complex data potentially usable for rapid identification of important risk factors	Difficult to perform; relationship to disease risk is technically difficult to prove; requires extensive laboratory validation; RNA and protein microarray assays are expensive; large-scale studies are needed; refined bioinformatic analysis required
No	No	Yes	Can be done in blood as surrogate tissue. Similar lesions observed in cancer. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; significant lack of specificity and wide overlap between smokers and nonsmokers
No	No	NDA	Facile assay	Lack of specificity
No	No	No	Easy to do in blood as surrogate tissue. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; predictivity for disease risk not established. Association with cancer in case-control studies may have case bias. Significant lack of specificity and wide overlap between smokers and nonsmokers
No	No	NDA	Similar lesions observed in cancer	Technically complex; relationship to cancer risk unknown

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TABLE 5-4 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
	Mutations in reporter genes (*HPRT, GPA*)	Yes	Yes	No	No	No
	Mutational load in target genes (p53, K-ras)	NA	NDA	Yes	No	No
Mitochondrial mutations	Deletions, insertions	NDA	NDA	Yes	No	No
Epigenetic cancer effects	Whole genome methylation	NDA	NDA	Yes	No	No
	Hypermethylation of promoter regions	NDA	NDA	Yes	No	No
Lipids	Blood lipids: HDL, LDL, oxidized LDL, triglycerides	Yes	NDA	Yes	Yes	No
Cardiovascular response	Heart rate, blood pressure	No	Yes	Yes	NA	No
Thrombosis	Bleeding time	No	NDA	Yes	No	No
	Fibrinogen	NDA	NDA	Yes	Yes	No
	Prothrombin time, partial thromboplastin time, plasminogen activator inhibitor, C-reactive protein	Yes	NDA	Yes	Yes	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	No	NDA	Facile assay in blood	Relationship to target tissue or blood unknown
No	No	NDA	Target gene specificity	Very difficult to do in normal tissues
No	No	NDA	Provides corroborative marker	Relationship to disease not established
No	No	No	Facile assay	Relationship to disease unknown
No	No	No	Similar lesions observed in cancers	Technically difficult; relationship to risk unknown
Yes	No	Yes	May be directly related to disease risk	Levels among heavy smokers cannot be distinguished. Wide interindividual variation. Many individuals under medication therapy. Significant confounders exist
NA	No	Yes	Easy to measure; intraindividual differences may be important for the individual	Both interindividual and intraindividual differences are significant. Substantial confounders exist, and many persons are on medications
No	No	No	Minimally invasive	Very nonspecific
Yes	No	NDA	Pathogenically related to disease	Does not distinguish levels of smoking. Nicotine might separately affect these parameters so limited use in persons using NRT
Yes	No	NDA	Leave a fingerprint at the site of their formation	

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TABLE 5-4 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
	Urinary thromboxane and prostacyclins	Yes	No	No	Yes	No
	Platelet activation and survival	Yes	NDA	Yes	No	No
Blood cell parameters	White blood cell counts (i.e., lymphocytes, neutrophils, total counts)	Yes	Yes	Yes	Yes	No
	Hematocrit, hemoglobin, red blood cell mass	Yes	Yes	Yes	No	No
Bronchio-alveolar lavage response	Inflammatory cells, protein, cytokines	Yes	Yes	Yes	No	No
	Neutrophil elastase a1-antiprotease complex	Yes	Yes	Yes	No	No
	α1-antitrypsin	No	No	Yes	Yes	Yes
Inflammatory mediators of response	Leukotrienes	Yes	NDA	No	Yes	No
Pulmonary function tests	FEV1, FVC	Yes	Yes	Yes	No	No
Periodontal disease	Periodontal height	Yes	Yes	Yes	No	No
	Gum bleeding	Yes	Yes	Yes	No	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
Yes	No	Yes	May be markers of platelet-vascular interactions; reflect chronic exposure	Technically difficult. Wide overlap of values due to individual differences in response
No	No	No	Platelet activation in vivo might be pathophysiologically related to cardiac artery thrombosis	Technically difficult to use for large numbers of subjects. Significant number of confounding variables. Smoking increases platelet counts
Yes	No	Yes	Can be a surrogate marker for several processes including atherosclerosis and thrombosis	Relationship to disease uncertain, although alterations in levels are linked epidemiologically to disease. Wide interindividual and intraindividual variation and large number of confounders
No	No	No	Can reflect both cardiac and respiratory disease risk	Insensitive; wide interindividual differences
No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
Yes	Yes	NDA	May be specific to tobacco smoke	Requires invasive test; short half-life
Yes	No	NDA	May be measured in urine, bronchioalveolar lavage, and serum	Substantial number of confounders
No	No	Yes	Widely available	Low sensitivity for mild disease. Decrease in function with aging. Large interindividual variation
No	No	Yes		
No	No	Yes		

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TABLE 5-4 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
Osteoporosis	Fractures	Yes	NDA	NA	No	No
	Bone density	NDA	NDA	Yes	No	No
Skin	Premature wrinkling	Yes	NDA	NA	No	No
Fetal and neonatal effects	Birth weight	Yes	Yes	Yes	No	No
Weight	Weight loss and gain	Yes	Yes	Yes	No	No

NOTE: NA=not applicable; NDA=no data available; FVC=Forced vital capacity; FEV_1=Forced expiratory volume in 1 sec; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

expected, other mechanisms are involved in the disease process that are not reflected by the biomarkers. Biomarkers may also underestimate the incidence of disease since none are necessarily present in all who develop disease. Therefore, the implication of potential benefit from a harm reduction strategy could be an overestimate or an underestimate, but this limitation in the scientific methodology for identifying sufficiently specific biomarkers of risk requires acceptance at the current time.

