Monograph 22
A Socioecological Approach to Addressing Tobacco-Related Health Disparities

Section II
Intrapersonal/Individual Factors Associated With Tobacco-Related Health Disparities

Chapter 4
Flavored Tobacco and Chemosensory Processes

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Introduction

Flavor additives such as menthol, ginger, vanilla, nutmeg, licorice, cocoa, and sugars are examples of ingredients that are added to cigarettes.[1,2] This chapter focuses on the chemosensory effects of flavors in cigarettes and, in particular, on menthol. The most common characterizing flavor in cigarettes, menthol has been added to cigarettes since the 1920s.[3] Menthol is the primary focus of this chapter because when used in cigarettes as a characterizing flavor, the compound affects multiple chemical senses, including the olfactory (smell), gustatory (taste), and trigeminal (burning, tingling, touch, temperature, nociception) senses.[4–6]

Three months after the date of its enactment, the Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act) banned characterizing flavors, other than menthol and tobacco, in cigarettes.[7] The Tobacco Control Act also required that within 1 year after its establishment, the U.S. Food and Drug Administration (FDA) Tobacco Products Scientific Advisory Committee (TPSAC) submit a report and recommendations on menthol in cigarettes and public health, including use among children, African Americans, Hispanics, and other racial and ethnic minorities. In its report *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, the FDA TPSAC concluded that "the availability of menthol cigarettes has led to an increase in the number of smokers and that this increase does have adverse public health impact in the United States."[8,p.220] (Other provisions of the Tobacco Control Act and their relationship to tobacco-related health disparities [TRHD] are discussed in chapter 11.)

Background

"Flavored" tobacco was made popular with the inadvertent invention of menthol cigarettes in 1924 by Lloyd F. (Spud) Hughes, a resident of Mingo Junction, Ohio. Hughes used menthol for medicinal purposes, inhaling the menthol crystals to treat his asthma. After hiding his cigarettes in a tin can that contained menthol crystals and baking powder, Hughes discovered that the menthol cigarette flavor created a cooling and soothing effect.[9] In 1924, he filed for a U.S. patent that specified the treatment of cigarettes with menthol, alcohol, and cassia oil derived from the *Cinnamomum cassia* tree. In his patent application, Hughes stated:

> This invention relates to a process of treating tobacco for use in the production of cigarettes, and it has for its object to provide a cigarette tobacco which, while cooling and soothing to irritated membranes of the mouth and throat of the smoker, is absolutely non-injurious and is pleasant to taste. The process consists in spraying upon the tobacco which is to be rolled into cigarettes a solution consisting of menthol ($C_{10}H_{20}O$), cassia oil, and alcohol.[3]

The patent was granted on September 29, 1925, and production of the new product began soon after. Hughes formed the Spud Cigarette Corporation in Wheeling, West Virginia, and Spud cigarettes were manufactured for Hughes's corporation by Bloch Brothers Tobacco Company (Figure 4.1). Hughes sold his cigarettes door to door, out of his car, and to railroad and mill workers who frequented his father's restaurant.[10] In 1926, Hughes sold his patent to the Axton Fisher Tobacco Company of Louisville, Kentucky, for $90,000. Spud was the fifth largest selling tobacco company in the United States until Brown and Williamson introduced two cheaper menthol cigarettes, Penguin in 1931 and Kool in 1933[11] (see Figure 4.1).

Figure 4.1 Cigarette Packs: Spud Menthol Cooled Cigarettes, 1924, and Kool Cigarettes, 1950

Sources: Trinkets & Trash.[186,187]

The pleasing mint flavor and cooling sensation of menthol in tobacco were used to market menthol cigarettes as “healthy,” and they increased in popularity in the 1950s.[12] In 1956 R.J. Reynolds Tobacco Company (RJR) introduced Salem, the first filter-tipped menthol cigarette. RJR sold the Kool and Salem brands to Imperial Tobacco Company in 2015.[11] In 1957, Lorillard Tobacco introduced the Newport menthol brand, which Reynolds America, RJR’s parent company, purchased in 2015.[11] According to 2016 sales data, Newport is the second most popular cigarette brand in the United States, having 13% of the market share. The domestic share of menthol cigarettes increased from 16% in 1963 to 30% in 2014.[13,14]

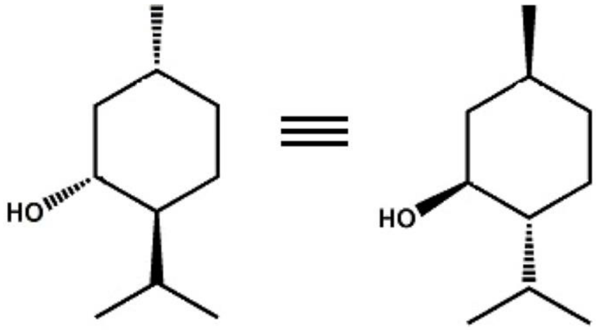
As described in chapter 2, menthol cigarettes are disproportionately smoked by youth, women, and African Americans. For example, the prevalence of menthol cigarette use in the past 30 days among black adolescent smokers is 95%.[15] Some populations groups, such as African Americans and Native Hawaiians and Pacific Islanders, have higher rates of tobacco-caused morbidity and mortality than others, and it has been suggested that menthol in cigarettes may play a role in the chronic disease pathway.[16–20]

The effects of menthol as a characterizing flavor can be immediately perceived by the consumer, whether the product is inhaled, chewed, smoked, or comes in contact with the skin. Other additives and constituents, such as cocoa and licorice, which are common additives in menthol cigarettes and other tobacco products, also act on the chemical senses.

