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The Expansion of Tobacco and Its Effect on Cigarette Mainstream Smoke Properties*

by

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SUMMARY

For nearly four decades, the expansion of tobacco has been recognized as one of eight technologies significant in the design of a "less hazardous" cigarette. The data previously presented at scientific conferences and/or published in several scientific monographs and journals on the effect of the expansion of tobacco on the composition and biological properties of the mainstream smoke from cigarettes containing it are summarized. In addition, previously unpublished data on the same subjects are presented in considerable detail. Included are 1) the effect of tobacco expansion on the yields of total particulate matter (TPM), nicotine, and several hundred components of cigarette mainstream smoke from control tobacco cigarettes vs. expanded tobacco cigarettes; 2) the changes in mainstream smoke yields of total particulate matter, nicotine, and specific smoke components produced by inclusion of various levels of expanded tobacco in a cigarette blend; and 3) the changes in composition of expanded tobacco. In the latter study, the decrease in levels of numerous significant flavorful components of the tobacco produced by expansion provides the need for inclusion of such compounds in flavor formulations. In study 2), the reductions in per cigarette yields of total particulate matter, nicotine, and several components of concern were determined and confirmed the significance of tobacco expansion as a cigarette design technology to produce what was originally defined as a "less hazardous" cigarette but more recently as a "potential reduced exposure product" (PREP). [Beitr. Tabakforsch. Int. 22 (2007) 317–345]

ZUSAMMENFASSUNG

Seit nahezu vier Jahrzehnten gilt die Expandierung des Tabaks als eine der acht Technologien zur Entwicklung einer „weniger schädlichen Zigarette". Die auf wissenschaftlichen Kongressen präsentierten und/oder in mehreren wissenschaftlichen Monographien und Zeitschriften veröffentlichten Daten über die Auswirkung der Tabakexpansion auf die Zusammensetzung und die biologischen Eigenschaften des Hauptstromrauchs von Zigaretten werden beschrieben. Zusätzlich werden unveröffentlichte, frühere Daten zur gleichen Thematik ausführlich dargestellt. Folgende Faktoren werden berücksichtigt: 1) Die Auswirkung der Tabakexpansion auf die Ausbeute an Gesamtpartikelmasse, Nikotin und mehrere Hundert Inhaltsstoffe des Hauptstromrauchs von Kontrollzigaretten im Vergleich zu Zigaretten mit Blähtabak; 2) Veränderungen in der Ausbeute an Gesamtpartikelmasse, Nikotin und spezifischen Rauchkomponenten des Hauptstromrauchs, die durch Zugabe verschiedener Mengen von expandiertem Tabak zur Tabakmischung induziert werden; 3) Veränderungen in der Zusammensetzung des Tabaks durch Expansion. In letzterer Untersuchung zeigt die Abnahme der Konzentrationen einer Vielzahl bedeutender Geschmackskomponenten des Tabaks durch die Expansion die Notwendigkeit, diese Substanzen zu Aromatisierungsmischungen hinzuzufügen. In der Untersuchung 2) wird die Abnahme des Ertrags, der Gesamtpartikelmasse, des Nikotins und verschiedener relevanter Verbindungen pro Zigarette bestimmt. Die Ergebnisse bestätigen die Bedeutung der Tabakexpansion für die Entwicklung einer – wie früher definiert – „weniger schädlichen Zigarette", heutzutage bezeichnet als PREP (potential reduced exposure product). [Beitr. Tabakforsch. Int. 22 (2007) 317–345]

RESUME

Depuis presque quatre décennies, l'expansion du tabac a été reconnue comme l'une des huit technologies de conception d'une cigarette « moins dangereuse ». Cet article passe en revue les données présentées lors de conférences scientifi-

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ques et/ou publiées dans des monographies et des revues scientifiques sur l'effet de l'expansion du tabac sur la composition et les propriétés biologiques de la fumée du courant principal de cigarette. De plus, cette revue rapporte en détail les résultats d'études non publiées jusqu'à présent. Celles-ci impliquent : 1) l'effet de l'expansion du tabac sur le rendement en matière particulaire totale, nicotine, et plusieurs centaines de composées de la fumée principale de cigarettes confectionnées avec du tabac expansé par rapport aux cigarettes conventionnelles. 2) Les changements dans les rendements en matière particulaire totale, nicotine et composants spécifiques de la fumée en fonction du taux de tabac expansé dans le mélange. 3) Les changements dans la composition du tabac en fonction de l'expansion. Dans cette dernière étude, la diminution de la teneur en composants aromatiques du tabac provoquée par l'expansion a montré la nécessité d'apporter de tels composants dans les formulations aromatiques. Dans l'étude 2), les diminutions du rendement par cigarette en matière particulaire totale, nicotine et plusieurs composée ont été déterminées et ont souligné l'importance de l'expansion du tabac comme technologie de conception d'une cigarette d'abord nommé « moins dangereuse » mais plus récemment nommé « produit d'exposition potentiellement réduit ». [Beitr. Tabakforsch. Int. 22 (2007) 317–345]

INTRODUCTION

In the design of a "less hazardous" cigarette, many approaches were investigated from the mid-1950s to date. These design technologies were listed and discussed in the mid-1960s by WYNDER and HOFFMANN (1, 2) as possible methods to reduce the toxicants in cigarette mainstream smoke (MSS). More recently RODGMAN (3) and RODGMAN and GREEN (4) summarized the several dozen technologies investigated by Tobacco Industry and non-Industry investigators, a list eventually reduced to the eight technologies [see Table 15 in RODGMAN and GREEN (4)] subsequently considered significant.

Their chronological impact on sales-weighted cigarette MSS Federal Trade Commission (FTC) 'tar' and nicotine deliveries has been noted frequently [cf. Figure 3 in RODGMAN (3)]. By the early 1960s, several cigarette design technologies developed by the Tobacco Industry and used in commercial products were categorized as significant in their contribution to a "less hazardous" cigarette (5). Ultimately, the initial four design technologies [tobacco blend, effective and efficient filtration, reconstituted tobacco sheet (RTS), air dilution via cigarette paper porosity] were increased to six (filter-tip additives, paper additives) and then to eight (expanded tobacco, air dilution via filter-tip perforation). As the additional significant technologies were developed, they were used in concert to different degrees and incorporated into commercial products. The eight design technologies may be used in concert and to different degrees, thus enabling the design of consumer-acceptable cigarettes with MSS FTC 'tar' yields ranging from 1 to 40 mg/cig and MSS nicotine yields ranging from 0.1 to 3.0 mg/cig. Their significance was eventually recognized in "less hazardous" cigarette design by the National Cancer Institute (NCI) during its program on the design of a "less hazardous" cigarette (6, 7, 8) and by the US Surgeon General in his annual reports on smoking and health (9, 10). The commendations also continued.

Throughout this account of the study of the effect of expansion on tobacco and smoke composition, the term "less hazardous" is used frequently to describe the performance of cigarettes, the design of which included one or more of the eight cigarette design technologies repeatedly commended for its contribution to a "less hazardous" cigarette [see Table 15 in (4)]. The term "less hazardous" or "less harmful" concerning a cigarette was defined in the early 1960s. Subsequently accepted by the World Conference on Smoking and Health, NCI, and others, the term "less hazardous" or "less harmful" was much used to describe such projects as the World Conference on Smoking and Health's 1967 workshop entitled "Toward a less harmful cigarette", subsequently published as an NCI monograph edited by WYNDER and HOFFMANN (11). In the more than a decade-long, multi-million dollar NCI Smoking and Health Program directed toward the design of a less hazardous cigarette, each of the numerous NCI published monographs describing the results of the program included the term "less hazardous cigarette" in its title (6, 7, 8). While the term "less hazardous cigarette" does not appear in the title of a sixth NCI monograph on its "less hazardous" cigarette project, it is used repeatedly throughout the Foreword, Summary, and Introduction of the monograph on filter-tipped cigarettes(12). Health agency personnel, some of whom were involved in proposing the definition of the "less hazardous" cigarette, not only were still using the term in 1980 (13) but used it as recently as 2001 (14). After more than three decades of use, the term "less hazardous" cigarette was criticized as inadequate. Some investigators have subsequently replaced the term "less hazardous" cigarette with the term "potential reduced exposure product' (PREP). If the reader is so inclined, he or she may substitute the term PREP for "less hazardous" cigarette throughout the reading of this article.

It should be remembered that the eight cigarette design technologies subsequently classified as significant by NCI, US Surgeon Generals, and other investigators [see Table 15 in (4)] on the basis of the 10-year NCI Smoking and Health Program on the "less hazardous" cigarette had been incorporated into one or more US commercial cigarette products not only prior to the first meeting of the Tobacco Working Group formed in 1968 for the NCI program but also prior to the first experiments conducted in the NCI program. In other words, from 1968 to 1978, not a single new design technology was generated in the NCI Smoking and Health Program on the "less hazardous" cigarette!

Most of the design technologies and their effect on cigarette MSS properties were discussed numerous times in detail after their development and inclusion in commercial products. During the last three and a half decades, little has been published about the tobacco expansion effect on smoke properties other than the results of the NCI experiments with expanded tobacco cigarettes described by GORI (7). Subsequently the results were tabulated and discussed in the 1970s by American Machine & Foundry (AMF) personnel, whose publication (15) and presentation (16) on RTS and tobacco expansion, because of the AMF market-

ing of RTS, obviously favored RTS vs. expanded tobacco. Since the mid-1990s, several publications on the "changing cigarette" have included discussions on the meaningful contribution of expanded tobacco to a "less hazardous" cigarette. However, each of the publications (14, 17, 18, 19) included a table in which the data reported by GORI (7) in the NCI study of the MSSs from three expanded tobaccos were copied or modified.

From 1970 through 1980, much of the information and data described herein were presented in seminars to various groups, e.g., DuPont, the supplier of the expansion agent, the directorate of the Verband der Cigarettenindustrie (German Cigarette Manufacturers' Association), and R&D management and/or executive management personnel at tobacco companies either licensing the RJRT expansion process or considering the licensing of the process (see Table 1). Although these data were not published, their dissemination was extremely wide and copies of the original report and/or the three subsequent revisions by RODGMAN (20) were provided to the auditors following many of the presentations. Overall, more than 125 copies of the original and/or revised reports were disseminated. The data were presented to the companies/organizations listed in Table 1 (the numbers in square brackets exceed unity because updated presentations included newly obtained data, particularly biological data).

Each presentation consisted of four main sections: 1) A brief chronology of the development of the tobacco expansion technology by FREDRICKSON and the selection of the most appropriate expansion agent, i.e., fluorotrichloromethane (Freon 11®) (21); 2) description of data pertinent to the expansion agent used, Freon 11®; 3) the effect of tobacco expansion on the chemical properties of its cigarette MSS as determined by GREEN and SCHUMACHER; and 4) the effect of tobacco expansion on the biological properties of its cigarette MSS as determined by INDUSTRIAL BIOTEST LABORATORIES, the NATIONAL CANCER INSTITUTE, and DONTENWILL *et al*.

Table 1. Presentations on the R.J. Reynolds Tobacco expansion process

Country	Audience [a]	Number
USA	Philip Morris [1], Lorillard [3], Liggett & Myers [3], Brown & Williamson [2], R.J. Reynolds [5], DuPont [3]	17
Canada	McDonalds [1]	1
UK	Imperial [4], BAT [3], Rothmans [2], Players [2]	11
West Germany	BAT [2], Reemstma [4], Brinkman [2], Haus Neuerberg [2], Verband der Cigarettenindustrie [2]	12
Austria	Austria Tabakwerke [2]	2
Japan	Japan Tobacco Monopoly [4]	4
China	[3]	3
Taiwan	[2]	2
Australia	[2]	2
South Africa	[3]	3
Total		57

[a] Number in square brackets represents number of presentations.

DEVELOPMENT OF THE TOBACCO EXPANSION PROCESS

In the early 1960s, examination of cigarette fabrication costs indicated that 60–65% of it involved the tobacco blend; the remainder involved manufacturing, cigarette paper, filter material, packaging, quality assurance, distribution, advertising, etc. To reduce significantly the cigarette cost, the logical place to start was the blend.

If a cigarette tobacco rod be filled with less tobacco, have the same rod firmness, and burn without appreciable change during puff and smolder, then the task of significantly reducing the cost of a cigarette may be accomplished. FREDRICKSON (22) proposed that tobacco laminae expansion might permit the fabrication of a cigarette with less tobacco, thus reducing its cost, and incorporation of less tobacco in the cigarette might alter both the MSS yield and its composition.

In 1964, FREDRICKSON (23) developed a tobacco expansion process which was successively translated to a pilot-plant facility and then to a full-scale manufacturing facility by 1968. Within RJRT and among other tobacco companies to which its licensing was offered, this tobacco expansion process became known as the RJRT G13 process.

FREDRICKSON successfully expanded tobacco laminae with a variety of organic solvents such as pentane, acetone, benzene, ethanol, diethyl ether, dichloromethane, and fluorotrichloromethane (Freon 11®). In the original process, the cut tobacco laminae at a specified moisture content was impregnated with the organic solvent and, after a specified time period, the organic solvent was rapidly vaporized with heat. This resulted in rapid distension of the laminar cell walls. They remained distended because of the heating effect, which "set" the cell walls in the distended position. Thus was the tobacco expanded.