Previously, the most common way to infer exposure reduction (e.g., through use of low-tar cigarettes) has been via methods that simulate human smoking behavior, such as the Federal Trade Commission (FTC) method. Although they provide a standardized way to assess cigarettes, it is clear that these methods have limited usefulness because people smoke cigarettes differently from the machine, with resultant qualitative and quantitative differences in exposure.

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	No	Yes	Easily measured	Numerous confounders
No	No	Yes		
No	No	NA		Lack of specificity; involves subjective evaluation
No	No	Yes	Data collection is easy	Nonspecific; numerous confounders
No	No	Yes	Both a biomarker for metabolism and an important outcome for some people.	Some people perceive weight loss as a benefit of smoking, despite significant adverse effects associated with smoking

[a]Selected examples; list is not all-inclusive.

[b]References are not provided in this table but can be found in the text of this and disease-related chapters.

[c]Any report related to a disease outcome associated with tobacco where the report is plausible but has not necessarily been replicated.

Biomarkers may be shown to reveal differences in individual susceptibilities and differences in response depending on dose. Thus, biomarkers that measure both complex exposures and single tobacco product constituents are needed and should be assessed for the range of possible human exposures, and those that assess complex exposures should carry a greater weight. Also, some biomarkers or sets of biomarkers should be developed that reflect exposure to many tobacco constituents in order to monitor for the introduction of new hazards from PREPs.

Today, there remain technical limitations to the use of biomarkers. Depending on the harmful effect, surrogate assays that represent effects in target organs may be easier to perform in humans because the target tissues might not be easily accessible. However, if such is the case, the relevance of the surrogate biomarker to the target organ effect should be demonstrated.

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The use of a biomarker for harm reduction assessments should include several qualities including reflection of disease pathogenesis, specificity, and sensitivity. Also, consideration must be given to available harm and harm regression dose-response data, target tissue effects, and validation methods. Each biomarker should be validated for its relationship to exposure and harm, and also as a laboratory assay that provides reliable and reproducible data. Separately, the way interindividual variation in response and smoking behavior affects biomarkers should also be considered.

The assessment of harm and harm reduction should be made through direct human experience, as these products are used by the general population. Most of what is known about harmful tobacco products has resulted from epidemiology and supported by in vitro studies, laboratory animal studies, and human experiments. However, although epidemiological studies can provide the most definitive data about tobacco harm and harm reduction products, the study of diseases with long latency (e.g., cancer, heart disease, COPD) is problematic because such studies often require many years before they provide useful data. Thus, because definitive evidence that a new PREP actually reduces harm will often be unavailable, short-term markers that reflect long-term outcomes are needed. If assessment of the harm reduction potential of a PREP were based only on epidemiological data measuring disease outcome prior to its use by the public, very few if any harm reduction products would be introduced. Importantly, the use of intermediate markers does not replace long-term follow-up and epidemiological surveillance, but it can be a basis for estimating effects before direct evidence from epidemiological studies is available.

Biomarkers of internal exposure, biologically effective dose, or potential harm have been validated to different degrees. It is typically easier to show a relationship between external exposure and biomarkers in the following order: internal exposure, biologically effective dose, and harm. Conversely, it is typically easier to show a relationship between disease outcome and biomarkers in the following order: harm, biologically effective dose, and internal exposure. It might be acceptable to rely on external exposure measurements for considering risk and dose-response, but only with substantial corroborative biomarker data. The best strategy for assessing the claims of risk reduction methods is to have several markers that range from exposure to outcome, one being linked to another, and at least one with which a dose-response risk assessment can be made.

The recommendation that PREPs be assessed by the use of biomarkers should reflect the available data, which show that individual use and response to tobacco products are affected by cultural and heritable traits.

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To achieve the greatest confidence that a PREP will reduce risks for persons who cannot stop smoking, well-validated methods for predicting risk, including external exposure indicators, and the best available biomarker assays should be used.

NICOTINE PHARMACOLOGY (SEE SECTION II, CHAPTER 9)

Nicotine is the addictive component of tobacco products, and the strength of this addiction affects the individual's ability to stop smoking (U.S. DHHS, 1988). Nicotine is also a component of most PREPs, and therefore, evaluation of the harm reduction potential of PREPs requires evaluation of nicotine's relative toxicity, especially during long-term use (see Chapter 4).

Structurally, nicotine is very similar to acetylcholine (Ach) and interacts with specific nicotinic receptors (nAchRs) in the central and peripheral nervous systems. The interaction between nicotine and its receptor affects the release of numerous neurotransmitters and results in upregulation of the nicotinic receptors leading to the physiological, cognitive, and sensory effects associated with tobacco use, addiction, and withdrawal. Nicotine also has well-documented effects on metabolism and on the cardiovascular, gastrointestinal, and hormonal systems (see Chapter 9).