The Menthol Compound

Menthol is a complex compound ($C_{10}H_{20}O$, molecular weight 156.27 g/mol) that has multiple biological effects on the human body. The chemical structure of menthol is shown in Figure 4.2. Menthol is a white or colorless crystalline substance that is solid at room temperature, partly soluble in water, and freely soluble in alcohol, diethyl ether, or chloroform.[21,22] This cyclic monoterpene alcohol has three asymmetric carbon atoms[23,24] and is present as four pairs of optical isomers: (+) and (–) menthol; (+) and (–) neomenthol; (+) and (–) isomenthol; and (+) and (–) neoisomenthol.[22–24] The menthol isomer (–) menthol (L-menthol), the isomer most widely found in nature,[23] is known for its flavor and cooling properties.[22]

Figure 4.2 Chemical Structure of Menthol



Menthol is found naturally in peppermint (*Mentha piperita*)[25] and cornmint plant oils (*Mentha arvensi*).[23] Menthol constitutes 50% of peppermint oil, and it can be extracted or synthesized from other essential oils like citronella, eucalyptus, and Indian turpentine oil.[23]

Menthol has been added to food and used in cosmetics and pharmaceutical products. Mint teas and peppermint candy and gum are widely used around the world. Menthol is commonly used in hygiene products such as toothpaste, mouthwash,[23,26–28] shampoo, and soap.[29,30] Menthol has been used as a local analgesic and an anesthetic, and for its antibacterial, antifungal,[22] and antipruritic properties. As an analgesic, menthol is an ingredient in topical rubs. Products that involve inhaling menthol are used to reduce respiratory discomfort due to colds and flu, because they inhibit airway irritation that leads to coughing.[31] Cough drops containing menthol are often used as an anesthetic to soothe throat irritation. Menthol inhibits the growth of bacterial strains[32–34] such as *Streptococcus* pneumonia.[35] It also has synergistic effects with antibiotics such as oxacillin and erythromycin.[35] As an antifungal agent, menthol compounds such as peppermint oil[36] have been known to be effective against *Candida albicans.*[37]

Tobacco industry documents suggest that menthol is the primary additive that creates multiple sensory effects.[4,5] Menthol is the only flavor additive that, when added at different concentrations, is known to act on the olfactory, gustatory, and trigeminal systems[30,38–41] to produce “desired” sensory effects for different types of smokers. Unlike strawberry, grape, or cherry characterizing flavors, menthol when used in cigarettes produces sensory effects that go beyond taste, flavor, and aroma; certain concentrations of menthol create cooling/tingling, analgesic, and smoothing effects. These sensory effects may serve as positive reinforcement for behavioral abuse of nicotine[6,42,43] and may affect the abuse liability of menthol.[44] As the World Health Organization Study Group on Tobacco Product Regulation has stated, “menthol is not only a flavouring agent but also has drug-like characteristics that modulate the effects of nicotine and tobacco smoke.”[45,p.30]

Brief Review of the Chemical Senses

Physiology and psychology meet in the study of the chemical senses.[46] To understand how menthol’s use in cigarettes influences experimentation, current use, and nicotine dependence, it is important to understand the complexities of the chemical senses and menthol’s effects on them. Much is known and much is still to be learned about how the chemical senses operate, interact, and signal each other to produce unique flavor sensations and experiences among smokers.[47]

The perception of chemical stimuli by sensory means is called chemosensation or chemoreception.[48] Flavor results from the complex interaction of the chemical senses[49] and will not be discussed in detail in this chapter. The primary chemical senses for distinguishing flavors include the olfactory and gustatory systems.[50] The trigeminal somatosensory system (cooling and pain) also plays a role in chemosensation and how flavor is experienced.[48] No compound activates only one sensory channel,[51] and a single compound may not have the same smell, taste, and cooling or pain thresholds either in different individuals or on each of the independent sensory channels in the human trigeminal system.[52,53]

Olfaction allows us to detect odors such as the minty smell of menthol cigarettes. Odors stimulate a series of biochemical activities within the cell when the odor molecule binds to an odor receptor in the ciliary membrane.[54] Olfaction is not, strictly speaking, an oral sense; however, olfactory sensations that arise from odorants in the mouth are perceptually localized to the oral cavity. Much of the sensation of taste is olfactory.[55] Olfactory receptors facilitate a sequence of events that lead to flavor sensation, perception, and cognition.[49]

