Pharmacological and Chemical Effects of Cigarette Additives

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We investigated tobacco industry documents and other sources for evidence of possible pharmacological and chemical effects of tobacco additives.

Our findings indicated that more than 100 of 599 documented cigarette additives have pharmacological actions that camouflage the odor of environmental tobacco smoke emitted from cigarettes, enhance or maintain nicotine delivery, could increase the addictiveness of cigarettes, and mask symptoms and illnesses associated with smoking behaviors.

Whether such uses were specifically intended for these agents is unknown. Our results provide a clear rationale for regulatory control of tobacco additives. (*Am J Public Health.* 2007;97:1981–1991. doi:10.2105/AJPH.2005.078014)

ACCORDING TO THE WORLD Health Organization, there were approximately 1.3 billion smokers worldwide in 2003, and that number is expected to increase to 1.7 billion by 2020.[1] It is estimated that about 1 billion people will die from smoking in the 21st century.[2] Research conducted over the past several decades indicates that tobacco companies have engaged in extensive efforts, including developing genetically engineered tobacco to enhance nicotine delivery[3–6] and using reconstituted tobacco and nicotine extracts, to manipulate cigarette nicotine levels and influence people's smoking behaviors.

Reconstituted tobacco, referred to as "sheet," is a major ingredient in modern cigarettes; sheet is manufactured from recycled stems, stalks, scraps, collected dust, and floor sweepings.[7] Those materials are ground up, nicotine is extracted from them, and chemicals, fillers, glue, and other agents are added to the slurry. The sheet is then pressed out and puffed, with the previously extracted nicotine sprayed onto it, and ground into tiny curls before being incorporated into cigarettes at the desired level.[7] Tobacco companies have studied nicotine extracts as a method to augment nicotine levels in cigarettes.[8–14]

In addition, tobacco companies have devoted a significant amount of research and development to the use and inclusion of additives in cigarettes, and the industry has acknowledged using 599 different cigarette additives.[15,16] According to various tobacco company documents, many of these additives are used to improve taste and decrease harshness.[17] We propose that, in contrast, tobacco companies have expended resources to exploit the pharmacological and chemical effects of cigarette additives.

The tobacco industry used few additives in US cigarettes before 1970.[18] However, current US-style cigarettes generally contain about a 10% level of additives according to weight, mostly in the form of sugars, humectants, ammonia compounds, cocoa, and licorice.[19,20] Most other additives are used in small amounts, less than 0.01% of total weight. There is evidence that the percentage of additives by weight may have increased in the 1990s, especially the use of sweeteners (which many researchers believe were added to entice younger people to smoke).[18] Those increases roughly coincided with the controversial Joe Camel cigarette advertising campaign initiated by RJ Reynolds in 1985.

Previous studies have reviewed the use of ammonia technology to increase levels of nicotine and free base nicotine in cigarette smoke[18]; the use of additives with additional or synergistic addictive potential, anesthetic properties, or

bronchodilator effects; and the use of additives that decrease environmental tobacco smoke (ETS) odor, visibility, and irritation without equivalent efforts to decrease the harmful effects of ETS.[18,21,22] These tobacco industry practices, motivated by awareness of public concern regarding ETS, may have led to nonsmokers as well as smokers being unaware or less aware of the presence of hazardous substances associated with ETS.[23–27]

In this study, we examined the tobacco industry's use of additives that inhibit nicotine metabolism and increase the addictive potential of cigarettes, with a particular focus on the neurological techniques used by Philip Morris to assess the effects of additives on smokers' central nervous system functioning. We also explored the addition of antioxidants and mitigants to cigarettes in an attempt to prevent illness, genetic modifications of tobacco to increase levels of beta-carotene and incorporate molecules intended to decrease carcinogenic tobacco-specific nitrosamines, the use of other "beneficial" additives and specific chemical additives, and the tobacco industry's objections[17] to scientific discussions[18] about additives used for cigarette engineering and nicotine addiction.