Many previous reports had described tobacco stem expansion (24), but the process developed by FREDRICKSON was the first to permit successful and significant expansion of tobacco laminae. Subsequently, patents were issued on his invention (25) and on the equipment design and process to expand tobacco laminae continuously and commercially (26).

Of the expansion reagents investigated by FREDRICKSON (23, 25), Freon 11® was the prime candidate for in-house commercial development and use in the tobacco expansion process. It is a low-boiling liquid that is non-flammable, non-explosive, stable at high temperatures, inert in a variety of chemical systems, and possesses no adverse biological effects. The other solvents investigated by FREDRICKSON were rejected for not fulfilling one or more of these criteria.

Although unknown at the time of the research by FREDRICKSON, it was subsequently, reported by ROWLAND and MOLINA (27) in 1976 that Freon 11® and other chlorofluoromethanes were involved in minimizing the ozone layer. Their discovery ultimately resulted not only in the banning of most commercial uses of the low molecular weight chlorofluoromethanes such as Freon 11® but also the receipt of the 1995 Nobel Prize in chemistry by ROWLAND and MOLINA.

DATA PERTINENT TO THE EXPANSION AGENT USED, FREON 11®

While the information on Freon 11®, particularly its biological properties, required considerable discussion during the many presentations, it will be abbreviated here because of the ultimate Freon 11® situation and the ban of its use because of involvement in the ozone layer situation (27).

The following questions required answers before tobacco laminae expanded with Freon 11® was introduced into a commercial cigarette product:

- Does Freon 11® possess any biological property of concern?
- Does treatment of tobacco laminae with Freon 11® result in a reaction between the expansion agent and any tobacco component which generates a compound of concern?
- What is the fate during the smoking process of the residual Freon 11® on the expanded tobacco?
- Does the residual Freon 11® generate phosgene during the smoking process?

All the studies conducted on tobacco expanded in the G13 process with Freon 11®, the effect of such treatment on MSS yield and composition, and the level and fate of residual Freon 11® were summarized by RODGMAN (20).

Extensive examination of the literature on the biological properties of Freon 11® revealed no problem with it even at levels much in excess of that anticipated in the MSS from a cigarette containing G13-expanded tobacco (20).

The American Conference of Governmental Industrial Hygienists set the Threshold Limit Value (TLV) for Freon 11® in air at 1,000 ppm in 1964 (28) and again in 1971 (29), a value repeated in 1973 by the American National Standards Institute (30). At that time, only carbon dioxide was assigned a TLV greater than Freon 11®, i.e., 5,000 ppm.

THOME (31) developed an analytical procedure based on electron capture detection to determine Freon 11® at the nanogram level in tobacco and cigarette MSS and sidestream smoke (SSS). This procedure was such an advancement in analytical methodology pertinent to Freon 11® that even R&D personnel at DuPont, the manufacturer of Freon 11®, were highly impressed.

THOME (32) used his analytical method in a "materials balance study" involving cigarettes containing G13-expanded tobacco with a Freon 11® residual level of 50 ppm. They were smoked and the Freon 11® levels were determined in the vapor phases of the MSS and SSS, in the particulate phase of the MSS and SSS, in the cigarette butt, and on the smoke-exposed surfaces of the SSS collection apparatus.

The data from this "materials balance study" indicated that the residual Freon 11® on G13-expanded tobacco is, within experimental error, totally accounted for in the smoke products, the butt, and on the walls of the SSS collection apparatus. This recovery precludes the reaction of the Freon 11® with tobacco or tobacco smoke components. Cigarettes with several levels of residual Freon 11® were examined in as many as 20 replicated experiments; the THOME findings at 50 ppm residual level of Freon 11® were confirmed not only by INDUSTRIAL BIO-TEST LABORATORIES repetition of the THOME study but also by its smoking cigarettes in air-Freon 11® atmospheres (33).

From 15% to 20% of the residual Freon 11® was transferred from the tobacco to the MSS vapor phase, 50% to 60% to the SSS vapor phase, 19% to 25% remained in the cigarette butt, less than 1% was found in the combined MSS+SSS particulate phases, and less than 0.1% was found on the walls of the SSS collection apparatus.

Various concerns about certain biological properties of Freon 11® appeared from time to time (20). Each was examined appropriately, and the problem was found not to be due to Freon 11®. A major example was the following: During a 1976 meeting of the American Legion in Philadelphia, Freon 11® was discharged from a malfunctioning air conditioning system. Because numerous attendees became ill with what was subsequently called the Legionnaire's Disease, Freon 11® somehow was thought to be the cause of the disease possibly through the formation of phosgene. It was alleged that the Freon 11® generated phosgene when drawn through lit cigarettes. In 1976, phosgene generated in this manner was proposed independently by RUNSDORF and COOK as the cause of the Legionnaire's Disease (34).

THOME showed that phosgene formation from residual Freon 11® did not occur in an expanded-tobacco cigarette smoked under FTC conditions (27, 35). In a study triggered by the Philadelphia Legionnaire's Disease incident, HANST *et al*. (36) at the EPA reported that no phosgene was generated when chlorofluoromethanes in air were drawn through a lit cigarette, a result that confirmed the THOME finding (35) and INDUSTRAL BIO-TEST LABORATORIES finding (33) on phosgene absence. A bacterium, not phosgene, was later identified as the causative agent of Legionnaire's Disease (37).

Based on thermodynamic data, POLERT (38) calculated that phosgene could not be present in the MSS from a cigarette containing 100 µg of Freon 11® [see pp. 57–64 in the RODGMAN 2nd revision (20)].

FREDRICKSON refluxed various individual tobacco components with Freon 11® for extended periods of time. No reaction was observed between Freon 11® and the tobacco component under study (39).

CHEMICAL PROPERTIES OF EXPANDED TOBACCO SMOKE

Table 2 lists the effect of expansion on the per cigarette yields of various components in the MSS from a tobacco blend typical of an American cigarette. The control and test cigarettes were fabricated with essentially the same pressure drop [a]. Examination of the data in Table 2 indicates that the per cigarette yields of all MSS components asserted to be toxicants were decreased for the test cigarette.

Another study with cigarettes containing a similar American-type blend was conducted to determine the effect of the inclusion of different levels of expanded tobacco in the cigarette. All cigarette samples in this study were

[a] Tobacco type and/or blend selection, cigarette fabrication, conditioning of cigarette prior to smoking, cigarette smoking regime, MSS collection, MSS fractionation, gas chromatography, and component identification are described in considerable detail in the references cited.

Table 2. Analysis of mainstream smoke from cigarettes (equivalent pressure drop) containing 100% control tobacco blend and 100% expanded tobacco blend

Analyte [a]	Control tob. blend	Expanded tob. blend	Decrease %
Cigarette wt., g [b]	1.303	0.855	34
Pressure drop, mm H_2O [c]	81.6	77.4	5
TPM, mg	35.7	26.5	26
FTC 'tar'	31.0	23.2	25
Nicotine, mg	1.88	1.20	36
Carbon monoxide, mg	14.0	12.6	10
Phenol, µg	82	55	33
Formaldehyde, µg	55	45	18
Acetaldehyde, µg	1050	793	24
Acrolein, µg	127	105	17
Hydrogen cyanide, µg	303	276	9
Nitrogen oxides, µg [d]	221	158	29
Benzo[*a*]pyrene, ng	20.8	12.4	40

[a] Value per cigarette.
[b] 85-mm nonfiltered cigarette
[c] Flow rate at 17.5 mL/s.
[d] Expressed as nitric oxide, NO.

fabricated to equivalent firmness. From examination of the data in Table 3, it is apparent that the levels of the MSS components decrease proportionally between the two extremes of 100% control tobacco and 100% expanded tobacco.

Table 4 summarizes analytical data collected on the effect of expansion on the per cigarette yields of components in the MSSs from individual tobacco types, namely flue-cured and burley tobaccos. In this study, the 85-mm non-filtered cigarettes were fabricated to equivalent firmness. For each tobacco type, cigarettes containing 100% control tobacco were compared with cigarette containing 100% expanded tobacco.

In a study involving a cased commercial tobacco blend, a detailed smoke comparison study was conducted by GREEN and SCHUMACHER (40) on the MSS from a G13-expanded tobacco blend vs. the MSS from its unexpanded control blend. The level of residual Freon 11® on the tobacco blend *at the time of smoking* of the cigarettes was set at 50 ppm, a level much higher than that anticipated in commercial cigarettes smoked by a consumer.

Both the vapor phase and the particulate phase of the MSSs from the expanded and the control tobacco blend were examined by gas chromatography. Over 270 components in each MSS were identified and quantitated. More than 500 additional peaks and shoulders in the chromatograms from the MSS phases and fractions were matched. Quantitative differences were observed between the levels of components, both identified and unidentified, in the MSSs from the two cigarettes, but qualitatively they differed in only one respect: One peak detected in the chromatograms of the expanded tobacco MSS was absent from the chromatograms of the control tobacco MSS. This "stranger" peak in the MSS vapor phase from the expanded tobacco cigarette was Freon 11® that had transferred from the expanded tobacco to its MSS.

Of the 271 identified components, the yields of 124 were at least 10% less in the expanded tobacco MSS than in the control MSS; the yield of 93 components were essentially the same (±10%, the experimental error) in both MSSs, the yields of 54 components were 10% or more in the expanded tobacco MSS than in the control MSS. Because of the length of the presentations in the 1970s, the information in Table 5 was presented with only a brief mention of a few of the 271 identified components. Table 6 lists the 271 identified components and their relative MSS yields from the expanded and control tobacco cigarettes. Over 70 of the MSS components identified in the 1971 GREEN-SCHUMACHER study had not been previously reported as tobacco smoke components.

Since the completion of the GREEN-SCHUMACHER study on the MSS components from expanded vs. control tobacco cigarettes, many of the 500 or so other components have

Table 3. Analysis of mainstream smoke from cigarettes (equivalent firmness) containing various levels of an expanded tobacco blend

Analyte [a]	Ratio of control to expanded tobacco blend					100% Control vs. 100% expanded, decrease, %
	100:0	90:10	75:25	50:50	0:100	
Cigarette wt., g [b]	1.106	1.050	0.984	0.916	0.727	34
Pressure drop, mm H_2O [c]	56.6	58.2	63.6	72.2	100.5	–44
TPM, mg	34.8	28.4	28.3	26.1	20.8	41
FTC 'tar'	28.6	24.4	23.6	21.1	17.0	41
Nicotine, mg	2.01	1.60	1.44	1.26	1.01	49
Carbon monoxide, mg	16.2	15.4	13.9	11.5	9.8	39
Phenol, µg	117	106	95	72	45	61
Formaldehyde, µg	53	48	41	39	36	32
Acetaldehyde, µg	965	955	925	880	790	18
Acrolein, µg	111	113	130	104	101	9
Hydrogen cyanide, µg	337	232	221	181	217	36
Nitrogen oxides, µg [d]	166	133	168	180	140	16
Benzo[*a*]pyrene, ng	16.1	13.0	11.1	10.4	7.1	56

[a] Value per cigarette.
[b] 85-mm nonfiltered cigarette.
[c] Flow rate at 17.5 mL/s.
[d] Expressed as nitric oxide, NO.

Table 4. Analysis of mainstream smoke from cigarettes (equivalent firmness) containing control and expanded flue-cured and burley blends

	Flue-cured blend			Burley blend		
Analyte [a]	100% Control	100% Expanded	Decrease, %	100% Control	100% Expanded	Decrease, %
Cigarette wt., g [b]	1.30	0.48	65	0.96	0.48	50
TPM, mg	40.8	23.4	43	27.7	17.7	36
FTC 'tar'	32.9	18.2	45	22.3	14.8	34
Nicotine, mg	2.75	1.25	54	1.92	1.13	41
Carbon monoxide, mg	15.6	7.0	57			
Phenol, µg	126	70	44			
Formaldehyde, µg	31	23	26			
Acetaldehyde, µg	970	575	41			
Acrolein, µg	117	93	21			
Hydrogen cyanide, µg	313	247	27	342	284	17
Nitrogen oxides, µg [c]	63	42	34	393	226	42
Benzo[*a*]pyrene, ng	28.5	8.7	69			

[a] Value per cigarette.
[b] 85-mm nonfiltered cigarette.
[c] Expressed as nitric oxide, NO.