Gustation, or taste, is another well-known chemical sense. When chemical stimuli come in contact with taste cells embedded in the taste buds in fungiform papillae on the surface of the tongue, taste is detected, and it is experienced in different ways. There are five basic classes of taste: salty, sour, sweet, bitter, and umami.[50] For example, compounds such as sugar may stimulate multiple receptors that translate into a sweet taste.[50] Bitter taste is evoked by more receptors than sweetness, and some of the bitter receptors have been identified, such as TAS2R.[56,57] Research suggests that bitter taste prevents mammals from ingesting potentially harmful food constituents.[58,59] Sensations arising from the oral and nasal cavities vary considerably; some of this variation is attributable to genetics, and some to common pathologies. This variation in oral sensations plays an important role in health by affecting dietary choices, drinking alcohol, and smoking cigarettes.

The capacity of the trigeminal nerve to detect chemicals is called chemesthesis.[48] The sensory properties evoked by smoking result from stimulation of the cranial nerves that innervate the oral and nasal cavities. Sensations from the tongue include taste and somatosensation (irritation/pain, temperature, touch). Taste is mediated by the chorda tympani nerve (CN VII) on the anterior tongue and the glossopharyngeal nerve (CN IX) on the posterior tongue. Somatosensation is mediated by the trigeminal nerve (CN V) on the anterior tongue and is mediated along with taste by the glossopharyngeal nerve on the posterior tongue. The endings of the trigeminal nerve can also be activated by physical stimuli and chemical agents[60] and can evoke sensations of touch, temperature, and pain[48] even in the absence of olfactory perceptions.[61] The trigeminal system produces protective responses through salivation, tearing, coughing, respiratory depression, and sneezing.[48] The trigeminal system is the least understood of the chemical senses, but this system is known to play an important role in the consumption of food and other substances.

Cigarette Smoking and the Chemical Senses

Cigarette smoking impairs the senses of smell and taste. Studies have shown that, compared to nonsmokers, smokers have less ability to identify the presence of a taste (i.e., low odor threshold), to identify a particular taste, and to discriminate between tastes.[62,63] Number of pack-years (number of packs smoked per day multiplied by number of years smoking occurred), a measure of cigarette dose, is inversely associated with odor thresholds, discrimination, and identification.[62]

The mechanisms by which smoking influences olfaction are under investigation, but several studies suggest that smoking damages the nasal epithelium and increases cell apoptosis, thus causing nasal congestion.[64] Some studies have found that smoking impairs olfaction,[62] but other data suggest that olfaction returns to normal in smokers who quit.[63] Some researchers have found that smokers are less likely than nonsmokers to perceive bitter taste.[65] Few studies, however, have examined the relationship between olfaction and smoking, particularly as it relates to menthol cigarette smoking. Little research has examined how menthol cigarettes' effects on olfaction differ from the effects of non-menthol cigarettes or how this might affect the likelihood of smoking initiation and continuation.

Characteristics of Flavor Additives and Constituents

Cigarette smoke is irritating,[66,67] and nicotine has a bitter flavor.[68] The chemosensory effects of menthol make menthol cigarettes easier to smoke and may contribute to continued smoking. Analysis of tobacco industry documents shows that the industry has conducted research to understand consumers' perception of menthol cigarettes for many decades.[69]

There are over 7,000 chemicals in cigarette smoke.[70] Flavor additives and constituents of tobacco products can act on the chemical senses to create specific expectations of the product, entice new users, neutralize the negative experiences of nicotine and tobacco, and create positive experiences that make it easier for current users to continue to use a product that causes chronic disease and death. The number of flavor additives and constituents in tobacco that stimulate the chemical senses is unknown. A 1994 report from the six major American cigarette companies listed 599 ingredients used in cigarettes; many of these—including vanillin, valerian root extract, rosemary oil, raisin juice concentrate, honey, cocoa, coriander, basil oil, almond bitter, licorice, and ginger—appear to be used as flavor additives.[2] Few studies have investigated how these and other known flavor ingredients affect the chemical senses and impact TRHD. The following sections describe the use of cocoa, licorice, and menthol as additives to cigarettes and other tobacco products.

Cocoa as an Additive

Derivatives of cocoa beans have been used for different purposes throughout history, and research is still being conducted on their pharmacological and phytochemical properties.[71] Records from the 1500s show that cocoa beans, derived from the *Theobroma cacao* tree, were used as a medicine by Maya and Aztec civilizations of South America to treat gastrointestinal, cardiovascular, and nervous system ailments.[71] Twentieth-century studies have suggested that cocoa has pharmaceutical value as a flavor to improve the taste and facilitate delivery of medicines.[71]