METHODS

We used 5 primary sources of information for our review. First, we examined an Indiana University Web site aggregate list of 599 known cigarette additives (the industry does not specify which brands use particular additives).[15] In 1984, the US Department of Health and Human Services began requiring tobacco companies to submit annually a confidential, aggregated list of ingredients added to cigarettes manufactured in or imported into the United States. In 1994, National Public Radio reported on a number of these ingredients, which caused a public outcry. Subsequently, in that same year, the 6 major US tobacco companies made the list public. This was the only time the list was made public, and there is no current public list of tobacco additives.

Second, we reviewed documents from 2000 to 2005 housed in the Legacy Tobacco Documents Library ("Legacy Library") at the University of California, San Francisco.[28] The Legacy Library contains 7 million documents related to different practices associated with tobacco products. Visitors can search, view, and download these documents from the library Web site. Included are documents posted on tobacco industry Web sites as of July 1999 in accordance with the Master Settlement Agreement, documents added to those sites since that time, and the document collections from the Tobacco Control Archives maintained by the University of California, San Francisco. New documents are added monthly as they are collected from industry sites.

Initially, we searched for documents about additives on the Indiana University list, as well as keywords such as "additive" and combinations of keywords such as "additive" and "environmental tobacco smoke." To further our understanding of the use of additives, we employed snowball sampling methods wherein the content of the documents we reviewed (e.g., names, references to other documents, and important concepts) would then be searched in the Legacy Library. We followed these document leads in an effort to better assess industry efforts associated with tobacco additives. In all, we reviewed more than 10 000 documents.

Third, we reviewed a Memorial Sloan Kettering Cancer Center Web site that included science-based information on herbs and other supplements.[29] Fourth, we searched US Patent and Trademark Office Web site databases[30] in an attempt to gain an understanding of patents referenced by numbers and titles in Legacy Library documents. Finally, we used Internet searches and tobacco-related and other reference textbooks[2,31] to gain greater insight into previously reviewed material. Internet search engine technology was used to locate information not in the Legacy Library and to verify the information found therein.

RESULTS

Nicotine Metabolism and Addiction Potential

Numerous chemical agents, including gamma-heptalactone, gamma-valerolactone, gamma-decalactone, delta-decalactone, gamma-dodecalactone, delta-undecalactone, and gamma-hexalactone, are mild to weak inhibitors of coumarin-7-hydroxylases (also known as CYP2A5 and CYP2A6; these are enzymes within the P450 enzyme system that metabolize compounds in the body).[32] These 7 chemicals are among those found on the additives list. Because CYP2A6 is involved in the metabolism of nicotine, the presence of these chemicals could decrease smokers' metabolism of nicotine and maintain higher blood levels (thus increasing smokers' exposure to nicotine by slowing degradation of nicotine in the bloodstream). Furthermore, the inhibitory effect of these chemicals on CYP2A6, although relatively weak in isolation, might be greater when the chemicals act in combination.

If nicotine were the only addictive chemical affecting smoking behavior, then puffing should decrease as the amount of inhaled nicotine increases. However, this hypothesis does not account for the effects of other addictive substances in cigarettes. Acetaldehyde is formed in high concentrations when cigarette constituents, including sugars, are burned. Animal research conducted by Philip Morris demonstrated a synergistic interaction between nicotine and acetaldehyde: rats pressed a bar more for the combination than for either substance alone.[33,34] If these data generalize to humans, then smokers would puff more with the combination of nicotine and acetaldehyde. Industry data show that the combination of sugar, sorbitol, and diammonium phosphate (DAP) increases tar and nicotine levels and number of puffs taken.[35]

Neuropsychological Assessments

Philip Morris developed the science of nicotine delivery and measurement of the effects of nicotine far beyond what was known by the medical community. One goal of the Philip Morris Behavioral Research Lab, described in a 1981 document, was to identify responses of the human brain that change in a predictable and reliable manner as a function of cigarette smoking.[36] In research projects conducted by Philip Morris from 1982 to 1995 (e.g., Project 1620[37]), electroencephalography (EEG), pattern reversal evoked potential (PREP), and chemosensory event-related potential (CSERP) were used to measure physiological, sensory, and cognitive changes related to nicotine and to cigarette additives.[38]