Table 5. Expanded tobacco smoke vs. control tobacco smoke

		Difference per g of condensate or its equivalent, no. of components			Difference per cigarette, no. of components		
Smoke fraction	Number of components [a]	< –10%	±10%	> 10%	< –10%	±10%	> 10%
Vapor phase	32	6	20	6 [b]	29	3	0
Particulate phase							
Ether-soluble	174 [c]	} 118 [d]	} 73	} 48 [e]	} 205 [f]	} 11	} 23 [g]
Water-soluble	73 [c]						
Totals	271	124	93	54	234	14	23

[a] Every compound (except Freon 11) found in the expanded tobacco MSS was found in the control tobacco MSS.
[b] Carbon monoxide, hydrogen cyanide, methanol, 2-methyl-1,3-butadiene (isoprene), 2-propanone (acetone), 2-propenal (acrolein).
[c] Eight identified components were abundantly present in both the ether and water layers of the initial partition.
[d] 118 of the 247 (174+73) identified particulate-phase components were present in the expanded tobacco MSS at yields ≥10% lower per gram of condensate than in the control MSS.
[e] Of the 48, 16 were phytosterols or long-chained aliphatic hydrocarbons; 32 were carbonyl and/or hydroxy compounds, most of which were isolated from the water-soluble fraction
[f] 205 of the 247 identified particulate-phase components were present in the expanded tobacco MSS at yields ≥10% lower per cigarette than in the control MSS.
[g] Of the 23, 8 were phytosterols or long-chained aliphatic hydrocarbons.

been identified in other tobacco smoke studies (41, 42). Mentioned previously were several publications (14, 18, 19) that reported the NCI results on MSS components from cigarettes containing three different expanded tobaccos. In those same publications were lists of MSS components considered to be carcinogenic or tumorigenic. Components, classified as carcinogens, were listed in HOFFMANN and HOFFMANN [see Table 8 in (18); see Table 5-4 in (19)] and HOFFMANN *et al.* [see Table 4 in (14)]. In addition to those lists, several others were published between 1990 and 2001. They were authored by HOFFMANN and HECHT [see Table 3 on components classified as tumorigens in (43)], HOFFMANN *et al*. [see Table 1 on components classified as tumorigens in (44)], the Occupational Safety and Health Administration (OSHA) [see Table II-2 on components classified as carcinogens to humans or animals in (45)], FOWLES and BATES [see Table 1 on components with cancer potency in (46)], and HOFFMANN and HOFFMANN [see Table 1 in (47)]. The latter article classified numerous MSS components as biologically active. The nature of the biological activity was not specified. In Table 6, the MSS components previously designated as carcinogenic, tumorigenic, or biologically active are highlighted in bold print. Some were listed in all eight publications, some were listed in a few of them, some were listed in only one.

BIOLOGICAL PROPERTIES OF EXPANDED TOBACCO SMOKE

The results of an acute respiratory toxicity study in mice indicated that the generation of MSS by smoking a cigarette (50) in an atmosphere of Freon 11® (1000 ppm in air) did not alter the biological properties or effects of the cigarette MSS (33).

The results of a macrophage suppression test indicated that inclusion of G13-expanded tobacco in a cigarette did not appreciably alter the biological properties of its MSS.

Table 6. Comparison of mainstream smoke compositions from cigarettes containing expanded vs. non-expanded tobacco

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
Acenaphthylene	208-96-8		−13	−35	—	–	—
Acetaldehyde [a, b]	75-07-0		—	−24	y<c [c]	y<c	vp
Acetamide [d]	60-35-5		−3	−28	—	—	—
Acetic acid	64-19-7		9	−18	y<c	y<c	—
Acetic acid, ethyl ester [a]	141-78-6	ethyl acetate	—	−24	—	—	—
Acetic acid, methyl ester [a]	79-20-9	methyl acetate	—	—	—	—	—
Acetonitrile [a]	75-05-8		0	−25	—	—	—
Ammonia [a, e]	7664-41-7		NI [f]	NI	y<c	y<c	—
Benzaldehyde	100-52-7		NI	NI	—	y<c	—
Benzaldehyde, 4-hydroxy-3-methoxy- [g, h]	121-33-5	vanillin	10	−18	—	—	—
Benzaldehyde, 3-hydroxy-4-methyl- [g]	57295-30-4		5	−22	—	—	—
Benzaldehyde, 4-hydroxy-3-methyl- [g]	15174-69-3		5	−22	—	—	—
Benzene [a, b]	71-43-2		—	−30	—	—	vp
Benzene, 1,1'-(dichloroethenylidene)bis[4-chloro- [i]	72-55-9	*p,p*'-DDE	−29	−47	—	—	—
Benzene, 1,1'-(2,2-dichloroethylidene)bis[4-chloro- [j]	72-54-8	*p,p*'-DDD; *p,p*'-TDE	−15	−36	—	—	—
Benzene, 1,2-dimethyl-	95-47-6	*o*-xylene	—	—	—	—	vp
Benzene, (1,1-dimethylethyl)-	98-06-6	*tert* butylbenzene	—	—	—	—	vp
Benzene, ethenyl- [k]	100-42-5	styrene	—	—	—	—	vp
Benzene, ethyl-	100-41-4		—	—	—	—	x
Benzene, methyl- [a]	108-88-3	toluene	—	−32	—	—	vp
Benzene, 1,1'-methylenebis[4-chloro-	101-76-8		x [l]	x	—	—	—
Benzeneacetic acid	103-82-2	phenylacetic acid	−13	−35	—	—	—
Benzeneacetonitrile	140-29-4	phenylacetonitrile	22	−8	—	—	—
Benzeneacetonitrile, 4-hydroxy- [g, h]	14191-95-8		−9	−32	—	—	—
1,2-Benzenedicarboxylic acid, diethyl ester	84-66-2	diethyl phthalate	NI	NI	y<c	y<c	—
1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester [m]	117-81-7	di(2-ethylhexyl) phthalate	37	3	—	—	—
1,2-Benzenediol [n]	120-80-9	catechol	−10	−33	—	—	—
1,2-Benzenediol, 4-ethyl-	1124-39-6		−12	−34	—	—	—
1,2-Benzenediol, 4-methyl-	452-86-8		−14	−36	—	—	—
1,3-Benzenediol	108-46-3	resorcinol	−10	−18	—	—	—
1,4-Benzenediol	123-31-9	hydroquinone	−12	−34	—	—	—
1,4-Benzenediol, ethyl- [g, h]	2349-70-4	ethylhydroquinone	10	−18	—	—	—
1,4-Benzenediol, methyl-	95-71-6	methylhydroquinone	18	−12	—	—	—
2(3*H*)-Benzofuranone, hexahydro-4,4,7a-trimethyl- [g, h]	16778-27-1	mariolide; dihydroactinidiolide	−76	−81	—	—	—
Benzoic acid	65-85-0		−27	−45	—	—	—
Benzo[*a*]pyrene [b]	50-32-8		—	−40	—	—	—
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene- [a]	127-91-3	β-pinene	—	−19	—	—	—
Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl- [a]	80-56-8	α-pinene	—	−19	—	—	—
1,1'-Bicyclohexyl [g, h]	92-51-3		−8	−31	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
1,1'-Biphenyl	92-52-4		0	-25	—	—	—
2,3'-Bipyridine	581-50-0	isonicoteine	-37	-53	—	—	—
1,3-Butadiene [o]	106-99-0		—	—	—	—	vp
1,3-Butadiene, 2-methyl- [k]	78-79-5	isoprene	—	-17	—	—	vp
Butanal [a]	123-72-8	butyraldehyde	0	-25	—	—	—
Butanal, 3-methyl- [a]	590-86-3	isovaleraldehyde	—	-28	—	—	—
Butanamide [g, h]	541-35-5		-54	-64	—	—	—
Butane	106-97-8		—	—	—	—	vp
Butane, 2-methyl-	78-78-4		—	—	—	—	vp
2,3-Butanediol [g, h]	513-85-9		-78	-82	—	—	—
2,3-Butanedione [a]	431-03-8	diacetyl	—	-30	—	—	vp [p]
Butanenitrile, 2-hydroxy-3-methyl-	15344-34-0		NI	NI	y<c	y<c	—
Butanoic acid, 2-methyl-	116-53-0		-8	-31	—	—	—
Butanoic acid, 3-methyl-	503-74-2	isovaleric acid	-8	-31	—	—	—
2-Butanol, 3-amino-2-methyl- [g, h]	6291-17-4		0	-25	—	—	—
2-Butanone [a]	78-93-3	methyl ethyl ketone	—	-24	—	—	vp [p]
2-Butenal [q]	4170-30-3	crotonaldehyde	—	—	—	—	vp [p]
3-Buten-1-amine, *N*-methyl-4-(3-pyridinyl)-	538-79-4	metanicotine	-40	-55	—	—	
1-Butene	106-98-9		—	—	—	—	vp
1-Butene, 2,3-dimethyl-	563-78-0		—	—	—	—	vp
1-Butene, 3,3-dimethyl-	558-37-2		—	—	—	—	vp
2-Butene, *cis*-	590-18-1		—	—	—	—	vp
2-Butene, *trans*-	624-64-6		—	—	—	—	vp
2-Butene, 2-methyl- [a]	513-35-9		—	-34	—	—	vp [r]
2-Butenoic acid	3724-65-0	crotonic acid	x	x	—	—	—
2-Buten-1-one, 1-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)- [g, h]	56915-02-7	4-hydroxy-β-damascone	x	x	—	—	—
2-Buten-1-one, 1-(2,6,6-trimethylcyclohexenyl)-	23770-92-3	damascone	NI	NI	y<c	—	—
Carbon monoxide [a, e]	630-08-0		x	-10	y<c	y<c	—
1,3,5-Cycloheptatriene	544-25-2	tropilidene	—	—	—	—	vp
1,3-Cyclohexadiene	592-57-4		—	—	—	—	vp
Cyclohexene, 1-methyl-	591-49-1		—	—	—	—	vp
Cyclohexene, 1-methyl-3-(1-methylethenyl)-	38738-60-2	sylvestrene	—	—	—	—	vp
Cyclohexene, 1-methyl-4-(1-methylethenyl)-	138-86-3	*p*-mentha-1,8-diene; limonene	-50	-63	—	—	vp
2-Cyclohexen-1-one, 4-(2-butenylidene)-3,5,5-trimethyl-	13215-88-8		NI	NI	y<c	y<c	—
2-Cyclohexen-1-one, 4-(3-hydroxy-1-butenyl)-3,5,5-trimethyl- [g, h]	34318-21-3	4-keto-a-ionol	x	x	—	—	—
2-Cyclohexen-1-one, 4-(3-hydroxybutyl)-3,5,5-trimethyl- [g, h]	60047-19-0	4-ketodihydro-a-ionol	x	x	—	—	—
Cyclopentadiene	542-92-7		—	—	—	—	vp
Cyclopentadiene, methyl-	26519-91-5		—	—	—	—	vp