Cocoa powder, cocoa butter, and cocoa liquor, derived from cocoa beans, have been used as both characterizing and non-characterizing flavors in cigarettes since as early as 1932,[42,72] and analysis of tobacco industry documents shows that the industry has "experimented with manipulating cocoa levels as a means of achieving sensory properties that appeal to women and youth."[42,p.984] These products can contain protein, amino acids, polyhydroxy phenols, starch, sugars, theobromine, caffeine, or fatty acid triglycerides when processed.[73] Cocoa enhances the taste and reduces the harshness of cigarettes when burned. Cocoa and cocoa extract are often used in the cigarette casing[74] to enhance the aroma and flavor of cigarettes and improve the overall smoking quality of blended cigarettes, but used in this way, cocoa is not detected as cocoa flavor by the smoker.[75] Tobacco industry documents state that cigarette companies have found cocoa useful because cocoa butter in tobacco products creates a smoother, enhanced tobacco flavor.[75]

Like menthol, cocoa derivatives are added to tobacco during cigarette manufacturing,[76,77] and industry documents suggest that levels typically do not exceed 0.5% (5,000 ppm total weight of tobacco) for cocoa and 0.1% (1,000 ppm) for cocoa extract.[77] Cocoa is used as a characterizing flavor in little cigars or chocolate-flavored electronic cigarette juice/liquid, which are advertised and marketed as flavored products.

Other than enhancing the taste of tobacco, it is not clear that cocoa as a characterizing or non-characterizing flavor in cigarettes has other sensory or pharmacological effects. A few in vivo and in vitro studies suggest that *Theobroma cacao* bean extract, known for its polyphenols, can suppress trigeminal nerve activity[78] and reduce inflammatory responses that cause pain,[78–80] but it is unclear what the effects of cocoa are on the trigeminal nerve system when cocoa is added to cigarettes. One study suggests that cigarettes do not contain enough theobromines, the primary bitter-tasting compound in cocoa, to have an effect on trigeminal nerve activity[81]; evidence from tobacco industry documents supports this as well.[42]

Licorice as an Additive

Although not a common characterizing flavor, licorice as a flavor additive has been used since the late 1800s in pipe tobacco and snuff.[82] The licorice plant is used for medicinal purposes, and licorice extract is also used as a sweet flavorant. Most of the sweet flavor comes from glycyrrhizin, which is found in the plant's root. A single company manufactures 70% of all licorice in the world, and almost 63% of its sales are to the tobacco industry.[83]

Unlike menthol, licorice is a non-volatile material added to cigarettes both as a flavorant and casing material.[84] Available in block, powder, and liquid forms, licorice has various effects when used in cigarettes. It is thought to enhance the smoke flavor, reduce dryness in the mouth and throat, reduce irritation, improve the absorption of flavors uniformly in tobacco, and minimize rough smoke by balancing the overall flavor of tobacco smoke.[84]

Licorice has been investigated for its potential health effects, such as its anti-inflammatory and immunoregulatory effects,[85] but it is also thought to raise blood pressure and induce hypertension.[86] Little is known of the health effects of licorice as an additive to cigarettes or how the amounts of licorice in sub-brands differentially influence the three chemical senses.

Menthol as an Additive

Research on menthol's effects on the olfactory, gustatory, and trigeminal chemical senses is more developed than research on the effects of other flavors. This research continues to clarify the role of menthol as a characterizing flavor in cigarettes and its multiple effects upon sensory processes. Enactment of the Tobacco Control Act in 2009 stimulated renewed interest in how this flavor additive may influence the harm of tobacco products.

As explained earlier in this chapter, menthol has been used in its natural and synthetic forms[87] in cigarettes since 1924. Menthol can be added by spraying it on tobacco during blending, applying menthol to the foil or filter,[88–90] injecting it into the tobacco stream in the cigarette maker, placing a menthol thread into the filter, inserting it into a crushable capsule (e.g., Camel Crush), or by a combination of these methods.[8] Regardless of the application process used, the volatility of menthol ensures that it diffuses through the cigarette, creating flavors and sensations that appeal to some smokers.

Manufacturers add menthol to an estimated 90% of cigarettes sold in the United States.[91] A study of 45 U.S. cigarette brands found menthol content varied widely; as expected, the menthol content of brands labelled as "menthol" (2.9–19.6 mg menthol/cigarette) was far higher than that of brands not labelled as menthol (0.002–0.07 mg/cigarettes).[92] Menthol, interacting with other compounds in tobacco smoke, can produce a variety of physiological effects. Nicotine and tobacco are bitter, irritating, and harsh, causing sensations of burning or pungency, which may signal the user to refrain from using the product.[66] Menthol and nicotine activate the olfactory, gustatory, and trigeminal systems, and menthol can greatly alter the sensory properties of tobacco smoke.