Increases in tobacco filler pH increased the "impact" (a tobacco industry term for smokers' subjective awareness of the drug effects of nicotine) and decreased PREP P_1 latencies (an objective electrophysiological measure of brain activity).[39] Philip Morris's research demonstrated "a systematic relationship between increases in filler pH and increases in gas phase (presumably unprotonated) nicotine."[37] Philip Morris researchers noted a significant positive correlation between impact scores and P_1-N_2 amplitudes (another objective electrophysiological measure of brain activity), both of which were shown to increase with increased nicotine or menthol delivery. However, the effect of the interaction between nicotine and menthol levels on impact and P_1-N_2 was not a simple linear relationship; rather, it was found to be complex.[40] Further research by Philip Morris determined that the addition of other chemicals (e.g., pyrazine, vanillin, and propylene glycol) increased P_1-N_2 amplitudes.[41]

Sensory CSERP studies investigated whether given flavorants stimulated the olfactory nerve, the trigeminal nerve, or both.[38] Gullotta, one of the Philip Morris researchers, reported that CSERPs provided an objective measure of both impact and odor discrimination, in that different tobacco flavorants (e.g., natural vs synthetic menthol) affected CSERPs differently, even when smokers were unable to discriminate subjectively.[38] In effect, Philip Morris developed a putative method of objectively measuring and quantifying "impact."[40]

Addition of Antioxidants and Mitigants

RJ Reynolds investigated the addition of beta-carotene to cigarettes, including development of genetically engineered tobacco plants with genes inserted for beta-carotene production. RJ Reynolds's beta-carotene study group consisted of representatives from 15 different departments within RJ Reynolds.[42–45] Documents describing this group's activity were found for 1992 and 1993, but no subsequent documents were found to allow determination of how long the group continued to operate or whether it was disbanded or why.

It is unknown whether the 1994 *New England Journal of Medicine* report[46] suggesting that oral beta-carotene supplements might have harmful effects on smokers (e.g., increased frequencies of lung cancer and ischemic heart disease) affected this group's disposition. Its original vision statement was "to enhance natural tobacco components that may have potential to either reduce or mitigate the biological activity of tobacco-burning cigarettes."[43] This statement was later amended as follows: "to provide smokers with products which contain biological activity mitigants."[42] Biological activities targeted included reducing nitrosamine levels, nitric oxide levels, carbonyl groups, Ames activity (a measure of mutagenic and carcinogenic potential), ciliostatic and cytotoxic response, and possibly free radical concentrations.[44]

Numerous RJ Reynolds documents showed that the company considered adding mitigants, such as beta-carotene, to cigarettes.[42,47–56] Mitigants were defined as antioxidants and other compounds for free radical reduction (i.e., reduction of the concentration of free radicals)[57,58]; compounds "that combat the biological effect of some compounds in cigarette smoke," such as reducing oxidative stress[47]; and compounds that "may reduce the risk of developing alleged smoking-related illnesses."[45] RJ Reynolds catalogued and studied mitigants.[42,53] Many of these compounds can be found within plant additives or as direct chemical additives to cigarettes. Of 127 chemicals included on one RJ Reynolds list of mitigants,[42] 12 were direct chemical additives to cigarettes (e.g., beta-carotene, vitamin C, tannic acid, vanillin), and 40 were contained in botanical additives on the tobacco industry additives list[15] (Table 1).

Genetic Modification of Tobacco

In addition to Brown and Williamson's efforts to genetically manipulate nicotine levels of cigarettes sold in the United States (which have been documented in the media[6]), other companies in the industry also engaged in biotechnology development projects. Two examples were RJ Reynolds's development projects designed to incorporate the beta-carotene gene, control nicotine levels, and genetically modify the tobacco plant in other ways[97–100] and Philip Morris's development of specific molecules (antisense RNA) to decrease carcinogenic tobacco-specific nitrosamines.[101]

Use of "Beneficial" Additives

A 1981 surgeon general's report, *The Changing Cigarette*, expressed concern about cigarette additives causing additional or new health care risks.[102(pp6,8,51–52,99–100)] After the publication of that report, incorporation of "beneficial" additives into cigarettes was discussed at a pair of Philip Morris meetings in 1981.[103] In addition to scientists and other research and development personnel from Philip Morris, Hamish Maxwell, the CEO and president of Philip Morris, attended the meetings.