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
Cyclopentane, 1,2-dimethyl-	822-50-4		—	—	—	—	vp
Cyclopentane, methyl-	96-37-7		—	—	—	—	vp
1,2-Cyclopentanedione, 3,5-dimethyl- [g, h]	13494-07-0		x	x	—	—	—
1,2-Cyclopentanedione, 3-ethyl- [g, h]	13494-08-1		x	x	—	—	—
1,2-Cyclopentanedione, 3-ethyl-5-methyl- [g, h]	71608-11-2		−34	−51	—	—	—
1,2-Cyclopentanedione, 3-methyl- [g]	765-70-8	cyclotene	47	10	—	—	—
Cyclopentene	142-29-0		—	—	—	—	vp
3-Cyclopentene-1,2-dione, 3-methyl- [g]	10130-95-7		x	x	—	—	—
2-Cyclopenten-1-one, 2,3-dimethyl-	1121-05-7		NI	NI	y<c	—	—
2-Cyclopenten-1-one, 3,4-dimethyl-	30434-64-1		NI	NI	y<c	y<c	—
2-Cyclopenten-1-one, 3-ethyl- [g, h]	5682-69-9		50	12	—	—	—
2-Cyclopenten-1-one, 2-hydroxy-3-methyl- [g, h]	80-71-7	methylcyclopentenolone	x	x	—	—	—
2-Cyclopenten-1-one, 3-methyl-	2758-18-1		245	152	—	—	—
2-Cyclopenten-1-one, 2,3,5-trimethyl-	5456-24-5		NI	NI	—	y<c	—
Cyclopropane, 1,1-dimethyl-	1630-94-0		—	—	—	—	vp
Cyclopropane, 1,2-dimethyl-	2511-95-7		—	—	—	—	vp
4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	57605-81-9		NI	NI	—	y<c	—
Decanoic acid	334-48-5	capric acid	x	x	—	—	—
1,3-Dioxalane-4-methanol, 2,2-dimethyl- [g, h]	100-79-8		−27	−45	—	—	—
1,3-Dioxalan-2-one	96-49-1	ethylene glycol carbonate	x	x	—	—	—
1,3-Dioxalan-2-one, 4-(hydroxymethyl)-	931-40-8	glycerol carbonate	x	x	—	—	—
Dodecanoic acid	143-07-7	lauric acid	x	x	—	—	—
Dodecanoic acid, methyl ester	111-82-0		NI	NI	y<c	—	—
2,6,10-Dodecatriene, 2,6,10-trimethyl-	3899-18-1		−23	−42	—	—	—
Dotriacontane	544-85-4		97	48	—	—	—
Dotriacontane, 2-methyl-	1720-11-2		72	29	—	—	—
2,6,10,14,18-Eicosapentaene, 2,6,10,14,18-pentamethyl-	7431-92-7		−56	−67	—	—	—
Ethanedial [a]	107-22-2	glyoxal	—	−20	—	—	—
1,2-Ethanediol [a]	107-21-1	ethylene glycol	12	−16	—	—	—
1,2-Ethanediol, monoacetate [g, h]	542-59-6		x	x	—	—	—
Ethanone, 1-(1*H*-pyrrol-2-yl)- [g, h]	1072-83-9	2-acetylpyrrole	50	12	—	—	—
Ethanone, 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)- [g, h]	1500-94-3		−12	−34	—	—	—
Ethanone, 1-(2-furanyl)-2-(acetyloxy)- [g, h]	19859-79-1		−12	−34	—	—	—
Ethanone, 1-(2-hydroxy-3-methoxyphenyl)- [g]	703-98-0		−9	−32	—	—	—
Ethanone, 1-(3-hydroxyphenyl)-	121-71-1	3-hydroxyacetophenone	−10	−18	—	—	—
Ethanone, 1-(4-hydroxyphenyl)-	99-93-4	4-hydroxyacetophenone	−9	−32	—	—	—
Ethanone, 1-(4-hydroxy-3-methoxyphenyl)- [g, h]	498-02-2		5	−22	—	—	—
Ethanone, 1-(4-methylphenyl)-	122-00-9	4-methylacetophenone	x	x	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
Ethanone, 1-(5-methyl-1*H*-pyrrol-2-yl)- [g,h]	6982-72-5	2-acetyl-5-methylpyrrole	6	−21	—	—	—
Ethanone, 1-phenyl-	98-86-2	acetophenone	NI	NI	y<c	—	—
Ethanone, 1-(3-pyridinyl)-	350-03-8	3-acetylpyridine	NI	NI	—	y<c	—
Ethene, trichloro-	79-01-6		—	—	—	—	vp [p]
9*H*-Fluorene	86-73-7		−25	−44	—	—	—
9*H*-Fluorene, 2-methyl- [g,h]	1430-97-3		−22	−42	—	—	—
Formaldehyde [b]	50-00-0		—	−18	y<c	y<c	—
Furan [o]	110-00-9		—	—	—	—	vp [p]
Furan, 2,5-dimethyl-	625-86-5		—	—	—	—	vp
Furan, 2-methyl- [a]	534-22-5		—	−34	—	—	vp
2-Furancarboxaldehyde	98-01-1	furfural; 2-furaldehyde	x	x	—	—	—
2-Furancarboxaldehyde, 5-methyl-	620-02-0		−90	−91	—	—	—
2-Furancarboxylic acid	88-14-2	furoic acid	7	−20	—	—	—
2-Furancarboxylic acid, 5-methyl-	1917-15-3		NI	NI	—	y<c	—
2,5-Furandione	108-31-6	maleic anhydride	x	x	—	—	—
2,5-Furandione, 3,4-dimethyl-	766-39-2		55	16	—	—	—
2,5-Furandione, 3-ethyl-4-methyl-	3552-33-8		62	21	—	—	—
2,5-Furandione, dihydro-3,4-dimethyl-	7475-92-5	pyrocinchonic anhydride	55	16	—	—	—
2-Furanmethanol	98-00-0	furfuryl alcohol	58	18	—	—	—
2(3*H*)-Furanone [g,h]	20825-71-2	butenolide	x	x	—	—	—
2(3*H*)-Furanone, 3-acetyldihydro- [g,h]	517-23-7		x	x	—	—	—
2(3*H*)-Furanone, 4-acetyldihydro- [g,h]	7400-67-1		x	x	—	—	—
2(3*H*)-Furanone, 5-acetyldihydro- [g,h]	29393-32-6		x	x	—	—	—
2(3*H*)-Furanone, 3-(acetyloxy)dihydro-	19405-99-3		x	x	—	—	—
2(3*H*)-Furanone, 3-(acetyloxy)dihydro-4-hydroxy-	61892-43-1		x	x	—	—	—
2(3*H*)-Furanone, dihydro-	96-48-0	butyrolactone	x	x	—	—	—
2(3*H*)-Furanone, dihydro-3,4-dihydroxy-4-methyl-	—		x	x	—	—	—
2(3*H*)-Furanone, dihydro-3-(hydroxymethyl)- [g,h]	18132-98-4		x	x	—	—	—
2(3*H*)-Furanone, dihydro-3-hydroxy- [g,h]	19444-84-9		x	x	—	—	—
2(3*H*)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-	52126-90-6		x	x	—	—	—
2(3*H*)-Furanone, dihydro-3-hydroxy-5-(2-hydroxyethyl)-5-methyl-	61892-50-0		x	x	—	—	—
2(3*H*)-Furanone, dihydro-4-(hydroxymethyl)-	36679-81-9		x	x	—	—	—
2(3*H*)-Furanone, 3,4-dimethyl- [g,h]	—		6	−21	—	—	—
2(5*H*)-Furanone	497-23-4	crotonolactone	x	x	—	—	—
2(5*H*)-Furanone, 4,5-dimethyl- [g,h]	10547-85-0		x	x	—	—	—
2(5*H*)-Furanone, 3,4-dimethyl-5-(1-propenyl)- [g,h]	66309-74-8		x	x	—	—	—
2(5*H*)-Furanone, 3-methyl- [g,h]	22122-36-7		x	x	—	—	—
2(5*H*)-Furanone, 4-methyl- [g,h]	6124-79-4		x	x	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
2(5*H*)-Furanone, 5-methyl- [g, h]	591-11-7	β-angelica lactone	x	x	—	—	—
2(5*H*)-Furanone, 5-methylene-	108-28-1	protoanemonin	x	x	—	—	—
2(5*H*)-Furanone, 3,4,5-trimethyl- [g, h]	33488-51-6		6	−21	—	—	—
3(2*H*)-Furanone, 4-hydroxy-2-(hydroxymethyl)-5-methyl- [g]	17678-20-5		91	42	—	—	—
Hentriacontane	630-04-6		49	11	—	—	—
Hentriacontane, 3-methyl-	4981-99-1		37	2	—	—	—
Heptacosane	593-49-7		11	−17	—	—	—
Heptacosane, 3-methyl-	14167-66-9		3	−23	—	—	—
1,5-Heptadien-3-yne	3511-27-1		—	—	—	—	vp
Hexacosane	630-01-3		−3	−27	—	—	—
Hexadecanoic acid	57-10-3	palmitic acid	−20	−40	—	—	—
2,6,10,14-Hexadecatetraene, 2,6,10,14-tetramethyl-	34083-18-6		−50	−63	—	—	—
1-Hexadecene, 3-methylene-7,11,15-trimethyl-	504-96-1	neophytadiene	12	−16	—	—	—
2,4-Hexadiene, 2,5-dimethyl-	764-13-6		—	—	—	—	vp
1,3-Hexadien-5-yne	10420-90-3		—	—	—	—	vp
Hexane [a]	110-54-3		—	−17	—	—	vp
Hexane, 2,5-dimethyl-	592-13-2	diisobutyl	—	—	—	—	vp
Hexanoic acid	142-62-1	caproic acid	NI	NI	y<c	y<c	—
2,6,10,14,18,22,26,30,34-Hexa-triacontanonaen-1-ol, 3,7,11,15, 19,23,27,31,35-nonamethyl-	13190-97-1	solanesol	x	x	—	—	—
1,3,5-Hexatriene	2235-12-3		—	—	—	—	vp
1-Hexene	592-41-6		—	—	—	—	vp
2-Hexene, 2,5-dimethyl-	3404-78-2		—	—	—	—	vp [p]
2-Hexene, 2-methyl-	2738-19-4		—	—	—	—	vp
3-Hexene	592-47-2		—	—	—	—	vp
1-Hexyne	693-02-7		—	—	—	—	vp [p]
2-Hexyne	764-35-2		—	—	—	—	vp
3-Hexyne	928-49-4		—	—	—	—	vp
Hydrocyanic acid [a, e]	74-90-8	hydrogen cyanide	—	−9	y<c	y<c	—
1*H*-Indene	95-13-6		7	−20	—	—	—
1*H*-Indene, 2,3-dihydromethyl- {2 isomers}	27133-93-3		−10	−29	—	—	—
1*H*-Indene, 2,3-dihydro-1-methyl-	767-58-8		−12	−34	—	—	—
1*H*-Inden-1-one, 2,3-dihydro-	83-33-0	1-indanone	x	x	—	—	—
1*H*-Indole	120-72-9		−43	−57	y<c	y<c	—
1*H*-Indole, 2,3-dimethyl-	91-55-4		−32	−49	—	—	—
1*H*-Indole, 3-ethyl-	1484-19-1		−13	−35	y<c	y<c	—
1*H*-Indole, 3-methyl-	83-34-1	skatole	−31	−48	y<c	y<c	—
1(3*H*)-Isobenzofuranone	87-41-2	phthalide	10	−18	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
1*H*-Isoindole-1,3(2*H*)-dione [g, h]	85-41-6	phthalimide	−9	−32	—	—	—
Isothiazole	288-16-4		NI	NI	—	y<c	—
Methane, chloro-	74-87-3		—	—	—	—	x
Methanol [a]	67-56-1		x	x	—	—	—
Naphthalene	91-20-3		−4	−28	—	—	—
Naphthalene, dihydrodimethyl- [g, h]	72692-88-7		−40	−55	—	—	—
Naphthalene, dihydromethyl- [g, h]	39292-53-0		−40	−55	—	—	—
Naphthalene, 1,2-dihydro-1,5,8-trimethyl-	4506-36-9		−40	−55	—	—	—
Naphthalene, dimethyl- {4 isomers}	28804-88-8		−33	−49	—	—	—
Naphthalene, 1,6-dimethyl-	575-43-9		−44	−58	—	—	—
Naphthalene, dimethyltetrahydro- [g, h] {3 isomers}	—		−40	−55	—	—	—
Naphthalene, 2-ethyl-7-methyl- [g, h]	17059-55-1		x	x	—	—	—
Naphthalene, 1-methyl-	90-12-0		−20	−40	—	—	—
Naphthalene, 2-methyl-	91-57-6		−19	−39	—	—	—
Naphthalene, tetrahydrotrimethyl- [g, h] {3 isomers}	72843-02-8		−44	−58	—	—	—
Naphthalene, tetramethyl- [g, h]	28652-74-6		−40	−55	—	—	—
Naphthalene, trimethyl- {4 isomers}	28652-77-9		−40	−54	—	—	—
Naphthalene, 1,2,4-trimethyl- [g, h]	2717-42-2		−46	−59	—	—	—
Naphthalene, 1,3,6-trimethyl-	3031-08-1		−46	−59	—	—	—
Nitrogen oxide (NO) [a]	10102-43-9		—	−29	y<c	y<c	—
Nitrogen oxides (NO_x = NO+NO_2+N_2O) [a, e]	—		—	−29	—	—	—
Nonacosane	630-03-5		39	4	—	—	—
Nonacosane, 3-methyl-	14167-67-0		13	−15	—	—	—
6,8-Nonadien-2-one, 8-methyl-5-(1-methylethyl)-	1937-54-8	solanone	x	x	—	—	—
3-Nonene-2,8-dione	38372-56-4		x	x	—	—	—
3-Nonene-2,8-dione, 5-(1-methylethyl)- [g, h]	60619-46-7	oxysolanone	18	−12	—	—	—
Octacosane	630-02-4		18	−12	—	—	—
Octacosane, 2-methyl-	1560-98-1		3	−23	—	—	—
9,12-Octadecadienoic acid	506-21-8	linoleic acid	−5	−29	—	—	—
Octadecanoic acid	57-11-4	stearic acid	−27	−45	—	—	—
9,12,15-Octadecatrienoic acid	463-40-1	linolenic acid	−15	−36	—	—	—
9-Octadecenoic acid	112-80-1	oleic acid	−15	−36	—	—	—
1,6-Octadiene, 4,7-dimethyl-	71607-91-5	2,5-dimethyl-2,7-octadiene,	—	—	—	—	vp
2,4-Octadiene, 7-methyl-	2216-70-8		—	—	—	—	vp
1-Octene, 2-methyl-	4588-18-5		—	—	—	—	vp
2-Octene	111-67-1		—	—	—	—	vp