Pharmacological nicotine replacement therapy (NRT) has proven to be a remarkably well-tolerated and effective strategy for many, leading to cessation of cigarette smoking at least in the short- to medium-term (Benowitz et al., 1998; Fiore et al., 2000). Although the experience is much more limited, it is also a potential strategy for reducing the number of cigarettes smoked by smokers who cannot or will not quit (Fagerström et al., 1997; Rennard et al., 1990; Shiffman et al., 1998; Transdermal Nicotine Study Group, 1991).

There are important considerations in evaluating nicotine products for possible tobacco harm reduction. First, nicotine is addictive, and although the daily exposure may be reduced by NRT use, continued usage implies psychological dependence, if not physical addiction. It is arguable whether this should be a concern, given the assumption of an undisputed reduction of risk compared to smoking. However, it would seem reasonable to include surveillance of the dependency potential and abuse liability of each NRT product. Furthermore, the effects of long-term nicotine intake on such factors as drug and alcohol consumption, the progression of coincidental diseases, the impact of aging on cognitive and other physiological functions, and susceptibility to other forms of addictive behavior are largely unknown. For example, observations suggesting that nicotine impairs endothelial function, a property it shares with cigarette smoking,

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raise questions about its effect on atherogenesis during long-term use (Chalon et al., 2000; Gairola and Daugherty, 1999; Sabha et al., 2000). Such an effect may take many years to emerge and highlights the importance of continued postmarketing surveillance of NRT. Although existing data do not suggest that nicotine is carcinogenic in humans, it would be prudent to have continued surveillance of the incidence of cancer among users of NRT.

Studies of long-term nicotine administration on surrogate variables that more closely resemble the mechanism under consideration (e.g., imaging of plaque progression) and attendant studies in animal models seem timely. Increasingly, the application of genomic and proteomic approaches will help clarify the differential effects of smoking and NRT on the expression and translation of genes related to the development of smoking-related diseases. Finally, the understanding of nicotine's effect on inflammation and the immune response is confused and limited (Sopori et al., 1998). More research is needed to clarify its effects on cytokine generation, the formation of nitric oxide (NO) and eicosanoids, and oxidative injury. Research should continue to explore other potential therapeutic efficacies of NRT, including for ulcerative colitis, analgesia, weight reduction, Parkinson's disease, and cognitive disorders associated with aging and schizophrenia.

The continued use of NRT in conjunction with continued, albeit reduced, smoking prompts additional questions. For example, the constituents of cigarette smoke that mediate tissue injury are not all precisely known, and it is also not known if modulating the coincident nicotine level might influence their absorption, metabolic disposition, mechanism of action, or elimination. Design of such studies will rely upon the development of more refined and tractable methodology to investigate the in vivo kinetics and dynamics of other constituents of cigarette smoke and their interactions with nicotine.

Finally, although ethnicity has been shown to be relevant (Sabha et al., 2000), the factors that determine interindividual differences in nicotine efficacy, safety, and addictive potential remain largely unexplored. Particular attention might be paid to genetic variation in proteins relevant to nicotine pharmacokinetics and dynamics and their interaction with environmental variables. As with other drugs, one anticipates increasing individualization of nicotine dosage and/or delivery when given as a therapeutic agent. Insight into the interaction of genetic and environmental factors which influence initiation (Gynther et al., 1999; Heath et al., 1999) of cigarette smoking, latency until the practice becomes habitual (Stallings et al., 1999), and the quantity that is then smoked (Koopmans et al., 1999) has been increasing. Clarification of how these factors interact is also likely to afford insights of value in predicting the individual likelihood

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of response to the use NRT as a strategy for quitting or reducing tobacco exposure.

CANCER (SEE SECTION II, CHAPTER 12)

Feasibility of Harm Reduction in Therapy

There are sufficient laboratory and human data to suggest that harm reduction for cancer might be an achievable goal for persons who cannot stop smoking. There is evidence of decreased risk of cancer for persons who abstain from smoking, and there is strong evidence of a positive relationship between smoking and risk of developing cancer. The risk varies by the different tobacco products used and how they are used. Clearly, abstinence from smoking is the most effective method for reducing cancer risk, and the cancer risk to former smokers is the lowest-level risk that might occur from the use of any PREP. Importantly, it must be recognized that the use of any harm reduction product will likely increase the risk of cancer at some level as long as there is exposure to tobacco carcinogens, in contrast to abstinence, which stops exposure to all tobacco constituents. Nonetheless, reduction in exposure to tobacco smoke and tobacco products to the lowest possible levels may provide some benefit to individual users and to the general population. However, there are insufficient data from which to conclude how much reduction in exposure would yield a measurable benefit and which individuals would benefit. Currently, it seems likely that methods that reduce exposure to tobacco constituents to the greatest extent would likely provide the greatest benefit, but this remains to be proven.

A systematic and thorough assessment of PREPs and cancer risk will require analysis of data obtained from well-designed laboratory and human studies. In laboratory animals, the shape of the dose-response curves differs for different tobacco constituents, indicating that the dose-response relationship of tobacco smoke is complex.