TABLE 1—Possible Pharmacological Effects of Selected Chemical Additives

Chemical	Possible Pharmacological Effects
Acetaldehyde[34,59–61]	Positive reinforcer that acts on the CNS, synergistic and enhanced reinforcing effects with nicotine, may contribute to addiction, carcinogen, production increased with increased use of sugars in cigarettes
Aconitic acid[17]	Unproven uses: treatment of neuralgia, serous skin inflammation, migraine, myalgia, rheumatism, pleurisy, mucosal diseases, pericarditis sicca, fever, anti-inflammatory, cardiac tonic (aconitin can trigger cardiac arrhythmia), and for disinfecting and wound treatment
Alpha-tocopherol [47,48,51–58]	Antioxidant/mitigant; extensively studied by RJR for addition to cigarettes for mitigant effect
Beta-carotene[47,48,51,58]	Antioxidant/mitigant; extensively studied by RJR for addition to cigarettes for mitigant effect
Benzyl salicylate[62]	Flavorant that is also anti-inflammatory, antipyretic, analgesic (partly to completely metabolized to salicylic acid)
Caffeic acid[51] (in botanical additives)	According to RJR, blocks the formation of nitrosamines in vivo, and "results of study suggest that dietary caffeic acid and ferulic acid may play a role in the body's defense against carcinogenesis by inhibiting the formation of N-nitroso compounds"[51]
Cocoa[13,63]	Contains theobromine, a bronchodilator; suspected to be added to entice young people to smoke
Chocolate[13,63]	Contains theobromine, a bronchodilator; suspected to be added to entice young people to smoke
Ethyl salicylate[62]	Flavorant, also anti-inflammatory, antipyretic, analgesic (partly to completely metabolized to salicylic acid)
Ethyl-vanillin[63]	Flavorant, subjectively experienced as similar to sugar
Eucalyptol (1,8-cineole)[64–68]	Antimicrobial, increases lung mucociliary clearance, suppresses arachidonic acid metabolism and cytokine production in human monocytes, anti-inflammatory activity in asthma patients; induction of apoptosis in human leukemia cell lines, antinocioceptive
Eugenol[31,69]	Used in cigarettes in 1970s and 1980s; a local anesthetic compound of interest to scientists because of potential CNS depressant effect that was possibly synergistic with barbiturates and alcohol, and because of a possible interaction of nicotine as a stimulant with eugenol as a depressant[31]; removed after possible hepatotoxic and carcinogenic effects of the compound were discovered.[70–74] An internal 1985 RJR document[69] indicated awareness of eugenol's pharmacological properties and stated that "eugenol is also used as a local anesthetic in temporary dental fillings and cements, as a fungicide in pharmaceuticals and cosmetics. . . . Pharmacologically, eugenol has been reported to exhibit antiseptic properties, analgesic action (local and general), spasmolytic and myorelaxant activities, parasympathetic effects (salivary gland secretion), and direct peripheral vasodilation."[69] RJR also knew that it was present in botanical agents. Although eugenol is no longer found in the list of additives, it is still present in many of the botanical agents that are used as additives, including basil, black pepper, Ceylon citronella, Ceylon cinnamon, lovage, licorice, mace, thyme, and other botanical additives
Farnesol[75]	Inhibits growth and viability of a variety of neoplastic cells
Ferulic acid[51] (in botanical additives)	According to RJR, blocks the formation of nitrosamines in vivo, and "results of study suggest that dietary caffeic acid and ferulic acid may play a role in the body's defense against carcinogenesis by inhibiting the formation of N-nitroso compounds"[51]
Glycyrrhizin, ammoniated[76–80]	Glycyrrhizin has anti-inflammatory, antiviral, and anti–gastrointestinal ulcer properties; may enhance interleukin 10 production
Isobutyl salicylate[62]	Flavorant, also anti-inflammatory, anti-pyretic, analgesic (partly to completely metabolized to salicylic acid)
Isovaleric acid[69,81,82,75–80,83]	Possible pheromone effect. Isovaleric acid is a component of the pheromones present in the vaginal secretions responsible in the female rhesus monkey for stimulating sexual behavior in the male. It is also found to be one of the major components of the subauricular gland secretion of the male pronghorn (antelope); its odor produces a strong response from the male as indicated by sniffing, licking, marking, and thrashing
Levulinic acid[19,84]	Nicotine levulinate and levulinic acid enhance the binding of nicotine to nicotinic receptors in rat and mouse brains. Levulinic acid also increases peak plasma nicotine levels while enhancing perceptions of smoothness and mildness; it desensitizes the upper respiratory tract, increasing the potential for cigarette smoke to be inhaled deeper into the lungs
D-limonene[29] (and its metabolites, perillic acid, dihydroperillic acid, perillyl alcohol, uroterpenol, and limonene1,2-diol)	Possible anticancer properties. May inhibit tumor growth via inhibition of p21-dependent signaling and apoptosis resulting from induction of the transforming growth factor beta-signaling pathway. D-limonene metabolites also cause G1 cell cycle arrest, inhibit posttranslational modification of signal transduction proteins, and cause differential expression of cell cycle–related and apoptosis-related genes. Animal studies show activity of D-limonene against pancreatic, stomach, colon, skin, and liver cancers. Data also indicate that D-limonene slows the promotion/progression stage of carcinogen-induced tumors in rats
Menthol[85]	Anesthetic action, complex interaction with nicotine, increase in P_1-N_2 amplitudes
Methyl salicylate[62]	Anti-inflammatory, antipyretic, analgesic, counterirritant (partly to completely metabolized to salicylic acid)