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
6-Oxabicyclo[3.2.1]octan-7-one, 1,3,4-trihydroxy-	640-06-2	cyclohexanecarboxylic acid, 1,3,4,5-tetrahydroxy-, γ-lactone; quinic acid lactone; quinide	8	−19	—	—	—
Oxazole, 4,5-dimethyl-	20654-94-8		NI	NI	y<c	—	—
Pentacosane	629-99-2		−8	−31	—	—	—
2-Pentadecanone, 6,10,14-trimethyl-	502-69-2	phytone	x	x	—	—	—
5,9,13-Pentadecatrien-2-one, 6,10,14-trimethyl-	762-29-8 1117-52-8	farnesyl acetone	NI	NI	y<c	—	—
1,2-Pentadiene	591-95-7	ethylallene	—	—	—	—	vp [p]
1,3-Pentadiene [a]	504-60-9	piperylene	—	−32	—	—	vp
1,3-Pentadiene, 2-methyl-	1118-58-7		—	—	—	—	vp
Pentanal [a]	110-62-3		—	−34	—	—	—
Pentanamide, 3-methyl- [g, h]	61892-69-1		−28	−46	—	—	—
Pentanamide, 4-methyl- [g, h]	1119-29-5		−26	−45	—	—	—
Pentane [a]	109-66-0		—	−38	—	—	vp
Pentane, 2-methyl-	107-83-5		—	—	—	—	vp
2,4-Pentanediol, 2-methyl- [g, h]	107-41-5		−30	−48	—	—	—
Pentanoic acid	109-52-4	valeric acid	x	x	—	—	—
Pentanoic acid, 3-methyl-	105-43-1	β-methylvaleric acid	−28	−46	—	—	—
Pentanoic acid, 4-oxo-	123-76-2	levulinic acid	42	6	—	—	—
2-Pentanone [a]	107-87-9		—	−34	—	—	—
3-Pentanone [a]	96-22-0		—	−34	—	—	—
Pentatriacontane	630-07-9		0	−25	—	—	—
1-Pentene [a]	109-67-1		—	−29	—	—	—
2-Pentene, *cis*-	627-20-3		—	—	—	—	vp
2-Pentene, 2-methyl-	625-27-4		—	—	—	—	vp
2-Pentene, 4-methyl-, *trans*-	674-76-0		—	—	—	—	vp
2-Pentyne	627-21-4		—	—	—	—	vp
Phenanthrene	85-01-8		−4	−28	—	—	—
Phenanthrene, 9,10-dihydro-	776-35-2		−27	−45	—	—	—
Phenol [e]	108-95-2		−23	−42	—	—	vp [p]
Phenol, 2-ethyl-	90-00-6		NI	NI	y<c	y<c	—
Phenol, 2,6-dimethoxy-	91-10-1	syringol	10	-18	y<c	y<c	—
Phenol, 2,3-dimethyl-	526-75-0	2,3-xylenol	NI	NI	y<c	y<c	—
Phenol, 2,4-dimethyl-	105-67-9	2,4-xylenol	−28	−46	—	—	—
Phenol, 2,5-dimethyl-	95-87-4	2,5-xylenol	NI	NI	—	y<c	—
Phenol, 4-ethenyl- [g, h]	2628-17-3	*p*-vinylphenol	−16	−37	—	—	—
Phenol, 4-ethenyl-2-methoxy-	7786-61-0		NI	NI	—	y<c	—
Phenol, 2-ethyl-	90-00-6	*o*-ethylphenol	—	—	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
Phenol, 4-ethyl-	123-07-9	*p*-ethylphenol	−28	−46	y<c	y<c	—
Phenol, 4-ethyl-2-methoxy-	2785-89-9	4-ethylguaiacol	−28	−46	—	—	—
Phenol, 4-ethyl-2-methyl- [g, h]	2219-73-0		−33	−50	—	—	—
Phenol, 2-methoxy-	90-05-1	guaiacol	−13	−35	—	—	—
Phenol, 2-methoxy-4-methyl-	93-51-6	4-methylguaiacol	22	−8	—	—	—
Phenol, 2-methoxy-4-(1-propenyl)-	97-54-1	isoeugenol	−19	−39	—	—	—
Phenol, 2-methoxy-4-(2-propenyl)-	97-53-0	eugenol	−5	−29	—	—	—
Phenol, 2-methyl-	95-48-7	*o*-cresol	−27	−45	—	y<c	—
Phenol, 3-methyl-	108-39-4	*m*-cresol	−22	−42	y<c	y<c	—
Phenol, 4-methyl-	106-44-5	*p*-cresol	−22	−42	—	y<c	—
Phenol, 2-methyl-6-propyl-	3520-52-3		x	x	—	—	—
Phenol, propyl- [g, h]	—		−32	−49	—	—	—
Phenol, 2-propyl-	644-35-9		x	x	—	—	—
2,6-Piperidinedione [g, h]	1121-89-7	glutarimide	−53	−65	—	—	—
2-Piperidinone [g, h]	675-20-7	3,4,5,6-tetrahydro-2-pyridone	−8	−31	—	—	—
Propanal [a]	123-38-6	propionaldehyde	—	−28	—	—	—
Propanal, 2-methyl- [a]	78-84-2	isobutyraldehyde	0	−24	—	—	—
Propanamide [g, h]	79-05-0	propionamide	0	−25	—	—	—
Propane	74-98-6		—	—	—	—	vp
Propane, 2-methyl-	75-28-5	isobutane	—	—	—	—	vp
1,2-Propanediol	57-55-6	propylene glycol	12	−16	—	—	—
1,2-Propanediol, 3-chloro- [g, h]	96-24-2		x	x	—	—	—
1,2,3-Propanetriol	56-81-5	glycerol	0	−25	y<c	—	—
1,2,3-Propanetriol, diacetate [g, h]	25395-31-7	diacetin	x	x	—	—	—
1,2,3-Propanetriol, monoacetate	26446-35-5	monacetin	−28	−46	—	—	—
1,2,3-Propanetriol, triacetate	102-76-1	triacetin	NI	NI	y	—	—
Propanoic acid	79-09-4		NI	NI	y<c	y<c	—
Propanoic acid, 2-methyl-	79-31-2	isobutyric acid	NI	NI	y<c	y<c	—
Propanoic acid, 3-(acetoxy)-	4272-12-2		NI	NI	—	y<c	—
2-Propanol [a]	67-63-0		0	−25	—	—	—
1-Propanone, 1-(2-hydroxyphenyl)- [g, h]	—		10	−18	—	—	—
2-Propanone [a]	67-64-1	acetone	—	−15	—	—	vp [p]
2-Propanone, 1-(acetyloxy)-	592-20-1		x	x	—	—	—
2-Propenal [b]	107-02-8	acrolein	—	−17	y<c	y<c	vp [p]
2-Propenamide [g, h, j]	79-06-1	acrylamide	−5	−29	—	—	—
Propene	115-07-1		—	—	—	—	vp
1*H*-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl- [g, h]	83-67-0	theobromine	5	−21	—	—	—
2*H*-Pyran-2-one, tetrahydro-	542-28-9	δ-valerolactone	x	x	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
2*H*-Pyran-2-one, tetrahydro-5-hydroxy-	33691-73-5		x	x	—	—	—
4*H*-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	28564-83-2		x	x	—	—	—
4*H*-Pyran-4-one, 3,5-dihydroxy-2,6-dimethyl- [g, h]	61892-86-2		−12	−34	—	—	—
4*H*-Pyran-4-one, 3,5-dihydroxy-2-methyl-	1073-96-7	hydroxymaltol	91	42	—	—	—
4*H*-Pyran-4-one, 3,5-dihydroxymethyl-2,6-dimethyl-	—		−12	−34	—	—	—
4*H*-Pyran-4-one, 3-hydroxy- [g, h]	496-63-9		x	x	—	—	—
4*H*-Pyran-4-one, 3-hydroxy-2-methyl- [g, h]	118-71-8	maltol	12	−16	—	—	—
4*H*-Pyran-4-one, 3-methyl-	50671-50-6		x	x	—	—	—
Pyrazine	290-37-9		NI	NI	z>y< [s]	y<c	—
Pyrazine, 2,5-dimethyl-	123-32-0		NI	NI	z>y<c	y<c	—
Pyrazine, ethyl-	13925-00-3		NI	NI	z>y<c	y<c	—
Pyrazine, 2-ethyl-3-methyl-	15707-23-0		NI	NI	z>y<c	y<c	—
Pyrazine, 2-(2-furanyl)-6-methyl-	32737-03-4		NI	NI	z>y<c	y<c	—
Pyrazine, methyl-	109-08-0		NI	NI	z>y<c	y<c	—
Pyrazine, tetramethyl-	1124-11-4		NI	NI	z>y<c	y<c	—
Pyrazine, trimethyl-	14667-55-1	collidine	NI	NI	z>y<c	y<c	—
Pyridine [e]	110-86-1		NI	NI	y<c	y<c	—
Pyridine, 3-(2-butenyl)-	78210-90-9		NI	NI	y<c	y<c	—
Pyridine, 2,3-dimethyl-	583-61-9	2,3-lutidine	NI	NI	y<c	y<c	—
Pyridine, 2,4-dimethyl-	108-47-4	2,4-lutidine	NI	NI	y<c	y<c	—
Pyridine, 2,5-dimethyl-	589-93-5	2,5-lutidine	NI	NI	y<c	y<c	—
Pyridine, 2,6-dimethyl-	108-48-5	2,6-lutidine	NI	NI	y<c	y<c	—
Pyridine, 3,4-dimethyl-	583-58-4	3,4-lutidine	NI	NI	y<c	y<c	—
Pyridine, 3,5-dimethyl-	591-22-0	3,5-lutidine	NI	NI	y<c	y<c	—
Pyridine, ethenyl-	1337-81-1		NI	NI	y<c	y<c	—
Pyridine, 2-ethyl-	100-71-0		NI	NI	y<c	y<c	—
Pyridine, 3-ethyl-	536-78-7		NI	NI	y<c	y<c	—
Pyridine, 4-ethyl-	536-75-4		NI	NI	y<c	y<c	—
Pyridine, 5-ethyl-2-methyl-	140-76-1		NI	NI	y<c	y<c	—
Pyridine, 2-methyl-	109-06-8	2-picoline	NI	NI	y<c	y<c	—
Pyridine, 3-methyl-	108-99-6	3-picoline	NI	NI	y<c	y<c	—
Pyridine, 4-methyl-	108-89-4	4-picoline	NI	NI	y<c	y<c	—
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-	54-11-5	nicotine	−10	−33	y<c	y<c	—
Pyridine, 3-(1-methyl-1*H*-pyrrol-2-yl)-	487-19-4	nicotyrine	3	−23	—	—	—
Pyridine, propenyl-	—		NI	NI	y<c	y<c	—
Pyridine, trimethyl- {2 isomers}	29611-84-5		NI	NI	y<c	y<c	—
Pyridinol, methyl-	—		x	x	—	—	—

Table 6 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
2-Pyridinol [g, h]	72762-00-6		−12	−34	—	—	—
3-Pyridinol	109-00-2		−14	−36	—	—	—
3-Pyridinol, methyl- [g, h] {2 isomers}	91491-14-4		−14	−36	—	—	—
3-Pyridinol, 6-methyl- [g, h, h]	1121-78-4		10	−18	—	—	—
2(1*H*)-Pyridinone	142-08-5		x	x	—	—	—
2(1*H*)-Pyridinone, 5,6-dihydro- [g, h]	6052-73-9		0	−25	—	—	—
9*H*-Pyrido[3,4-*b*]indole	244-63-3	norharman	−23	−42	—	—	—
9*H*-Pyrido[3,4-*b*]indole, 1-methyl-	486-84-0	harman	−37	−53	—	—	—
1*H*-Pyrrole, 1-methyl-	96-54-8		—	—	—	—	vp [p]
1*H*-Pyrrole, 1-phenyl- [g, h]	635-90-5		0	−25	—	—	—
1*H*-Pyrrole-2-carboxaldehyde	1003-29-8		NI	NI	y<c	y<c	—
1*H*-Pyrrole-2-carboxaldehyde, 5-methyl- [g, h]	1192-79-6		6	−21	—	—	—
1*H*-Pyrrole-3-carbonitrile [g, h]	7126-38-7		10	−18	—	—	—
1*H*-Pyrrole-2,5-dione, 3,4-dimethyl-	17825-86-4		NI	NI	y<c	y<c	—
1*H*-Pyrrole-2,5-dione, 3-ethyl-4-methyl-	20189-42-8		NI	NI	y<c	y<c	—
1*H*-Pyrrole-2,5-dione, 3-methyl- [g, h]	1072-87-3	3-methylmaleimide	6	−21	—	—	—
2,5-Pyrrolidinedione [g, h]	123-56-8	succinimide	7	−20	—	—	—
2,5-Pyrrolidinedione, 1,3-dimethyl- [g, h]	15542-96-8		−59	−70	—	—	—
2,5-Pyrrolidinedione, 3,4-dimethyl- [g, h]	33425-47-7		42	6	—	—	—
2,5-Pyrrolidinedione, 3-ethyl- [g, h]	5835-19-8		−54	−66	—	—	—
2,5-Pyrrolidinedione, 3-ethyl-4-methyl- [g, h]	—		−12	−34	—	—	—
2,5-Pyrrolidinedione, 3-ethylidene-1-methyl-	61892-74-8		−40	−55	—	—	—
2,5-Pyrrolidinedione, 3-ethylidene-4-methyl- [g, h]	16395-79-2		−40	−55	—	—	—
2,5-Pyrrolidinedione, 1-methyl- [g, h]	1121-07-9		69	26	—	—	—
2,5-Pyrrolidinedione, 3-methyl- [g, h]	5615-90-7		−40	−55	—	—	—
2-Pyrrolidinone [g, h]	616-45-5		−26	−45	—	—	—
Quinoline [t]	91-22-5		18	−12	—	—	—
Quinoxaline, methyl-	64828-56-4		NI	NI	y<c	y<c	—
Stigmast-5-en-3-ol, (3β)-	83-46-5	β-sitosterol	18	−12	—	—	—
2,6,10,14,18,22-Tetracosahexaene, 2,6,10,15,19,23-hexamethyl-	7683-64-9		−14	−36	—	—	—
Tetradecanoic acid	544-63-8	myristic acid	−22	−42	—	—	—
Tetratriacontane	14167-59-0		0	−25	—	—	—
Thiophene	110-02-1		—	—	—	—	vp [p]
Thiophene, methyl-	25154-40-9		—	—	—	—	vp
Triacontane	638-68-6		59	19	—	—	—
Triacontane, 2-methyl-	1560-72-1		15	−14	—	—	—