In their review of published research analyzing the tobacco industry documents, Kreslake and Yerger conclude that "the tobacco industry has conducted extensive research on the chemosensory and physiological effects of menthol in tobacco smoke and has actively promoted menthol's sensory characteristics,"[93,p.S98] and "the industry has established internally that menthol's effects extend far beyond its use as a characterizing flavor, and have used it to ease inhalation and reduce irritation from smoking."[93,p.S98] They note that previous studies of internal tobacco industry documents have described tobacco industry research on a variety of menthol's properties including stimulation of nociceptors and cold receptors in the trigeminal nerve and stimulation of olfactory and gustatory receptors. The researchers also find evidence that menthol is added to cigarettes in concentrations to achieve "desired" effects and to appeal to smokers with different chemosensory perceptions. The properties of menthol have also been studied by other authors. For example, menthol has been shown to reduce irritation and sensitivity to nicotine.[94] Its analgesic and anesthetic effects reduce irritation from nicotine on the tongue[95] to make it easier to smoke. A study found that applying menthol to the side of the tongue of study participants significantly diminished the irritation from nicotine, compared with the non-treated side.[94] Menthol flavor additives may also influence the self-administration of nicotine.[96,97]

Four possible mechanisms by which menthol may alter tobacco smoking are highlighted in a review by Wickham: (1) menthol may reduce the initially aversive experiences of tobacco smoking; (2) menthol may serve as a highly reinforcing sensory cue when associated with nicotine and thus may promote smoking behavior; (3) menthol's actions on nicotinic acetylcholine receptors may alter the reinforcing value of nicotine; and (4) menthol may alter nicotine metabolism and increase nicotine bioavailability.[12] Regarding chemical sensation, the review states,

> Recent publicly available data from tobacco company records strongly suggested the reason for including menthol as an additive was to minimize the aversive experiences associated with tobacco smoking and, thus, decrease smoking's perceived health risk. These documents revealed that smokers of mentholated cigarettes report using them because they have less harsh, less irritating, and more soothing sensory profiles. Moreover, the flavor profile of mentholated cigarettes [was] reported to be improved compared to non-mentholated cigarettes, likely due to the appetitive minty flavor of menthol as well as its ability to mask aversive flavors of tobacco.[12,p.280]

How Menthol Produces Chemical Sensations

Menthol reduces the negative sensations of the smoking experience through its interaction with the chemical senses. When it is added to the cigarette and sprayed on the foil and package of cigarettes,[88–90] menthol likely acts on the olfactory system before, during, and after combustion. Odorants like menthol can reach the olfactory cleft from the mouth to the nasal cavity,[50] and even low concentrations of menthol, just above detection level, can activate the olfactory receptors, which results in odor sensation.[38,52,53] Medium concentrations evoke both the smell and the cooling sensation.[41,52,53] Because menthol itself is bitter, higher concentrations can result in the sensation of pain in addition to the smell and cooling sensation.[52] Menthol may independently affect each of the senses of smell, cooling, and pain.[53]

Menthol produces these various sensations by acting on transient receptor potential (TRP) ion channels. The ions TRPM8, TRPV1, and TRPA1 are primarily expressed in the neurons of the trigeminal and dorsal root ganglia.[98] TRPM8 is associated with cooling and easing of pain sensations. Menthol also stimulates heat-activated TRPV3,[30,99] which is mainly expressed in keratinocytes (skin cells)[98] and also has thermal and nociceptive properties, activating TRPV1.[30] At 16 ppm, which is less than the amount in menthol cigarettes, menthol can activate TRP receptors and halt irritant responses via TRPA1 and TRPV1.[31]

The menthol isomer (–) menthol (L-menthol) is known for its flavor and cooling properties.[22] Whether at low or high concentrations, menthol produces a cooling sensation when it is applied topically, ingested, inhaled, or chewed,[100] and this cooling sensation alters smokers' sensory perceptions. The cooling and refreshing effects are experienced when the concentration of menthol is high enough to activate TRPM8 ion channels[101–103] and when menthol is inhaled. Menthol increases intracellular calcium influx through the channels. One study showed that the cooling effects can last up to 70 minutes in about 65% of study participants.[100] The cooling effect is not a result of lowering of body temperature; studies have not shown that menthol causes any change increase in body temperature.[104]

The cooling sensation of menthol distracts from the pain of nicotine and blocks pain by inhibiting TRPA1.[105] It also reduces irritation and sensitivity to nicotine,[106] an irritant known to act on TRPA1 receptors as menthol does,[107,108] and reduces sensitivity to tobacco smoke.[107–109] If, by stimulating cold receptors, menthol results in the smoker holding his or her breath for extended periods, exposure to nicotine and the particulate matter of cigarette smoke would be increased.

Menthol's analgesic effects are a result of TRP activity as well. L-menthol can induce analgesia via TRPM8.[110] Because menthol cigarette brands vary in their analgesic effects, it is important to understand the levels of menthol used in particular tobacco products. It has been suggested that menthol's analgesic properties may mask early respiratory problems caused by smoking cigarettes.[18,19] The cooling effect plus the analgesic properties of mentholated cigarettes may give the smoker a false sense of well-being and reduce the likelihood of seeking medical attention for respiratory distress.[18]

Menthol's induction of various sensations depends not only on the concentration of menthol, but also on the part of the body to which it is applied.[111–113] Although at high concentrations menthol itself is an irritant, studies show that menthol reduces irritation from nicotine when applied to the tongue,[94] and menthol desensitizes the oral cavity to irritation.[112] Menthol may be a more effective stimulus to the mouth than it is to skin.[111]

Menthol may increase the bioavailability of nicotine.[12] Menthol has been shown to inhibit the metabolism of nicotine[114] and may also increase nicotine absorption.[115] If menthol's cooling effects facilitate smoke inhalation[31] or its smell reinforces smoking, these sensory effects could help explain higher levels of nicotine dependence and smoking maintenance among smokers of menthol cigarettes. Modern psychophysical tools now permit accurate assessment of sensory variability and thus have made it possible to link such sensory variation with specific health risks such as risk for smoking. The next section describes what is known about sensory variability and its importance to TRHD.