Dose-Response Relationship

In humans, the carcinogenic response increases most around five cigarettes per day, and there is relatively little increase in carcinogenicity above 20 cigarettes a day. However, while there are sufficient data to conclude that a dose-response relationship exists for the use of tobacco products and cancer risk, the precise dose-response relationship is really not known in part because exposure is not accurately measured without considering actual smoking behavior. There is some evidence to indicate that when internal exposure is considered through biomarkers, the shape

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of the curve follows a quadratic equation, indicating a greater benefit in exposure reduction for persons who smoke more. Thus, data are insufficient to predict the harm reducing effect of a change from any intensity of smoking to a PREP. There are sufficient data to suggest that dose-response relationships differ as a function of gender, race, age, and ethnicity, although the actual risk levels have not been sufficiently defined to draw definitive conclusions about risks among groups. Based on these types of data and possible modifiers of cancer risk (e.g., genetic susceptibilities, diet, lifestyle, occupation), it is likely that PREPs would affect risk differently in different people and not at all in some.

There is no evidence of a threshold below which tobacco smoking does not increase cancer risk. This conclusion is consistent with the fact that there are many carcinogens in tobacco smoke, and the aggregate might increase risk at any level. Modeling for low-dose exposures indicates that there is an increased risk with less than one cigarette per day. Thus, persons who initiate smoking with harm reduction products that contain tobacco would be likely to have an increased risk for cancer, and there is unlikely to be a "safe" cigarette. Former smokers who resume smoking with such products would increase their risk further.

Regression of risk using PREPs might eventually bring a smoker to a risk equal to some lower level of lifetime exposure to conventional products. However, there are insufficient data to validate this assumption or indicate that a decrease in risk would be measurable for some or all smokers. There are insufficient data to indicate the shape of the curve for regression of risk for any PREP.

The data are sufficient to conclude, with some caveats, that filtered cigarettes compared to nonfiltered cigarettes pose a lower risk of lung cancer and possibly other cancers. The caveats are that this occurs only in persons who do not substantially increase the number of cigarettes they smoke per day or otherwise compensate by their smoking behavior for lower levels of nicotine. Also, these studies may be confounded by diet, lifestyle, or other characteristics of people who use filtered cigarettes, which might be different in smokers of filtered compared to nonfiltered cigarettes. The available data are suggestive, but not sufficient, to conclude that smokers of low-tar cigarettes have a lower cancer risk compared to smokers of higher-tar cigarettes, with the same caveats as for the filter smoking studies. However, there are insufficient data to assess the differences in risk for ultralow-, low-, and high-tar cigarettes that are filtered. These cigarettes only became available more recently, so there has not been a long enough latency period in the general population to assess them until recently. There are insufficient data to adequately consider how risk changes when switching types of cigarettes.

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This report has not reviewed potential cancer risks due to fibers released from cigarette filters or tobacco additives, because it is thought that the risk of these exposures are substantially lower than the risk from the constituents of tobacco smoke. However, there are no existing data to prove this assumption. Importantly, as harm reduction products are developed that substantially reduce exposure to tobacco constituents, the relative role of fibers and additives in carcinogenesis might become more important. Thus, fiber and additive exposure should be considered when assessing PREPs.

Utility in a Preclinical Setting

There are some experimental models (e.g., in vitro cell cultures, laboratory animals) that may be useful for the assessment of the carcinogenicity of tobacco-related PREPs. Although there are many reasonable models with which to assess individual tobacco smoke products, better models are needed for assessing exposures to complex mixtures. Such studies are not alone sufficient to support claims of potential harm reduction. No claim of potential harm reduction should be allowed without adequate human clinical and epidemiological studies. In vitro and animal studies, however, are very important for (1) determining those products that are not likely to result in measurable harm reduction (e.g., if the product results in exposures that increase genotoxicity, then there would be less enthusiasm for it and so should not be tested in a human clinical study and should not be introduced into the marketplace); (2) identifying unforeseen reactions (e.g., if a product reduces exposure but does not decrease tumors), then there might be some constituent or combination of constituents that is either new or more important than those changed in the product); (3) providing supportive evidence for the use of a particular bioassay in humans (e.g., if a biomarker predicts cancer risk in experimental animals); and 4) assessing the dose-response and the shape of the regression of risk for the PREP as exposure is reduced, although the data should be considered qualitative or semiquantitative and cannot be extrapolated directly to human smoking risk. Both in vitro cell culture and experimental animal studies should be used in assessing PREPs, where both can assess genotoxic and nongenotoxic end points, and chronic animal bioassays are needed to assess the end point of cancer risk. It is beyond the scope of the committee to recommend the specific panel of assays, but such a panel will need to be developed. Also, these studies should assess changes due to both specific carcinogens and to complex mixtures, where the latter should be mandatory.

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Clinical Assessment of Tobacco-Related Disease and Biomarkers of Tobacco-Related Disease

There is sufficient evidence to conclude that human experimental studies and short-term clinical studies provide evidence of the harmful effects of tobacco products. Thus, such studies can be used in assessing harm reduction. These studies, through the use of biomarkers and surrogate indicators of cancer risk, can evaluate the manipulation of carcinogens and nicotine to reduce exposures and how these changes might affect smoking behavior, metabolic activation, enzymatic induction, conjugation, excretion, biologically effective doses (or their validated surrogates), and biomarkers of potential harm. Separately, these studies can assess differences in risk and provide evidence for modifying effects due to genetic susceptibilities, diet, lifestyle, occupation, and so forth. However, at the current time, no single biomarker or panel of biomarkers can be considered sufficient indicators of cancer risk by themselves, in part because most have not been sufficiently validated. New technologies are offering new opportunities for biomarkers. Thus, a panel of experts will be needed to devise a set of biomarkers that reflect different exposures, biologically effective doses, and pathways for potential harm.