Continued

TABLE 1—*Continued*

Mitigants[15,42,86]	Of 127 chemicals on a list of mitigants,[42] 12 are direct chemical additives to cigarettes (beta-carotene, ascorbic acid/vitamin C, L-histidine, cinnamaldehyde, histidine, tannic acid, lauric acid, octanoic acid, oleic acid, vanillin, essential oils), and 40 are contained within botanical additives on the University of Indiana list of tobacco additives[15] (carotenoids, beta-carotene, ascorbic acid/vitamin C, bioflavonoids, catechin, myricetin, quercitin, isoquercitrin, quercitrin, rutin, kaemferol, naringenin, naringin, epigallocatechin gallate, caffeic acid, L-histidine, alpha-tocopherol/vitamin E, tryptophan, glutathionine, provitamin A, chlorophylls, chlorophyllin, cinnamaldehyde, curcumin, ellagic acid, eugenol, ferulic acid, gallic acid, histidine, tannic acid, chlorogenic acid, linoleic acid, linolenic acid, lauric acid, octanoic acid, oleic acid, vanillin, vitamin B2, polyphenols, essential oils)
Phenethyl salicylate[62]	Flavorant, also anti-inflammatory, antipyretic, analgesic (partly to completely metabolized to salicylic acid)
Propylene glycol[31]	Alters P_1-N_2 amplitude, an objective CNS activity measure correlated with favorable sensory characteristics of cigarettes
Pyrazine[31]	Alters P_1-N_2 amplitude, an objective CNS activity measure correlated with favorable sensory characteristics of cigarettes
Pyridine[13,87]	Has documented similar peripheral effects, but opposite CNS effects, to nicotine; has suspected synergistic CNS effects
Salicy-acetaldehyde[62,88]	Metabolized by oxidation to salicylic acid. Promotes wound healing and granulation when applied topically, and was shown in a rat study to be a less potent analgesic and anti-inflammatory agent. Equipotent with salicylic acid, methyl salicylate, and aspirin in hindpaw edema assay; equipotent with aspirin in acute inflammation
Thiamine hydrochloride	Vitamin B1
5,6,7,8-tetrahydroquinoxaline[89,90]	Tetrahydroquinolines, on the basis of experimental data, have been hypothesized to act as "false neurotransmitters" in catecholamine-containing neurons. In the 1960s, formaldehyde was shown to condense with endogenous catecholamines to form tetrahydroquinolines. That acetaldehyde is highly reactive with catecholamines was one of the reasons for DeNoble pursuing his research on the reinforcing effects of acetaldehyde.[91] Might serve as a "false neurotransmitter"[91] and might have an addictive effect
Valeric acid[92-96]	Flavorant. Chemical in botanical Valeriana officinalis, which is also a listed additive. Valeric acid has documented direct sedative effects and interactions with neurotransmitters such as GABA
Gamma-valerolactone[32]	Inhibits CYP2A6, a nicotine metabolizing enzyme, which could lead to higher nicotine blood levels. There are 20 known chemically related lactone compounds that are included on the University of Indiana list of additives and are known to inhibit CYP2A6. In addition, on the basis of a study noting that the level of inhibition of CYP2A6 varies by side chain substitutions, at least 14 other lactone compounds also on the University of Indiana list of additives may act as CYP2A6 inhibitors as well
Vanillin[31,63]	Flavorant. Also increases P_1-N_2 amplitude, an objective CNS activity measure correlated with favorable sensory characteristics of cigarettes, subjectively experienced as similar to sugar