Chemical Senses and Variation

Variations in taste physiology, particularly in relation to gender and race/ethnicity, have been the subject of research on preference for menthol cigarettes. One source of this variation in taste makeup is the ability to taste the bitterness of 6-*n*-propylthiouracil (PROP) or phenylthiocarbamide (PTC).

Genetic variation in taste was discovered in the 1930s thanks to an accident in the laboratory of Arthur Fox at DuPont. Fox was synthesizing PTC when some of it blew into the air. A colleague nearby noted a bitter taste, which Fox did not perceive. A test revealed other "tasters" who could perceive the bitter taste of PTC (and other chemically related compounds like PROP, a less toxic bitter compound) and "nontasters" who could not.[116] A test of attendees at a meeting of the American Association for the Advancement of Science found that 28% of the 2,550 individuals tested were nontasters.[117] Snyder[118] tested families and concluded that nontasting was due to a single recessive gene. In the 1960s, Fischer and colleagues began to relate this genetic variation to health issues (e.g., nontasters were more likely to be smokers).[119] PROP sensitivity has also been associated with sweet preferences among children.[120,121] Studies show that there are fewer nontasters among children than among adults because taste perception changes over time[122,123]; with age, experience, and diseases, people become less sensitive to PROP.[123]

Multiple studies have further documented the finding that sensitivity to bitter tastes is a genetic trait[124,125] mediated by TASR38 and possibly 25 other bitter taste receptors expressed on the tongue.[125] PTC and PROP are perceived as bitter by 70%–75% of the population.[126–128] PTC and PROP have been used as markers of genetic variability in perceptions of taste[129] and to help distinguish three taster groups. Although earlier studies using PTC suggested that taste was bimodal, substantial evidence shows that taste sensitivity is a continuous measure of intensity extending from nontasters, to medium tasters, to supertasters.[126,127,130]

Earlier work on taste sensitivity used thresholds to classify individuals as nontasters (high thresholds) and tasters (low thresholds). In the 1960s, the pioneering work of S.S. Stevens introduced direct scaling methods (especially magnitude estimation) that enabled researchers to assess the rate at which the bitterness of PTC and PROP grew with concentration. In the 1970s, a new method (ultimately called "magnitude matching")[131,132] permitted comparisons of taste intensities across individuals with varying genetic abilities.[133,134] Magnitude matching is based on cross-modality matching, a phenomenon studied by Stevens and his students[135,136] and extended in the modern era by the work of Luce and colleagues.[137] Essentially, cross-modality matching refers to matching sensations for intensity across different qualitative continua. This permits an investigator to select a standard from a continuum unrelated to the continuum of primary interest. For example, nontasters and tasters of PROP were asked to compare PROP bitterness to loudness. This rests on the assumption that taste and loudness are not related; thus, any variation in the perception of loudness should be similar across nontasters and tasters of PROP. Surprisingly, three groups emerged. Nontasters of PROP matched the bitterness they perceived in PROP to a very soft sound. Tasters of PROP fell into two groups. One group (later called supertasters of PROP) matched their bitterness to a very loud sound; another group (medium tasters of PROP) matched their bitterness to an intermediate sound. Since loudness and taste intensity are not related, average loudness for the three groups is assumed to be the same, which permits a comparison of PROP bitterness across the three groups. Subsequent research using magnitude matching has provided considerable information about chemosensory variation across these three groups (see Table 4.1).

Table 4.1 Sample Characteristics of Taster Types

Highly sensitive tasters (supertasters)	Moderately sensitive tasters (medium tasters)	Mildly sensitive tasters (nontasters)
Strong sensations from PROP as a bitter flavor; strong sensation from mint, which is more pleasant	Moderate to strong bitterness from PROP; moderate sensation from mint	Weak or no bitterness from PROP; weak sensation from mint
High FPD	Less FPD than supertasters	Less FPD than medium tasters
Less likely to smoke than nontasters	Less likely to smoke than nontasters	More likely to smoke than tasters
Higher perception of irritation and pain from oral irritants; higher tactile perception in mouth	Moderate perception of irritation and pain from oral irritants; moderate tactile perception in mouth	Lower perception of irritation and pain from oral irritants; lower tactile perception in mouth
Food flavors important	Food flavors important	Food flavors not that important
Smell perception very strong	Smell perception moderately strong	Smell perception not very strong

Notes: PROP = 6-n-propylthiouracil; FPD = density of fungiform papillae on the tongue.