It is clearly possible to assess the effects of PREPs on cancer as the ultimate outcome, and only such studies can provide definitive evidence for the success of a product. However, the long latency for cancer makes these studies infeasible for making such claims today or in the near future. This relatively long latency period for cancer and the slower decline, probably years or decades, in risk from exposure reduction compared to cardiovascular disease and other tobacco-related diseases will have an impact not only on the time frame of PREP assessment and but also on the health effects experienced by and apparent to the individual. Preneoplastic lesions or the identification of harmful effects in single cells might be used as indicators for the carcinogenetic pathway, but the technology to identify these in the general population or large epidemiological studies is not yet available. In such studies, the characterization of smoking history and behavior is well validated for recent exposures but less accurate for assessing lifetime exposure. Also, self-reported smoking history is insufficient to adequately assess risk in the context of PREP assessments, so biomarkers also are needed to assess exposure, biologically effective doses, and potential harm.

Currently, the best approach to assessing PREPs and cancer risk is to focus on lung cancer, because this is the most common cancer and so will provide studies with the greatest statistical power. However, data are sufficient to conclude that there is a risk that the widespread use of PREPs will shift the burden of cancer in the population from one type to another or from cancer to a different disease. Thus, a particular cancer type cannot

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be the sole indicator for the success of a PREP, and other cancers, diseases, and overall mortality must be evaluated as well.

Many studies of nicotine suggest that nicotine is unlikely to be a cancer-causing agent in humans or, at worst, that its carcinogenicity would be trivial compared to that of other components of tobacco. The consideration of nicotine as a carcinogenic agent, if at all, is trivial compared to the risk of other tobacco constituents.

Some smokeless tobacco products increase the risk of oral cavity cancers, and a dose-response relationship exists. However, the overall risk is lower than for cigarette smoking, and some products, such as Swedish snus, may have no increased risk. It may be considered that such products could be used as PREPs for persons addicted to nicotine, but these products should undergo testing as PREPs using the guidelines and research agenda contained herein.

The effects of PREPs on cancer risk from environmental tobacco smoke (ETS) are uncertain because of the difficulties in measuring reductions in exposure. Also, although there is clearly an increased risk of lung cancer from ETS, the determination of changes in risk from the use of PREPs will require studies of large numbers of people, and smoking is currently in this country prohibited in many places where ETS might have occurred.

CARDIOVASCULAR DISEASE (SEE SECTION II, CHAPTER 13)

Dose-Response Relationship

Highly informative information on the existence of a dose-response relationship between cigarette exposure and cardiovascular risk comes from many studies such as the CPS-II (Thun et al., 1997) and Harvard Nurses' Health Studies (Kawachi et al., 1997). In both instances, there is a relationship between the number of cigarettes smoked and the incidence of cardiovascular events. This is illustrated for the incidence of myocardial infarction and stroke. In both cases, the most striking difference is between nonsmokers and individuals who smoke the least number of cigarettes recorded. The relationship becomes somewhat less pronounced as the number of cigarettes smoked per day increases. Interestingly, ex-smokers tend to occupy a space intermediate between nonsmokers and those with the lowest daily smoking frequency.

This dose-response curve prompts several considerations. First, there is no persuasive evidence of a threshold below that a cardiovascular risk does not exist. This observation affirms the primary objective of encouraging smokers to quit completely. Second, the shallow dose-response relationship, with the impression of a plateau, accords with similar observations relating the number of cigarettes smoked and measurements of

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systemic bioavailability, such as nicotine and cotinine. The same is true of the relationship with CO (Gori and Lynch, 1985). Although this may represent saturation kinetics of nicotine or CO, the most likely explanation is compensation for lower numbers of cigarettes smoked. Thus, the smoker titrates nicotine delivery toward a range of convergence that is reflected by the measurement of nicotine delivery, which in turn, may reflect dose-dependent convergence of the delivery of additional toxic, but unmeasured, constituents of cigarette smoke. The relative contribution of distinct constituents of cigarette smoke to smoking-related cardiovascular morbidity and mortality is unknown. In this regard, the available information is incomplete regarding any differences between the dose-response relationship of filter or low-tar versus high-tar or unfiltered cigarettes.