Table 8 (*cont.*)

Component	CAS No.	Alternate name	Freon 11®-expanded tobacco (40) Expanded vs. control, % difference		Pentane-expanded tobacco (48)	Freon 11®-expanded tobacco (48)	Freeze-dried tobacco vapor phase (vp) (49)
			Per g of CSC	Per cig			
Tridecane	629-50-5		NI	NI	y<c	y<c	—
Tritriacontane	630-05-7		67	25	—	—	—
Tritriacontane, 3-methyl-	14167-69-2		114	60	—	—	—

[a] Primarily a MSS vapor-phase component.
[b] This tobacco smoke component was listed as possessing cancer potency (46) or as being tumorigenic (43, 44), carcinogenic (14, 18, 19, 45), or biologically active (47).
[c] y<c indicates that the per cigarette MSS yield from the expanded tobacco cigarette was less than that from the control tobacco cigarette.
[d] This tobacco smoke component was listed as being carcinogenic (14, 19) or biologically active (43).
[e] This tobacco smoke component was listed as being biologically active (47).
[f] NI = not identified
[g] Component not reported in cigarette MSS prior to 1971.
[h] Component reported in cigarette MSS by other investigators after 1971.
[i] This tobacco smoke component was listed as being carcinogenic (14, 18, 19, 45) or biologically active (47). However, it is not a naturally occurring component of tobacco that transfers to MSS during the smoking process. It is the result of an agronomic treatment of tobacco.
[j] This tobacco smoke component was listed as being carcinogenic (14, 18, 19) or biologically active (47). It is not a naturally occurring component of tobacco that transfers to MSS during the smoking process but is a degradation product of DDT, used in an agronomic treatment of tobacco.
[k] This tobacco smoke component was listed as possessing cancer potency (46) or as being carcinogenic (14, 18, 19), or biologically active (47).
[l] x indicates the component was identified but not quantitated.
[m] This tobacco smoke component was listed by IARC in 1982 as being carcinogenic (18) or biologically active (47). In its re-evaluation of 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester in 2000, the IARC classified it as noncarcinogenic [see Footnote c, Table 5-4 in (19)]. Phthalate esters found in tobacco and smoke are not likely to be naturally occurring components, but probably result from their widespread use in plastics.
[n] This tobacco smoke component was listed as being carcinogenic (14, 19, 45) or biologically active (47).
[o] This tobacco smoke component was listed as being carcinogenic (14, 18, 19) or biologically active (47).
[p] Component identified in MSS vapor phase from freeze-dried tobacco cigarette but not in MSS vapor phase from control tobacco cigarette.
[q] This tobacco smoke component was listed as possessing cancer potency (46) or as being tumorigenic (43, 44) or biologically active (47).
[r] Component identified in MSS vapor phase from control tobacco cigarette but not in MSS vapor phase from freeze-dried tobacco cigarette.
[s] z>y<c indicates that the MSS pyrazine yield from the pentane-extracted tobacco cigarette was greater than that from the Freon 11® extracted version.
[t] This tobacco smoke component was listed as possessing cancer potency (46) or as being tumorigenic (43, 44), carcinogenic (14, 18, 19), or biologically active (47).

Table 7. Cigarette mainstream smoke analyses from Standard Experimental Blend, SEBII, tobaccos expanded by the R.J. Reynolds (RJRT) Freon 11® process, Philip Morris (PM) NH_3/CO_2 process, and North Carolina State University (NCSU) freeze drying process (7)

Analyte	Standard experimental blend, SEBII	RJRT Freon 11® process		PM NH_3/CO_2 process		NCSU process	
		Per cig	% Decrease from SEBII	Per cig	% Decrease from SEBII	Per cig	% Decrease from SEBII
Total particulate matter (TPM), mg/cig	32.76	18.66	43	22.33	32	19.56	40
Nicotine, mg/cig	1.79	0.78	57	0.74	59	0.82	54
Carbon monoxide, mg/cig	19.8	11.7	41	14.8	25	15.4	22
Formaldehyde, µg/cig	31	21	32	22	29	33	-6
Acetaldehyde, µg/cig	986	814	17	720	27	968	2
Acrolein, µg/cig	102	105	-3	88	14	92	10
Phenol, µg/cig	124	48	61	66	47	68	45
Hydrogen cyanide, µg/cig	354	199	44	287	19	234	34
Nitrogen oxides, µg/cig	386	247	36	293	24	235	39
Benz[*a*]anthracene, ng/cig	30.5	16.4	46	14.5	52	18.4	40
Benz[*a*]anthracene, ng/mg TPM	0.93	0.88	5	0.65	30	0.94	-1
Benzo[*a*]pyrene, ng/cig	23.3	14.2	40	10.0	57	11.1	53
Benzo[*a*]pyrene, ng/mg TPM	0.71	0.76	–7	0.45	37	0.57	20
Tumor-bearing animals, %							
at 25 mg/day dose	48	37	23	36	25	36	25
at 50 mg/day dose	48	48	ND	47	ND	47	ND

Macrophages exposed to the MSS from cigarettes with G13-expanded tobacco and a residual Freon 11® level of 50 ppm recovered their activity slightly more rapidly than similar cells exposed to the MSS from control unexpanded tobacco cigarettes (51).

The results of an 18-month mouse skin-painting bioassay [b] (dose = 25 mg/day of the appropriate CSC) contracted by RJRT to Industrial Bio-Test Laboratories, Inc. indicated that the MS CSC from cigarettes containing G13-expanded tobacco (residual Freon 11® level = 50 ppm at time of smoking) showed a slightly reduced specific tumorigenicity when compared to the control tobacco CSC (52). This reduction (35.0% tumor-bearing animals for the expanded tobacco CSC vs. 37.7% for the control tobacco CSC) was not statistically significant. The survival rates to the end of the experiments (18 months) were 50.5% for the expanded tobacco CSC group vs. 45.9% for the control group.

These findings with RJRT G13-expanded tobacco were duplicated by NCI (7, 53) and by DONTENWILL and his colleagues (54).

In the "less hazardous" cigarette study of the NCI Smoking and Health Program, the chemical properties of the MSSs and the biological properties of the cigarette smoke condensates (CSCs) from G13-expanded tobacco (25, 26) were examined, the latter in a mouse skin-painting study at two dose levels (25 and 50 mg/day) (7). The chemical and biological results are summarized in Tables 7 and 8, respectively. At the low dose level (25 mg/day), the % tumor-bearing animals (% TBA) were reduced from 47.5 to 37.0% (–22%); at the high dose level (50 mg/day), no difference in the % TBA was noticed. It should be recalled that throughout the numerous NCI "less hazardous" cigarette studies, problems were repeatedly encountered between the results obtained at high-dose levels of CSC (50 mg/day) vs. those obtained at the low-dose levels of CSC (25 g/day) (6, 7, 8). These differences will not be discussed here.

As part of the NCI study on the second series of cigarettes (7) with Standard Experimental Blend II (SEBII), the MS CSCs from cigarettes containing two other expanded SEBII tobaccos were examined chemically and biologically: SEBII expanded by the Philip Morris (PM) ammonia/carbon dioxide process (55) and SEBII expanded by the North Carolina State University (NCSU) freeze-drying process (56).

The chemical composition data (Table 7) collected in the NCI study on the MSSs from cigarettes containing the three expanded tobaccos were limited to those smoke components categorized in the mid-1970s as possible toxicants. However, a 1971 publication by ENZELL *et al.* presented the results of a comparison of the composition of the MSS vapor phase from cigarettes containing freeze-dried tobacco vs. that from cigarettes containing a control tobacco (49). One of the participants in the ENZELL *et al.* study was JOHNSON, the major contributor to the freeze-dried tobacco concept (56).

The MSS vapor-phase components identified by gas chromatography/mass spectrometry are listed in Table 6. The authors concluded that there were no significant differences in composition between the vapor phases of the MSSs derived from the two differently treated tobaccos. Surprisingly however was the fact that several components identified in the MSS vapor phase from the freeze-dried tobacco cigarette were not found in the MSS vapor phase from the control cigarette. These components, previously reported many times in cigarette MSS, included 2,3-butanedione, 2-butanone, phenol, 2-propanone (acetone), and 2-propenal (acrolein). Despite the fact that these components, demonstrated to be ciliastatic (57), were not

[b] The protocol used in the mouse skin-painting bioassay paralleled that described in the NCI "less hazardous" cigarette studies except for one major difference: A Borgwaldt 30-port smoking machine was used to circumvent the problems associated with the 360-port Process and Instruments Corporation smoking machine used throughout the NCI studies.

Table 8. Summary of mouse skin-painting and inhalation bioassays with expanded tobacco mainstream smoke

Cigarette tobacco blend			Tumor-bearing animals, %		
Control, %	RJR-expanded, %	Host	Carcinoma	Papilloma	Total
Skin-painting bioassay					
Industrial Bio-Test study (52): 25 mg/day, 6 times/week					
100%	0	220 mice	21 (9.5) [a]	62 (28.1)	83 (37.7)
0	100	220 mice	14 (6.4)	63 (28.6)	77 (35.0)
National Cancer Institute study (7): 25 mg/day, 6 times/week					
100%	0	400 mice	93 (23.3)	97 (24.3)	190 (47.5)
0	100	100 mice	15 (15.0)	22 (22.0)	37 (37.0)
National Cancer Institute study (7): 50 mg/day, 6 times/week					
100%	0	400 mice	127 (31.8)	66 (16.5)	193 (48.3)
0	100	100 mice	23 (23.0)	25 (25.0)	48 (48.0)
Dontenwill *et al*. study (54): 34.6 mg/day, 6 times/week					
100	0	111 mice	18 (16.2)	22 (19.8)	40 (36.0)
50	50	75 mice	6 (8.0)	14 (18.7)	20 (26.7)
Inhalation bioassay					
Dontenwill *et al.* study (58): Two exposures/day to MSS from 30 cigarettes					
100	0	160 hamsters	16 (10.0)	38 (23.8)	54 (33.8)
50	50	160 hamsters	10 (6.3)	25 (15.6)	35 (21.9)

[a] Number in parentheses = %.

found in the control tobacco smoke vapor phase, ENZELL *et al*. reported that the ciliastatic effect of the smoke from the two tobacco-type cigarettes showed no significant difference between the number of puffs required to achieve complete ciliastasis in an in vitro study.

As indicated in Tables 7 and 8, all three tobacco expansion processes were found to beneficially modify the MSS compositions and to reduce the specific tumorigenicities of the CSCs.

In the summary report of the NCI Smoking and Health Program on "less hazardous" cigarette studies (53), the expansion processes received the following comment:

> Condensates of the Reynolds puffed, Philip Morris expanded, and [NCSU] freeze-dried SEB II blends showed no statistically differences among themselves, but the expanded and freeze-dried SEB II blends showed significantly lower condensate tumorigenicity than SEB II.

The second mouse skin-painting study of G13-expanded tobacco was conducted by DONTENWILL *et al*. (54). They reported a reduction in the specific tumorigenicity elicited by G13-expanded tobacco CSC vs. control tobacco CSC: The % TBA was reduced from 35.1% for the control tobacco CSC-treated mice to 26.7% for the expanded tobacco CSC-treated mice, a reduction of 24%. The CSC dose level used by DONTENWILL *et al*. was 34.6 mg/day but the test cigarettes containing the expanded tobacco were a 50:50 (by weight) blend of expanded and unexpanded tobaccos. DONTENWILL *et al*. wrote:

> Significant lower effects were observed in the test series from cigarettes with expanded tobacco.

In a study involving 50:50 expanded tobacco:control tobacco, DONTENWILL *et al*. (58) also examined the effect of whole MSS administered by inhalation to golden hamsters. The % TBA for expanded tobacco smoke exposure represented 22.0% vs. 33.8% for the control MSS-exposed group, an overall specific tumorigenicity reduction of 35%. The results from the skin-painting and inhalation studies of DONTENWILL *et al*. are summarized in Table 8.

In a more recent study, COGGINS *et al*. (59) in the search for an alternative to Freon 11® compared the inhalation effect in rats of the MSS from a cigarette containing a tobacco alternatively expanded with Freon 123® (dichlorotrifluoroethane) with the inhalation effect in rats of a cigarette containing Freon 11®-expanded tobacco. The bioassay involved three inhalation dose levels (1-h/day exposure, 5 day/week for 13 weeks) with 64 Sprague-Dawley rats (32 males, 32 females) exposed at each level. No significant difference was noted between the MSSs from the Freon 11®- and Freon 123®-expanded tobaccos.

With regard to the definition of a "less hazardous" cigarette, expanded tobacco incorporated into a cigarette tobacco blend: It lowers 1) the MSS FTC 'tar' and nicotine deliveries of the cigarette, 2) the levels per mg of 'tar' of several components allegedly responsible for the tumorigenic response observed in mouse skin-painting studies, 3) the specific tumorigenicity to mouse skin of the MSS 'tar' obtained from such cigarettes and the specific tumorigenicity observed in whole smoke inhalation studies with hamsters, and 4) the levels delivered per cigarette of several vapor-phase components considered problems by some investigators. With Freon 11®-expanded tobacco, only one known qualitative change occurs in the MSS composition, i.e., the presence of extremely low levels of the expansion agent Freon 11®.