Note. CNS = central nervous system; RJR = RJ Reynolds. This is not an exhaustive list of specific chemical additives with pharmacological effects; rather, it represents selected examples of additives with possible pharmacological effects.

The Philip Morris document summarizing these meetings defined "beneficial" as follows: (1) "creating more profit (sales) to Philip Morris"; (2) "creating a positive public image"; (3) "being safe, good for you as well as pleasurable"; and (4) "creating a favorable image with government agencies."[103] The document also stated that "rather than deliver a physiological effect directly we might incorporate an additive which causes the body to produce its own physiological agent. Thus, we could alleviate pain, increase sex drive, etc., without adding agents to do this but by adding a naturally occurring promoter."[103] Moreover:

> It was noted that one beneficial attribute ascribed to smoking is appetite suppressance [sic]. A thorough study of this effect and publication of the results may have a beneficial impact on the image of smoking. If particular compounds responsible for the effect can be found, it might be possible to enhance the effect in a cigarette aimed at people desiring help with weight control. Care must be taken not to make specific claims or to invoke a "drug additive" image.[103]

Finally, according to the document:

> Other factors were thought of (in addition to appetite suppression) that could be screened for beneficial effects of smoking. The idea again is to ascribe the effect to an additive that is already naturally occurring in tobacco, and then to possibly manipulate that additive: a) dental caries [tooth decay], b) reduction in constipation, c) heart rate regulation, d) effects in colds (i.e., mentholated brands), [and] e) anxiety reduction.[103]

No information is available on the extent to which Philip Morris engaged in subsequent action to study or incorporate the "beneficial" additives discussed at these meetings.

A separate Philip Morris document titled *Nontobacco Biological/Botanical Smoking Materials*[104] included a long list of patent numbers associated with specific plants (patents listed in reviewed documents were reviewed to gain additional insight into what the tobacco documents were discussing and research that

specific tobacco companies were considering or pursuing). Several of those patents discussed direct "beneficial" physiological actions of botanical additives. In one US patent cited,[105] it was noted that nicotine in cigarettes has a deleterious vasoconstrictive effect on the cardiovascular system, particularly the blood vessels within and surrounding the heart. It was also noted that vaporized niacin in cigarette smoke has a vasodilating action that helps counteract the vasoconstrictive effect of nicotine. Furthermore, additional "beneficial" effects may be obtained when niacin is combined with rutin (a chemical found in botanicals), "which is considered effective in reducing and preventing capillary fragility."[105]

The patent went on to state that "niacin and rutin may also be incorporated in a smoking composition which is made from vegetable materials other than nicotine-containing tobacco and de-nicotinized tobacco."[105] It was noted that both compounds should be in the range of 0.1% to 2.5% by weight of the cigarette.[105] It is not known whether cigarettes were ever manipulated to have that concentration range of those chemicals. However, it is known that Philip Morris studied niacin in cigarettes,[106,107] investigated commercial production of niacin (i.e., nicotinic acid) and the cost associated with purchasing niacin in lots of 5000 or more kilograms,[108] and studied naturally occurring rutin in cigarettes.[109]

The patent listed 33 botanicals or vegetable materials, or compounds within them, that also appear on the tobacco industry cigarette additive list, including beets, carrots, chamomile, corn, eucalyptus, maple and maple syrup, menthe piperita, oak, patchouli, rose, and vanilla plantifolia. In its discussion of cigarette casing material, the patent listed caramel, licorice root, niacin, rutin, and glycerol as possible additives and noted that the following aromatics, flavoring agents, sweeteners, coloring agents, and humectants could be added or substituted in a vegetable material preparation that would naturally contain niacin and rutin: sage, honey, sucrose, vanillin, coumarin, vanilla bean, fruit flavors, molasses, propylene glycol, apple juice, apple cider, essential oils, anise, angelica, and prune juice. It is noteworthy that so many botanical agents listed in the patent are also mentioned on the tobacco industry's list of additives.[105]