Feasibility of Harm Reduction in Therapy

There are no data that are directly informative on the issue of harm reduction. Thus, although a dose-response relationship exists for cardiovascular and cerebrovascular events, we do not know if reducing the number of cigarettes smoked results in a quantitative reduction in the risk of these events. However, the intuitively appealing prospect that this is indeed the case is supported by evidence from individuals who quit smoking. Thus, quitting results in a time-dependent reduction in the incidence of myocardial infarction and stroke. The latter is most nicely illustrated by data relating to subarachnoid hemorrhage, which was significantly elevated in women smokers in the Nurses' Health Study. In addition to evidence from such unequivocal clinical events, there is evidence that the increase in biomarkers of oxidant stress, platelet activation, and inflammation (Benowitz et al., 1993), all of potential mechanistic relevance to tobacco-related cardiovascular injury, rapidly falls toward the normal range on quitting cigarettes. The offset kinetics of more functional surrogates, such as endothelial dysfunction, remain to be determined in smokers. In summary, the data from quitters encourage the prospect that a graded reduction in cardiovascular risk and in biomarkers of this risk may accompany a reduction in the number of cigarettes smoked in pursuit of a harm reduction strategy. It is possible, indeed likely, that individuals and perhaps populations, differ in their susceptibility to tobacco-induced cardiovascular risk and, indeed, in their potential benefit from a harm reduction strategy. Data from quitting studies indicate a considerable variance in the rate of offset of risk, which declines with time. No data are available to address such issues across ethnic groups or gender. Acquisition of such information and research on the environmental and genetic factors that condition interindividual variability in exposure-risk relationships are necessary.

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Utility in a Preclinical Setting

Studies in cell culture and model systems can afford much needed information on tobacco-related cardiovascular risk. These might include a profiling of gene expression and translation in cardiovascular tissues in response to cigarette smoke, constituents of smoke, and potential harm reduction substituents. These might identify proteins of potential functional relevance to the transduction of cardiovascular risk. Such studies might be coupled with gene inactivation and overexpression studies to address the role of these proteins in vivo. Similarly, studies of exposure to cigarette smoke or to discrete constituents of smoke might be deployed to investigate effects on atherosclerosis progression, susceptibility to vascular injury, thrombotic stimuli, graft rejection, cardiovascular development, or endothelial dysfunction in model systems such as mice. Studies of cardiovascular genomics and ultimately proteomics can also be extended to model systems to investigate gene expression and translation in response to exposure to tobacco-related products in vivo. These observations may, in turn, be related to the pattern of gene expression and translation in cardiovascular tissues obtained from cigarette smokers.

Biomarkers of Tobacco-Related Disease

The predominant mechanisms by which cigarette smoking induces cardiovascular injury is unknown. However, small studies in smokers of potentially relevant biomarkers of platelet and vascular activation, lipid peroxidation, and inflammation afford evidence of a dose-response relationship and a decline on quitting. There is even evidence of a signal in individuals exposed to ETS in the case of some of these markers. More mechanism-based clinical studies are required to confirm and expand these findings. Where possible, these should be related to surrogate measurements of cardiovascular function, such as hemodynamics, flow-mediated endothelial function and estimates of plaque progression by ultrasound or electron-beam computerized tomography (EBCT). Furthermore, biomarker studies can usefully be integrated into many studies in model systems as well as studies of clinical outcome to afford their ultimate validation.

Clinical Assessment of Tobacco-Related Disease

The time course of offset of myocardial infarction and stroke in people who stop smoking suggests that cardiovascular disease represents a tractable scenario in which one might evaluate harm reduction strategies. Clearly, the health effects experienced by the individual and the assessment

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of the impact of such events can occur in a more reasonable time frame than from cancer in which declines in risk from tobacco exposure reduction may only be apparent after years or decades.

NONNEOPLASTIC RESPIRATORY DISEASE (SEE SECTION II, CHAPTER 14)

In evaluating harm reduction strategies for tobacco-related lung disease, three major nonneoplastic respiratory diseases linked to cigarette smoking are considered: COPD, asthma, and respiratory infections. Respiratory diseases are major tobacco-related illnesses, and there is a clear need to mitigate the harmful effects of exposure to both mainstream and secondary tobacco smoke. It is generally accepted that cessation of smoking slows or stops the progression of the lung diseases related to smoking and it is plausible that decreasing smoking will reduce the severity of chronic lung diseases and the incidence of respiratory infections. However, there is no adequate scientific evidence to support this because the effects of reduced smoking on harm reduction have not been extensively studied in man.

Dose-Response Relationship

There is a need to determine dose-response relationships more precisely and to develop biomarkers of respiratory disease. Rational design of studies to assess harm reduction requires knowledge of the dose-response relationship. At present, such data for respiratory diseases are limited and of uncertain quality. Study design would also incorporate biomarkers of disease, and the testing of current and new biomarkers might be done concurrently in the models and populations studied for dose-effects. The Cancer Prevention Studies I and II, large-scale prospective studies, however, do suggest a direct dose-response relationship between cigarettes smoked per day and mortality rates from COPD (NIH, 1996, 1997), indicating that decreasing the number of cigarettes smoked may lead to fewer deaths from COPD.

Biomarkers of Tobacco-Related Disease

There are currently no specific molecular biomarkers of the nonneoplastic respiratory diseases due to smoking tobacco products. No unique molecular or genetic defect specific for tobacco-related respiratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory

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diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture of tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke. The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing. These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on lungs (U.S. DHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes for clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Ichinose et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the greatest obstacle for rational development of a specific biomarker is the lack of fundamental information on mechanisms of how tobacco smoke exposure causes specific respiratory diseases.

The availability of dose-response data and validated biomarkers may improve the design of contemplated intervention studies and allow greater confidence in the results. However, the time frame for generating dose-response data and testing biomarkers is uncertain. The inclusion of dose-response considerations and biomarkers in the design of clinical trials on reduction of harm from respiratory diseases must also be validated.