The three taster groups can be distinguished by examining variations in the density of fungiform papillae, structures that hold the taste buds on the anterior dorsal surface of the tongue. Supertasters have more fungiform papillae than medium tasters or nontasters. Studies show that PROP sensitivity is highly correlated with fungiform papillae density: Supertasters have more than twice as many taste buds per square centimeter as medium tasters.[138–142] Fungiform papillae are the primary sensor of chemesthetic stimuli on the front of the tongue[143]where cigarettes are smoked.

It is important to note that supertasting is not limited to bitter taste.[133] In addition to bitter compounds such as PTC and PROP, Bartoshuk suggests that supertasters perceive stronger taste intensities from sweet compounds.[126,144] Compared to the perceptions of medium tasters and nontasters, supertasters perceive virtually all tastes as more intense.

Supertasters who have the most fungiform papillae[145] experience more intense sensations from oral burn (e.g., chili peppers, ethanol) and oral touch (e.g., fats, thickeners in foods).[144] These properties of supertasting presumably result from anatomy; fungiform papillae are innervated by nerve fibers mediating oral burn and touch as well as by those mediating taste.

Olfactory sensations can be evoked in two different ways. (1) Sniffing odorants from the outside world (orthonasal olfaction) draws odorants through the nostrils into the olfactory cavity where turbinate bones cause a sample to be directed upward through the olfactory cleft and onto the olfactory mucosa. There, odorants contact the olfactory receptors; this is called "smell." (2) When food is placed in the mouth, chewing and swallowing forces any odors emitted from the food up behind the palate into the nasal cavity from the rear (retronasal olfaction). Taste combined with retronasal olfaction make up what is usually called “flavor.” As predicted by Rozin[146] and confirmed by functional magnetic resonance imaging (fMRI) studies,[147] orthonasal and retronasal olfaction do not project to identical central areas, and these areas apparently do not interact in the same way with taste. Taste can enhance retronasal olfaction without enhancing orthonasal olfaction.[148] Thus, supertasters experience more intense retronasal olfaction (i.e., perception of flavor).[149] In other words, supertasters live in a “neon food world” compared to the “pastel food world” of those who have the fewest fungiform papillae.

Confusion Between Individual Bitter Genes and Supertasters

Although supertasters were originally discovered in the context of PROP research, supertasting cannot be explained by PROP genetics. It is now known that the PROP gene expresses a receptor that is quite specific to PROP. This receptor cannot be responsible for supertasters’ perception of more intense non-bitter tastes, oral burn, oral touch, and flavor. Clearly, density of fungiform papillae is a crucial part of supertasting. The density of fungiform papillae is essentially independent of the PROP genotype.[57] To clarify the terminology, “nontaster” should only be used in the context of PTC or PROP. Nontasters are not the opposite of supertasters. This point is important to understanding associations between smoking and chemosensory genetics.

Taster Group and Variance Across Populations

In addition to the existence of three taster groups in the world’s populations, prior data show that perceptions of taste vary by gender,[150] age,[123,151] and ethnicity.[142,152,153] Studies suggest that about 75% of the population are tasters (medium tasters or supertasters) and 25% are nontasters[144,154–157] and that 35% of women and 15% of men are supertasters.[50] Asians and African Americans may be more likely than whites to be supertasters.[151] Since the early research on this variability, studies have shown that women are more responsive to the bitter taste of PROP and PTC.[145]

As discussed above, analysis of tobacco industry documents indicates that menthol is added to cigarettes in part to reduce the negative sensory characteristics of smoking. Does menthol facilitate smoking among African Americans and women? The targeting of blacks and women through advertisements for menthol cigarettes may have encouraged smoking among people who would be less likely to smoke, based on their chemosensory physiology. To examine this possibility, the next section discusses some chemosensory issues related to the addition of menthol to cigarettes.

Smoking Among Taster Groups

The idea that variation in the unpleasant sensory properties of cigarette smoke as it affects users’ ability to perceive these properties may lead to differences in smoking behavior is an old one. Nicotine and tobacco are generally perceived as bitter tastes.[68,158] Studies suggest that PTC/PROP tasters are likely to find cigarettes adversely bitter, and taster status may protect against smoking bitter toxic compounds like tobacco.[159–162] In the 1960s, investigators studying individual differences in taste perception observed that heavy smokers were less sensitive to the bitterness of PTC/PROP than nonsmokers.[119,160] Subsequent studies have produced similar findings, indicating that being a “taster” of PTC or PROP may protect against consuming bitter toxic compounds like tobacco.[50,142,150,159,161] Differences in smoking and taster status have been found among American Indians as well. American Indian nonsmokers and social smokers tend to be PTC/PROP tasters, and regular smokers tend to be nontasters.[150]

Variations in the bitter taste receptor TAS2R38 in particular are associated with smoking behaviors. Black women expressing the "nontaster" form of this gene are especially likely to smoke,[56] and whites expressing the "taster" variant report that tobacco-related sensations do not drive their motivation to smoke.[161] Smoking-related links with other oral sensory receptor genes are likely to generate interest as sequence analysis for those genes becomes available. Recent data suggest that variations in the TRPA1 irritant receptor gene are linked to stronger preferences for menthol cigarettes among heavy smokers.[163]

Two oral sensations associated with menthol—bitter and burn—can lead to rejection by the user if they are sufficiently intense. To better assess the potential role of menthol cigarettes in TRHD, bitter and burn should be further studied.