Through the years, Philip Morris has maintained listings of patents on vitamins and therapeutic ingredients in cigarettes[110] as well as listings of patents on medicated cigarettes[111,112] The documents focusing on medicated cigarettes[111,112] discussed patents on cigarettes with therapeutic or anticarcinogenic additives and additives that relieve or treat bronchial irritation through means other than cigarette mentholation. Many of the ingredients were derived from pharmacologically active botanicals. However, as noted, it is not known how much effort Philip Morris engaged in to incorporate "beneficial" additives for the uses described in this section.

Other Specific Chemical Additives

Tobacco companies have added many other chemicals with a wide variety of possible effects (Figure 1). Table 1 includes a summary of chemical additives that may have pharmacological effects.[59–96,113]

Tobacco Industry Objections

Tobacco industry representatives attempted to refute the conclusions of Bates et al.[18] that cigarette additives were added to enhance nicotine addiction and induce other pharmacological effects. A 1999 industry statement denied that use of ammonia compounds increased the amount of ammonia in cigarette smoke, increased smoke pH, increased the amount of nicotine in smoke, or influenced nicotine yield as determined by the Federal Trade Commission/International Organization for Standardization method.[17] This refutation ignored tobacco industry documentation of extensive research on ammonia technology and its effect on nicotine form and physiology.[18,21]

Also, the 1999 industry document just cited[17] stated that a synergistic effect of nicotine and acetaldehyde is unlikely.[17] However, Philip Morris research has clearly documented a synergistic effect on addictive behavior in rats. The document further stated that plasma levels of theobromine in smokers are far below the dose necessary for a pharmacological effect[17] and that glycyrrhizin is not transferred into mainstream smoke and has no bronchodilator effect.[17] Furthermore, the industry statement denied that levulinic acid and pyridine are used in the production of cigarettes.[17] However, levulinic acid and pyridine are on the list of additives prepared by the tobacco industry.[15] This industry statement emphasized that the additives discussed were used in casings or were used to enhance flavor.[17]

DISCUSSION

Increased knowledge about cigarette additives makes it clear that modern cigarettes are very different from cigarettes of the past, in that they have been extensively engineered to be delivery devices for nicotine and other ingredients. Evidence from tobacco industry documents indicates that additives have been used to increase free base nicotine and addiction potential and to mask and treat symptoms.

Free Base Nicotine and Addiction Potential

Previous research[18,21,114] makes it clear that the industry expended significant resources to develop and use methods to increase free base nicotine via ammonia technology and other methods. Industry research and development programs designed to develop methods to manipulate nicotine levels and forms (i.e., salt particulate, free base particulate, vapor free base) took place over 4 decades, starting in the 1960s. Increases in free base nicotine have been implicated in

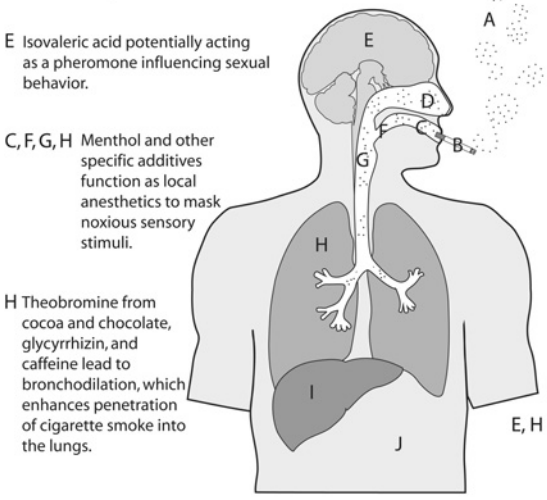

FIGURE 1—Summary of pharmacological and chemical effects of cigarette additives.

increasing the addictive potential of cigarettes.[18,21,114]

The tobacco industry's scientific efforts were far more advanced compared with public scientific efforts to understand nicotine addiction. Philip Morris's research into EEG, PREP, and CSERP shows that the tobacco company attempted to quantify "impact" and to monitor the neurological effects of specific additives to maximize "cigarette acceptance" (which encompasses factors such as cigarette "satisfaction" and is influenced by a number of elements, including primary reinforcement [e.g., nicotine addiction] and secondary reinforcement[115]).