Clinical Assessment of Tobacco-Related Disease

An alternative is to proceed with interventional trials based on current knowledge if there are uncertainties about the added value of dose-response data or untested biomarkers to study design. As an example, an intervention study of the effect of smoking reduction on COPD could be considered, similar in design to the Lung Health Study (Anthonisen et al., 1994), a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 (forced expiratory volume at 1 second) in middle-aged smokers with mild COPD. Another approach is to conduct a trial using a low-tar and moderate-nicotine product made available from a noncommercial source to avoid product endorsement issues.

Design of population studies for harm reduction of major respiratory diseases is challenging because of uncertainties about effectiveness and long-term compliance with harm reduction interventions. Reduction in the burden of tobacco-related respiratory diseases through harm reduction strategies should be a major priority for the nation's public health.

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REPRODUCTIVE AND DEVELOPMENTAL EFFECTS (SEE SECTION II, CHAPTER 15)

Feasibility of Harm Reduction in Therapy

Cigarette smoking is a major cause of fetal and infant morbidity and mortality (U.S. DHHS, 1988, 1990; Kleinman et al., 1988). This is particularly true for the associations with low-birthweight and its consequences, as well as preterm delivery and SIDS (CDC, 2000; Leach et al., 1999; Shah and Bracken, 2000; U.S. DHHS, 1983). For several important adverse reproductive effects of maternal smoking, a decrease in smoking has been found to be associated with a decrease in risks to the fetus and infant (Li et al., 1993; Hebel et al., 1988). The greatest benefit, of course, comes from smoking cessation. However, the smoking cessation rate for women smokers who become pregnant is very low and remain comparable to those in the general population, despite knowledge of the harmful effects of smoking and personal experience with adverse fetal and infant conditions. Moreover, as current rates of smoking increase slowly among adolescent women, these adverse effects associated with tobacco smoke exposure while pregnant are likely to worsen.

Dose-Response Relationship

On average, infants exposed to maternal smoking in utero are 200 grams lighter and 1.4 cm shorter than those unexposed (Wang et al., 1997). A strong dose-response relationship has been supported in numerous studies (Li et al., 1993),and a decrease in dose (number of cigarettes) in controlled studies has led to increased birthweights in a predictable pattern (Wang et al., 1997). What is known about the mechanism of effect of cigarette smoke on the fetus suggests that several agents in tobacco smoke contribute to the adverse effects. There is evidence that CO plays a major role in growth retardation through increased tissue hypoxia (Benowitz et al., 2000). Nicotine has also been thought to play a role through increasing vasoconstriction and decreasing perfusion through the placenta.

Although nicotine replacement products and buproprion are currently not approved by the Food and Drug Administration for use by pregnant women, the Agency for Healthcare Research and Quality's (AHCRQ) Clinical Practice Guidelines for Treating Tobacco Use and Dependence (Fiore et al., 2000) recommend that "Pharmacotherapy should be considered when a pregnant woman is otherwise unable to quit, and when the likelihood of quitting, with its potential benefits, outweighs the risks of the pharmacotherapy and potential continued smoking". It is generally thought that NRT can reasonably be used with pregnant patients

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if prior behavioral modifications have failed and the patient continues to smoke at least 10-15 cigarettes per day (ACOG, 1997). There are no data regarding the efficacy of potential reduced-exposure products (PREPs) during pregnancy, but there is the presumption that the tobacco-related PREPs are likely to have adverse effects at some level and that until further evidence is produced, existing guidelines concerning pharmacologic PREPs still pertain.

Clinical Assessment of Tobacco-Related Disease and Utility in a Preclinical Setting

To practically assess the health effects of PREPs, reliable measures of health outcomes that can be utilized in a relatively short time are desired. Among the reproductive outcomes of maternal smoking, intrauterine growth retardation resulting in low-birthweight babies has been studied extensively, and a large body of evidence has supported a causal link with cigarette smoke exposure. The committee recommends, based on currently available scientific knowledge, that fetal birthweight be used as a reliable outcome measure for evaluating the harm reduction potential of specific PREPs. Study designs should include repeated cohort or case-control studies of pregnant women, with an appropriate distribution of exposures to both PREPs and conventional products, and suitable contrast groups. Concomitant, coordinated toxicological studies should be undertaken to provide biological correlations with clinical outcomes. Such outcomes as fetal birth weight and the incidence of other reproductive and developmental health outcomes (e.g., fertility outcomes, placental complications, gestational age at birth, incidence of sudden infant death syndrome [SIDS], spontaneous abortions) should be considered primary objects of study in order to assess the harm reduction potential of specific PREPs.

Findings in pregnant women exposed to PREPs may have value beyond maternal or fetal outcomes. The nature of adverse effects derived from PREP exposure will likely be determined much sooner in this case than findings on chronic disease outcomes in humans, such as various cancers and cardiovascular disease. Should adverse findings become apparent, there may be substantial implications for chronic illnesses among older adults, and coordinated pathogenic studies might allow conclusions on new tobacco product outcomes in advance of studies exploring longer "incubation periods."