In his 1979 report on smoking and health, the US Surgeon General summarized the effect of inclusion of expanded tobacco in cigarettes as shown in Table 9 (9).

TOBACCO EXPANSION PROCESSES

Inclusion of expanded tobacco in a cigarette blend in combination with other cigarette design parameters (air dilution by paper porosity and/or filter-tip perforation), filter-tip efficiency) permits the design of cigarettes whose FTC

Table 9. Effect of tobacco expansion on cigarette mainstream smoke properties

Property	Effect
'Tar'	50% or more reduction
Nicotine	50% or more reduction
Benzo[*a*]pyrene	50% or more reduction
Carbon monoxide	Significant reduction
Specific tumorigenicity [a] of 'tar'	questionable reduction
Tumor promotion [a]	questionable reduction
Ciliatoxicity	questionable reduction

[a] Mouse skin-painting bioassay.

'tar' delivery may be less than 1 mg/cig. Appropriate combination of such design parameters has permitted the design of cigarettes which deliver 0.1 mg of FTC 'tar'.

Obviously, expanded tobacco is a substantial economic plus for the manufacturers, but it is also a powerful design tool for the generation of low-FTC 'tar' cigarettes. That this is true is demonstrated by the several expansion processes that were developed immediately after the RJRT expansion process became public. The RJRT expansion process and the effect of the inclusion of expanded tobacco in the cigarette tobacco blend on the chemical and biological properties of cigarette MSS were presented to personnel at numerous cigarette manufacturing companies in many countries.

The ammonia/carbon dioxide expansion process has an interesting history. As a result of experimentation by FREDRICKSON *et al*. (60), RJRT was issued a Belgian patent in May 1971 on the expansion of tobacco with ammonia/carbon dioxide (61). Three months later, Philip Morris was issued a similar Belgian patent (62). Because RJRT failed to submit a US patent application within the requisite allotted time period and Philip Morris did so, a US patent on the ammonia/carbon dioxide expansion of tobacco was subsequently issued to Philip Morris personnel in 1973 (63).

At RJRT, MAYS *et al*. (64) investigated the preparation of ammonia/carbon dioxide-expanded tobacco by the procedures described in the US patent issued to Philip Morris. The MSS chemical properties of the tobacco thus expanded were assessed and compared to those from the same tobacco blend expanded with Freon 11®. Both ammonia/carbon dioxide-expanded flue-cured and burley tobaccos were studied. Table 10 summarizes the comparison data for two expanded flue-cured tobaccos. From the analytical data on the tobacco expanded in a laboratory procedure with ammonia/carbon dioxide, it was apparent the expanded tobacco was not only denicotinized but also, on the basis of increased % nitrogen, the expanded tobacco contained additional ammonia bound to one or more tobacco components.

In the mid-1995s, any processing of tobacco that involved ammoniation was criticized by various governmental agency, e.g., the US Food and Drug Administration in its 1995 report (65), because of the alleged effect of residual ammonia on MSS pH and the effect of increased MSS pH and tobacco-to-MSS transferred ammonia on properties of MSS nicotine and its absorption by the smoker. However, such criticism should be contrasted with the recent findings reported by ARMITAGE *et al*. (66). They reported that comparison of the MSSs from a control cigarette, one treated with diammonium hydrogen phosphate (DAP), and one treated with urea indicated that the "smoke pH" of the control was almost identical with that of the DAP-treated cigarette, 5.6 vs. 5.5, and the "smoke pH" of the urea-treated cigarette was slightly higher at 6.1. In all cases, there were no significant differences between the indices of nicotine uptake into venous blood for the three cigarettes.

Table 7 summarizes data on the MSS from ammonia/carbon dioxide-expanded tobacco vs. control tobacco. These data were obtained in the second series (7) of experimental cigarettes in the NCI Smoking and Health Program on "less hazardous" cigarettes. The nicotine level in the expanded tobacco was substantially less than that in the control tobacco (0.95% vs. 1.80% represents a 48% reduction). This reduction translated to the per cigarette FTC nicotine yields in the expanded-tobacco MSS vs. control-tobacco MSS: 0.74 mg/cig vs. 1.79 mg/cig, a 59% reduction.

Data on the effect of ammonia/carbon dioxide expansion of tobacco indicate that the levels of pyrazine and several

Table 10. Freon 11® and ammonia/carbon dioxide expansion of flue-cured tobacco

Analyte	100% FCC [a]	90% FCC 10% FCA	90% FCC 10% FCF	100% FCA	100% FCF
Total particulate matter (TPM), mg/cig	40.8	36.7	34.5	25.6	23.4
Nicotine, mg/cig	2.75	2.34	2.37	1.18	1.25
FTC 'tar', mg/cig	32.9	28.9	27.7	19.9	18.2
Carbon monoxide, mg/cig	15.6	15.2	15.0	9.2	7.0
Ammonia, µg/cig	48	55	41	188	24
Formaldehyde, µg/cig	31	28	33	15	23
Acetaldehyde, µg/cig	970	875	800	645	575
Acrolein, µg/cig	117	108	106	99	93
Phenol, µg/cig	126	127	134	81	70
Hydrogen cyanide, µg/cig	313	324	334	363	247
Nitrogen oxides, µg/cig	97	101	104	104	64
Benzo[*a*]pyrene, ng/cig	28.5	26.8	29.0	10.2	8.7
Benzo[*a*]pyrene, ng/mg TPM	0.70	0.73	0.84	0.40	0.37

[a] FCC = Flue-cured control; FCA = flue-cured tobacco expanded with ammonia/carbon dioxide; FCF = flue-cured tobacco expanded with Freon 11®.

Table 11. Ammonia/carbon dioxide expansion of flue-cured tobacco: Effect on tobacco and mainstream smoke composition (68,69)

Analyte	Flue-cured tobacco			Burley tobacco	
	100% Control	90% Control: 10% Expanded	100% Expanded	100% Control	100% Expanded
		Tobacco analysis			
Nicotine, %	2.26		1.56	3.50	2.82
Sugars, %	15.10		8.61	0.99	0.70
Ammonia, %	0.14		0.82	0.50	0.89
Total N, %	1.90		3.19	3.8	4.2
		Mainstream smoke analysis [a]			
TPM, mg	40.8	36.7	25.6	27.7	21.5
Nicotine, mg	2.75	2.34	1.18	1.92	1.28
FTC 'tar', mg	32.9	28.9	19.9	22.3	17.4
Formaldehyde, µg	31.2	28.0	15.2		
Acetaldehyde, µg	970	875	645		
Acrolein, µg	117	108	99		
Ammonia, µg	48	55	188	78	223
Benzo[*a*]pyrene, ng	28.5	26.8	10.2		
			% Increase over control MSS yield		
Pyrazines					
Pyrazine			236		148
Pyrazine, 2-methyl-			345		139
Pyrazine, 2-ethyl-			103 [b]		98
Pyrazine, 2,3-dimethyl-			436		84
Pyrazine, 2,5-dimethyl-			412		142
Pyrazine, 2,6-dimethyl-			918		102
Pyrazine, 2,3,5-trimethyl-			361		208
Pyrazine, 2-ethyl-5-methyl-			229		121
Pyridines					
Pyridine			<10		0
Pyridine, 2-methyl-			14		58
Pyridine, 3-methyl-			<10		–12
Pyridine, 4-methyl-			42		19
Pyridine, 2-ethyl-			51		–18
Pyridine, 3-ethyl-			–26		–19
Pyridine, 2,3-dimethyl-			34		21
Pyridine, 2,4-dimethyl-			58		ND [b]
Pyridine, 2,5-dimethyl-			103 [c]		25

[a] Per cigarette delivery.
[b] ND = not determined.
[c] Mixture of 2-ethylpyrazine and 2,5-dimethylpyridine.

flavorful alkylpyrazines are increased significantly (Table 11). Also, the expansion reduces the level of nicotine in tobacco and its level in MSS not only because of the reduced level of nicotine available for transfer from tobacco to MSS but also because of its enhanced decomposition (67) to pyridine and alkylpyridines whose per cigarette yields, like those of pyrazine and the alkylpyrazines, are also increased in the MSS of ammonia/carbon dioxide expansion of tobacco (68, 69). If, however, the ammonia treatment of the tobacco moderately reduces the nicotine level of the tobacco, the levels of the alkylpyridines in MSS from such tobacco are not necessarily increased over those in the control tobacco MSS.

Ammonia/carbon dioxide expansion of tobaccos with high sugar levels, e.g., flue-cured tobaccos with 15–20% sugars, substantially increased the levels of alkylpyrazines in the MSS from such tobaccos. Only a slight increase in MSS alkylpyrazines was observed with low sugar tobaccos such as burley (sugar levels usually less than 2%).

The flavorful properties of pyrazines have been well documented over the years. They contribute significantly to the desirable flavor of a variety of foodstuffs, including tea and coffee (70), cocoa and chocolate (71), roasted peanuts and peanut butter (72), roasted meats (beef, poultry, fish) (70), etc.

While it has been argued by critics of tobacco smoking, particularly cigarette smoking, that the smoker's habit is significantly influenced by MSS pH, MSS per puff nicotine yield, and their effect on nicotine absorption (65), it may equally well be argued that the increased per cigarette yields of flavorful components such as the pyrazines plus the decreased per cigarette yields of such irritants as the low molecular weight acids (formic, acetic) and aldehydes [formaldehyde, acetaldehyde, 2-propenal (acrolein)] are responsible for the consumer's preference for cigarettes containing ammoniated blend components (69).

Tobacco, treated with ammonia under certain conditions, may generate cigarette TPM which, when evaluated in the

Table 12. Specific tumorigenicity and mutagenicity of mainstream smokes from cigarettes containing different tobacco types

Analysis	Sequence of mainstream smoke from different tobacco types
	Specific tumorigenicity
Mouse skin painting, % TBA	flue-cured ≥ Oriental > Maryland > burley
B[*a*]P, ng/mg TPM	flue-cured > Oriental > Maryland > burley
Phenol, mg/mg TPM	flue-cured > Oriental > Maryland > burley
N-Nitrosamines, ng/mg TPM	flue-cured < Oriental < Maryland = burley
	Specific mutagenicity
Ames test, revertants/mg TPM [a]	flue-cured < Oriental < Maryland < burley
Total N, % of filler	flue-cured < Oriental = Maryland < burley
N-Nitrosamines, ng/mg TPM	flue-cured < Oriental < Maryland = burley
B[*a*]P, ng/mg TPM	flue-cured > Oriental > Maryland > burley

[a] Results reported by SMEETON *et al*. (73) and MIZUSAKI *et al*. (77)

Table 13. Effect of expanded stems on mainstream smoke composition (79)

Analyte	Standard Experimental Blend, SEBIV,100% [a]	SEBIV:RJRT expanded stems 50:50		RJRT expanded stems, 100%	
		Per cig	% Decrease from SEBIV	Per cig	% Decrease from SEBIV
Total particulate matter (TPM), mg/cig	31.3	19.5	38	11.4	64
Nicotine, mg/cig	1.96	0.64	68	0.18	91
Carbon monoxide, mg/cig	20.1	17.8	12	14.8	26
Formaldehyde, µg/cig	32	28	12	35	−9
Acetaldehyde, µg/cig	985	801	19	546	45
Acrolein, µg/cig	109	118	−8	95	13
Phenol, µg/cig	146	91	38	57	61
Hydrogen cyanide, µg/cig	334	204	39	146	56
Nitrogen oxides, µg/cig [b]	297	247	17	269	9
Benz[*a*]anthracene, ng/cig	35.7	17.6	51	14.7	59
Benz[*a*]anthracene, ng/mg TPM	1.14	0.90	21	1.29	−13
Benzo[*a*]pyrene, ng/cig	22.2	14.8	33	11.6	49
Benzo[*a*]pyrene, ng/mg TPM	0.71	0.76	−7	1.02	−44
Tumor-bearing animals, %					
at 12.5 mg/day dose	28	23	18	4	86
at 25 mg/day dose	54	45	17	27	50

[a] Average of quadruplicate analyses.
[b] Expressed as nitric oxide, NO.

Ames-type bioassay (*Salmonella typhimurium*), gives a higher specific mutagenicity, *i.e.*, an increased number of revertants/mg, than the TPM from the control tobacco (73). However, the meaning of this finding is unclear when one considers the results in the NCI study from the mouse skin-painting bioassay on the CSC from the Philip Morris ammonia/carbon dioxide-expanded tobacco (7). As may be noted from Table 8, the specific tumorigenicity at a 25 mg/day dose of the CSC from ammonia/carbon dioxide-expanded tobacco was significantly lower than that for the CSC from the control tobacco. Thus, we have the paradox of an ammoniated tobacco product which generates a TPM that possesses reduced specific tumorigenicity in the mouse skin-painting bioassay but increased specific mutagenicity in the Ames test! This is not the first time that such a paradox between specific tumorigenicity and specific mutagenicity of various CSCs was observed.