From a public health perspective, increasing the addictive potential of cigarettes with additives (e.g., via formulas including sugar, sorbitol, and DAP) increases the likelihood that new smokers will become addicted and that current smokers will have more difficulty quitting. Consequently, there will be greater levels of morbidity and mortality associated with smoking.

Masking and Treating Symptoms

The tobacco industry has stated that additives are used primarily for flavoring and "smoothing" the smoker's experience. However, a review of botanical medicine sources[103,116] indicates that many botanical and phytochemical additives have other properties, including anesthetic, antibacterial, anticancer, anti-inflammatory, antifungal, and antiviral properties. Industry documents[65,104,110–112] show awareness of and interest in these additional properties.

Unregulated botanical and chemical additives might have "multiple use" purposes, such as enhancing flavor and providing for a "smoother" smoking experience as well as preventing or masking symptoms associated with illnesses induced by smoking. Because inclusion of botanical and chemical additives could reduce, mask, or prevent smokers' awareness of the adverse symptoms caused by smoking (e.g., cough), smokers might continue to smoke even when they are ill, preventing reductions in cigarette consumption and sales revenues.

RJ Reynolds's addition of beta-carotene to cigarettes suggests that adverse health effects can occur even when a seemingly benign additive is used and points to the need for regulation by the Food and Drug Administration. Although the actions of beta-carotene and other additives may have decreased the carcinogenicity of cigarettes, their use may have unintentionally increased the risk for and rate of lung cancer in smokers.

A 1994 study concluded that there was no reduction in the incidence of lung cancer among male smokers after 5 to 8 years of oral supplementation with alpha-tocopherol or beta-carotene. That study raised the possibility that oral beta-carotene supplements might actually have harmful effects in smokers and might increase lung cancer rates.[46] A newer study[117] also has documented the possible adverse effects of oral beta-carotene on

lung cancer. This is an example of the potential occurrence of unwanted and unanticipated dangerous effects if appropriate regulatory agencies do not monitor the use of additives.

Unresolved Issues

The actual composition of extracts used, the parts of plants used, and the physiological and pathological effects of these additives are unknown. It is not clear whether sufficient amounts of pharmacologically active chemicals derived from these additives remain after pyrolysis; no information is available on the effects of combustion of these compounds in cigarettes at the concentrations used, let alone whether the combustion products actually have any of the listed properties in vivo when smoked. For example, only scientific experimentation will be able to reveal whether theobromine, glycyrrhizin, and other cigarette additives induce a bronchodilator effect.

Conclusions

Modern cigarettes have been extensively engineered and optimized as nicotine delivery devices developed through major national and international research and development programs. The average smoker has been unaware of these efforts by the tobacco industry and of the extensive manipulation of cigarette chemistry.

Our results indicate that more than 100 of 599 documented cigarette additives have pharmacological actions. Previous research[18,21,22] has documented extensive efforts by the tobacco industry to use additives to mask the presence of ETS by reducing the visibility, odor, and irritability of tobacco smoke. Similar to the findings of previous studies, our results show that the tobacco industry used additives (1) that enhance or maintain nicotine delivery and could increase the addictiveness of cigarettes and (2) that mask symptoms and illnesses associated with smoking behavior.

To our knowledge, there has been no systematic evaluation of the public health effects of cigarette additives or their combustion products. The tobacco industry has actively manipulated cigarette content by using potentially hazardous chemical and phytochemical additives that should be regulated. Unregulated use of additives in tobacco products subjects billions of smokers and nonsmokers alike to an uncontrolled experiment with potentially devastating health effects. ■

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Contributors

M. Rabinoff was involved with all aspects of research, writing, and editing of the article. N. Caskey was involved in all aspects of editing and helped with research on many of the issues brought up during the review process. A. Rissling helped with most areas of research and did some writing for the initial version of the article. C. Park helped with research on numerous issues, especially on the topic of additives affecting environmental tobacco smoke.

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