The committee recommends that further basic research be undertaken to elucidate the components of cigarette smoke that are primarily responsible for adverse health outcomes. In order to evaluate the safety of many PREPs, it is important to understand the toxicity of specific smoke

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components, especially nicotine and CO, on the pathogenesis of intrauterine growth retardation, spontaneous abortion, and other health outcomes. In addition, a better understanding of the risks of bupropion SR use by pregnant women (i.e., seizure risk) and the teratogenic effects of nicotine on the central nervous system (CNS) is needed for adequate risk-benefit analysis of the harm reduction potential of these products.

Surveillance of Tobacco Use Patterns Among Pregnant Women

Central to understanding exposure to tobacco products is continuous population information on usage patterns among pregnant women. This may not be attainable by general population survey methods because of inadequate sample sizes and insufficient representation of various geographic or demographic groups or of the earliest stages of pregnancy. There is a need for surveys devoted specifically to pregnant women in all stages of gestation, irrespective of the receipt of medical care. Survey content should include other known or putative causes of adverse maternal or fetal outcomes, as well as detailed product types and usage patterns. Recommendations for general population surveillance can be found in Chapter 6 of this report.

Biochemical and toxicological exposure measures should be a routine part of surveillance for exposure to conventional products as well as PREPs. These will be necessary to conduct more precise, coordinated toxicological studies and also to assess actual exposure rates more accurately. For example, dose may be measured by maternal serum and urine cotinine levels, which have shown reliable correlations with maternal, and consequently fetal, tobacco smoke exposure. Self-reported data have been found unreliable, since pregnant women tend to underreport tobacco use because of the stigma attached to smoking. Also, self-reports do not adequately account for differences in depth and frequency of puffs among smokers.

OTHER HEALTH EFFECTS (SEE SECTION II, CHAPTER 16)

Feasibility of Harm Reduction in Therapy

Several important diseases and conditions of adults, in addition to cardiovascular diseases, chronic obstructive lung disease and various cancers, have been associated with tobacco use, including—but not limited to—peptic ulcer disease, poor wound healing, inflammatory bowel disease, rheumatoid arthritis, oral disease, dementia, osteoporosis, ocular disease, diabetes, dermatological disease, schizophrenia, and depression (see Chapter 16). Some of these associations are supported by substantial

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scientific evidence, and a causal linkage is likely. These illnesses must ultimately be subjected to the same evaluation of changing risks and outcomes associated with PREPs, because these are common and clinically important conditions, even if they are not as often fatal as cancer, cardiovascular disease or pulmonary disease. Further, each of the conditions for which the association with tobacco use is substantial also offers the opportunity to address pathogenic mechanisms related to the varying constituents of PREPs, as well as the impact on disease incidence of concomitant behaviors and exposures such as alcohol use, various dietary elements, and certain medications.

Utility of Preclinical Studies and Short-term Indicators of Clinical Harm Reduction

Some of the conditions reviewed in this chapter may be applied as indicators of the general biological effects of new tobacco products. For example, cigarette smoking has been consistently found to be an independent risk factor for an adverse clinical course of both peptic ulcer disease and wound healing. The effects of smoking on ulcer formation and healing have been clearly described clinically and in animal models (Ma et al., 1999). Peptic ulcers have been found to be larger, slower to heal, and more likely to recur among smokers and to exhibit clinically improved healing upon cessation (Tatsuta et al., 1987). Surgical and traumatic wounds heal more slowly among cigarette smokers (Kwaitkowski et al., 1996; Mosely et al., 1978). The committee recommends that rigorous clinical studies be designed and executed to determine whether variations in ulcer and wound-healing rates are related to various categories of tobacco products, including those with claims of harm reduction. This may offer the opportunity to define some clinical outcomes that have clinical relevance in their own right and to identify potential indicators of harm alteration much sooner after the introduction of PREPs than would be possible when evaluating heart disease and cancer.

Other candidate diseases for such evaluation might include periodontal disease (Bergstrom, 2000; Haber, 1994), Crohn's disease (Rhodes and Thomas; 1994), and rheumatoid arthritis (Uhlig et al., 1999). Here the outcomes to assess would be the effect of various conventional tobacco products and PREPs on the natural history of these conditions, including intermittancy, progression or regression, and longitudinally collected biomarkers of disease severity. As noted above, PREPs that alter the history and outcomes of these conditions could be further evaluated for specific constituent exposures associated with this altered history. This may lead to a more refined understanding of pathogenic mechanisms as well.

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Clinical and basic research on intermediate clinical outcomes is also needed. For example, as noted in this chapter, the risk of osteoporosis has also been strongly linked to cigarette smoking. In controlled observational studies, bone mineral density has been found to be significantly lower among cigarette smokers, which contributes to a greater risk of osteoporotic fractures among older populations. While the effects of smoking on fracture rates may take a few decades or longer to detect, it is possible that surveillance of bone mineral density among those using PREPs and conventional products may be informative in a shorter time period and, thus, serve to detect important outcomes over an interval in which tobacco policy and clinical preventive interventions may have their greatest effects.

Surveillance

The committee recommends that selected conditions, as reviewed in this chapter, be part of a comprehensive, population-based surveillance program, outlined in Chapter 6. This will allow determination of the relationship between the use of PREPs and of trends in occurrence for these tobacco-related conditions and assessment on a national basis of whether changes in tobacco product use have an effect on these important health problems. Based on these surveillance findings, more specific population, clinical, and basic research studies can be directed to evaluate PREPs to pursue causal mechanisms and to suggest more effective interventions.

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