WYNDER and HOFFMANN (74) and HOFFMANN and WYNDER (75) asserted that the specific tumorigenicities of CSCs from different tobacco types, their B[*a*]P contents, and their phenol contents follow the sequence indicated in Table 12. DEMARINI (76), in his review of the mutagenicity of CSCs from cigarettes containing different tobacco types, noted the significant difference between the specific mutagenicity (measured in the Ames test with *Salmonella typhimurium*) and specific tumorigenicity (measured in the mouse skin-painting bioassay). DEMARINI cited the findings of MIZUSAKI *et al.* (77). The sequence of tobacco type specific mutagenicities is summarized in Table 12.

The supposed significant correlation between the specific mutagenicity of a compound or material and its specific tumorigenicity raises the question *Which bioassay should be relied on to satisfy the biological aspect of the definition of a "less hazardous" cigarette?*

In the late 1970s, ethane and propane were proposed as alternatives to Freon 11® as expansion agents for tobacco: Both were found to be effective (78).

As noted previously in this report, two of the design technologies considered significant in the design of a "less hazardous" cigarette are RTS and expanded tobacco. A large percentage of RTS is tobacco stems. In the NCI "less hazardous" cigarette program, the effect of a combination of these expanded tobacco stems on MSS properties was studied in the fourth set of experimental cigarettes (79). The results are summarized in Table 13. The

specific tumorigenicity decreased at both CSC dose levels (12.5 and 25 mg/day) despite the increased per mg of 'tar' yield of B[*a*]P.

In 1979, DUBE *et al*. (48) compared the MSS composition from cigarettes fabricated from tobaccos expanded in the G13 process with Freon 11® with that from cigarettes fabricated from tobaccos expanded with pentane, one of the original expansion agents studied by FREDRICKSON (22, 23). Except for traces of Freon 11® in the G13-expanded tobacco MSS, the compositions of the two MSSs were qualitatively the same. The effect of the residual pentane on its level in MSS would be difficult to ascertain since pentane is a normal component of tobacco smoke (80). The pentane-expanded tobacco contained slightly higher levels of such flavorful components as the pyrazines than did the G13-expanded tobacco.

With the availability of improved fractionation technology and a wealth of spectral data from several smoke studies (40, 41), an informative study was conducted in the late 1970s on the effect of tobacco expansion (by Freon 11®) on the level of natural flavorful components of the tobacco. HECKMAN and WENDELBOE compared the levels of over 75 identified essential oil components in a control and expanded cased and flavored tobacco (81). They concluded that the expansion process resulted in moderate decreases for most essential oil components. Their results are summarized in Table 14. Highlighted in bold print are 33 tobacco components which, according to the DOULL *et al.* (82) list of 460 compound ingredients [see Table 1 in RODGMAN (83)], are used in flavor formulations by one or more members of the US Tobacco Industry. Of the highlighted components, the levels of 25 of them in the processed tobacco are reduced by expansion, the levels of the other eight are either increased [benzeneacetic acid, benzoic acid, 1-(1*H*-pyrrol-2-yl)ethanone (2-acetylpyrrole), 1-pentanol, 2-methoxyphenol (guaiacol), 1*H*-pyrrole] or remain unchanged [decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2(1*H*)-one (sclareolide), 6,10-dimethyl-5,9-undecadien-2-one (geranyl acetone)]. The statements that many tobacco ingredients used in the US Tobacco Industry are identical with known tobacco components (4, 82, 84, 85, 86) are substantiated by the findings of HECKMAN and WENDELBOE (81) on expanded tobacco vs. control tobacco.

Thus, the addition in a flavor formulation of compounds reduced in level by tobacco processing fits the previous statement (83):

> If a specific flavorful compound is already a tobacco component, then its addition is an attempt to enhance its flavorful effect.

During the investigations from the late 1960s through the late 1970s of the composition of MSS from cigarettes containing expanded tobaccos or blends of various ratios of expanded tobacco to control tobacco, considerable data were generated on the per cigarette yields of some of the components classified at that time as toxicants. The analytical data generated are summarized in Table 7. It is interesting to note that many of the MSS components determined quantitatively in industrial and governmental laboratories were eventually classified in the late 1990s as "Hoffmann analytes" because of their frequent listing as harmful smoke components by HOFFMANN *et al.* [(18, 19, 87), see also Table 2 in RODGMAN (88)]. In addition to the data compiled in Table 7, the per cigarette MSS yields were determined for several other components subsequently classified as carcinogens or tumorigens. They include acetamide, 1,3-butadiene, 2-methyl-1,3-butadiene (isoprene), benzene, 1,2-benzenediol (catechol), di(2-ethylhexyl) phthalate, DDE, DDD, and quinoline. They are highlighted in bold print in Table 6 with an indication of their per cigarette MSS levels from control vs. expanded tobacco cigarettes.

CONCLUSIONS

Because of previously presented data on the effect of the expansion of tobacco on the composition and biological properties of the MSS from cigarettes containing it, tobacco expansion has long been recognized as a technology significant in the design of a "less hazardous" cigarette. Previously unpublished data pertinent to expanded tobacco and its smoke, presented in detail herein, not only confirm but also bolster the significance of expanded tobacco and its smoke in "less hazardous" cigarette design. The MSS yields per cigarette of many of the MSS components classified as tumorigenic, carcinogenic, or biologically active are reduced as a result of inclusion of expanded tobacco in the blend. The reduction of the levels of significant flavorful tobacco components as a result of expansion provides a logical reason for inclusion of such compounds in flavor formulations as a means to retain consumer acceptance.

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Table 14. Effect of expansion of tobacco on its essential oil composition (81)

Tobacco component	CAS No.	Alternate name	Freon 11®-expanded tobacco vs. control tobacco: difference, %
Benzaldehyde [a]	100-52-7		**−12**
Benzaldehyde, 4-hydroxy-3-methoxy-	121-33-5	vanillin	**−50**
Benzene, methyl-	108-88-3	toluene	−10
Benzeneacetaldehyde	122-78-1	phenylacetaldehyde	**−16**
Benzeneacetic acid	103-82-2	phenylacetic acid	**7**
Benzeneethanol	60-12-8	phenethyl alcohol	**−22**
Benzenemethanol	100-51-6	benzyl alcohol	**−21**
2(3*H*)-Benzofuranone, hexahydro-4,4,7a-trimethyl-	16778-27-1	dihydroactinidiolide; mariolide	−19
Benzoic acid	65-85-0		**2**
1,3-Benzodioxole-5-carboxaldehyde	120-57-0	heliotropin; piperonal	0
7*H*-1-Benzopyran-7-one, 2,3,5,6,8,8a-hexahydro-2,5,5,8a-tetramethyl-	20194-67-6		−22
7*H*-1-Benzopyran-7-one, octahydro-2,5,5,8a-tetramethyl-	5835-18-7		−21
Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, acetate	32214-91-8	β-caryophyllene acetate	—
2,3'-Bipyridine	581-50-0	isonicoteine	−26
Butanoic acid	107-92-6		**−85**
Butanoic acid, 2-methyl-	116-53-0		**−80**
Butanoic acid, 3-methyl-	503-74-2	isovaleric acid	**−55**
Butanoic acid, 3-methyl-, 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester [b]	76-50-6	bornyl isovalerate	−12
1-Butanol, 3-methyl-	123-51-3	isoamyl alcohol	6
2-Buten-1-one, 1-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-	56915-02-7	4-hydroxy-β-damascone	−20
2-Buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-	23696-85-7	β-damascenone	−8
2-Buten-1-one, 1-(2,6,6-trimethylcyclohexenyl)-	23770-92-3	β-damascone	−24
3-Buten-2-one, 4-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-	1203-08-3		9
Cyclohexane-1,4-dione, 2,6,6-trimethyl-	20547-99-3	4-ketodihydroisophorone	−21
2-Cyclohexene-1,4-dione, 2,6,6-trimethyl-	1125-21-9	4-ketoisophorone	13
2-Cyclohexen-1-one, 4-(2-butenylidene)-3,5,5-trimethyl- {4 isomers}	13215-88-8	megastigmatrienone	**−17, −18, −17, −17**
2-Cyclohexen-1-one, 4-(3-hydroxy-1-butenyl)-3,5,5-trimethyl-	34318-21-3	4-keto-a-ionol	−11
2-Cyclohexen-1-one, 4-(3-hydroxybutyl)-3,5,5-trimethyl-	60047-19-0	4-ketodihydro-a-ionol	−4
2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl-, acetate	29548-30-9	farnesyl acetate	−6
Ethanone, 1-(2-furanyl)-	1192-62-7	2-acetylfuran	871
Ethanone, 1-(1*H*-pyrrol-2-yl)-	1072-83-9	2-acetylpyrrole	**131**
Furan, 3-(4,8,12-trimethyltridecyl)-	42933-00-6	phytofuran	27
2-Furancarboxaldehyde	98-01-1	furfural; 2-furaldehyde	79
2-Furancarboxaldehyde, 5-methyl-	620-02-0		27
2-Furanmethanol	98-00-0	furfuryl alcohol	101
2-Furanmethanol, 5-methyl-	3857-25-8		95
2(3*H*)-Furanone	20825-71-2	butenolide	18
2(3*H*)-Furanone, dihydro-	96-48-0	butyrolactone	3
2(3*H*)-Furanone, dihydro-2-methyl-	3188-00-9		146
2(5*H*)-Furanone, 3-methyl-	22122-36-7		−28
2(5*H*)-Furanone, 5-methylene-	108-28-1	protoanemonin	104
Heptanoic acid	111-14-8	enanthic acid	**−60**

Table 14 (*cont.*)

Tobacco component	CAS No.	Alternate name	Freon 11®-expanded tobacco vs. control tobacco: difference, %
5-Hepten-2-one, 6-methyl-	110-93-0		**−7**
Hexadecanoic acid	57-10-3	palmitic acid	9
Hexadecanoic acid, methyl ester	112-39-0	methyl palmitate	10
1-Hexadecene, 3-methylene-7,11,15-trimethyl-	504-96-1	neophytadiene	−8
2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-	150-86-7	phytol	19
Hexanoic acid	142-62-1	caproic acid	**−46**
2-Hexenal	505-57-7		**−29**
3-Hexen-1-ol (*Z*)	928-96-1	leaf alcohol	**−32**
1*H*-Indole	120-72-9		−15
2(3*H*)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-	4674-50-4	nootkatone	−20
Naphtho[2,1-*b*]furan-2(1*H*)-one, decahydro-3a,6,6,9a-tetramethyl-	564-20-5	sclareolide	**0**
6,8-Nonadien-2-ol, 8-methyl-5-(1-methylethyl)- {2 isomers}	40525-38-0	solanol	−27, −16
6,8-Nonadien-2-one, 8-methyl-5-(1-methylethyl)-	1937-54-8	solanone	−4
Nonanoic acid	112-05-0	pelargonic acid	−63
3-Nonene-2,8-dione, 5-(1-methylethyl)-	60619-46-7	oxysolanone	−16
9,12-Octadecadienoic acid, methyl ester	2462-85-3	methyl linoleate	**−4**
9,12,15-Octadecatrienoic acid, methyl ester	301-00-8	methyl linolenate	**−35**
1,6-Octadien-3-ol, 3,7-dimethyl-	78-70-6	linalool	**−35**
Octanoic acid	124-07-2	caprylic acid	−18
3-Octanol, 3,7-dimethyl-	78-69-3	tetrahydrolinalool	−5
2-Pentadecanone, 6,10,14-trimethyl-	502-69-2	phytone	2
5,9,13-Pentadecatrien-2-one, 6,10,14-trimethyl-	762-29-8	farnesyl acetone	4
Pentanoic acid	109-52-4	valeric acid	**−81**
Pentanoic acid, 3-methyl-	105-43-1	β-methylvaleric acid	**−34**
1-Pentanol	71-41-0	amyl alcohol	**17**
Phenol	108-95-2		22
Phenol, 4-ethenyl-	2628-17-3	*p*-vinylphenol	−43
Phenol, 4-ethenyl-2-methoxy-	7786-61-0	4-vinylquaiacol	**−19**
Phenol, 2-methoxy-	90-05-1	guaiacol	**0**
Propanoic acid	79-09-4	propionic acid	**−79**
2-Propanone, 1-hydroxy-	116-09-6	acetol	80
2-Propanone, 1-[tetrahydro-6-methyl-3-(1-methylethyl)-2*H*-pyran-2-yl]	39815-68-4		−23, −21
2*H*-Pyran-2-one, tetrahydro-4-(1-methylethyl)-	56947-55-8		−11
4*H*-Pyran-4-one, 3-hydroxy-2-methyl-	118-71-8	maltol	871
Pyridine, 3-(1-methyl-1*H*-pyrrol-2-yl)-	487-19-4	nicotyrine	−26
1*H*-Pyrrole	109-97-7		**16**
1*H*-Pyrrole-2,5-dione, 3-ethyl-4-methyl-	20189-42-8		−23
5,9-Undecadien-2-one, 6,10-dimethyl-	3796-70-1	geranyl acetone	**0**

[a] Tobacco components presented in bold print are listed by DOULL *et al*. (82) as additives used by one or more members of the US Tobacco Industry.
[b] While not listed by DOULL *et al*. (82) as an cigarette additive used by one or more members of the US Tobacco Industry, it is used as a cigarette additive elsewhere (85).

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