Inhibition of oral burn is commonly invoked as one of the reasons why menthol is added to cigarettes.[164] On the tongue, menthol desensitizes polymodal nociceptors responsive to heat and to mechanical and chemical irritation,[52] similar to its inhibitory action on respiratory irritation leading to cough.[31] At first glance, menthol's effects on oral irritation would appear unrelated to any effects menthol might have on bitterness, but this is not actually the case. Bitter taste receptors would not be expected to respond to irritants, but bitterness and irritation are connected through supertasting. Supertasters perceive bitter taste and oral irritation more intensely because they express the most fungiform papillae. Thus, if investigators use genotyping to classify PROP nontasters and tasters, they will not capture the full range of variation in bitterness or irritant perception. Attempts to relate sensory variability to variability in smoking behavior would profit from an examination of multiple sources of sensory variability.[57]

To illustrate, the authors compared white smokers and nonsmokers in terms of TAS2R38 genetics (which differentiates tasters from nontasters) and suprathreshold PROP bitterness (which identifies supertasters among tasters). Consistent with earlier reports,[161] genetic analysis alone showed no relationship with smoking behavior. However, a study that combined genetic and psychophysical analysis found that smokers are less likely to perceive PROP bitterness, attributing this finding largely to an absence of supertasters among smokers.[165] In other words, using methods that capitalize on the full range of oral sensory variation revealed that differences in bitter taste perception predict tobacco use in whites[166] just as they do in other racial/ethnic groups.[56,150]

Alexander and colleagues have suggested "that there is an interactive effect of age, race/ethnicity, bitter taste sensitivity, and trigeminal sensitivity related to menthol" which could help explain low rates of smoking among African American youth, followed by transitions to regular smoking as young adults.[16,p.S94] As these authors note, this hypothesis remains to be tested.

Chemosensation and TRHD

Chemosensory alterations that result from radiation therapy for head and neck cancer are of particular interest. Radiation therapy for head and neck cancer typically damages the glossopharyngeal nerve because the radiation is directed toward the rear of the oral cavity, the location of many head and neck tumors. Although some studies claim that any damage to taste by radiation for head and neck cancer is of short duration, other studies contradict this conclusion.[167,168] Damage produced by radiation is generally limited to the glossopharyngeal nerve, leaving the chorda tympani intact. These two taste nerves project to the brain where they interact via inhibitory connections.[169–171] Damage to one nerve releases inhibition on the intact nerve, thus intensifying the sensations mediated by the intact nerve. Thus, many survivors of head and neck cancer may experience changes in chemosensory experience that could not only influence their quality of life but also affect future behavior so as to increase risk factors for other health problems. For example, damage to the glossopharyngeal nerve by tonsillectomy is associated with enhanced fat preference produced by release of inhibition on fat sensations[172]; increased fat intake is hypothesized to lead to the weight gain associated with tonsillectomy.[173] Similar changes among survivors of head and neck cancer might not lead to weight gain (given eating problems among head and neck cancer survivors) but might increase fat intake, leading to increased risk for cardiovascular disease.

A second phenomenon involving interactions between taste and pain in non-oral body locations may be of special interest with regard to head and neck cancer. In patients with more extensive taste damage (e.g., damage to both cranial nerves VII and IX), pain sensations may be intensified in a variety of body locations.[174] A study of head and neck cancer patients found that current smokers reported higher pain levels than never-smokers and former smokers; the authors hypothesize that smoking may have analgesic properties and that pain management may enhance smoking cessation in this population.[175]

A similar interaction may induce long-term obesity risk early in life. Perinatal tobacco exposure is linked to childhood obesity,[176] and both early tobacco exposure and childhood obesity promote ear infection.[177,178] In severe cases, ear infection can damage the chorda tympani and compromise anterior taste sensation.[179] Based on the disinhibition model described above, such damage appears to elevate fat sensation and preference in a progressive manner. Consequently, overweight children tend to become overweight adults,[180] but data show that childhood ear infection is also linked to obesity in adulthood.[181,182] In similar fashion, children of smokers tend to become smokers themselves,[183] and data have shown that adult male smokers raised in homes with multiple smokers have higher body mass. Consistent with the idea that nontasters are more likely to smoke overall, these men also gain the most weight when they quit smoking,[184] suggesting that sensory cues play a significant role in their tobacco use.[161] A direct link between menthol cigarette smoking, its sensory characteristics, taste sensitivity, and cancer risk has not been identified; this subject deserves greater attention from investigators.

Chapter Summary

The tobacco industry uses flavor additives and ingredients to make the experience of smoking more palatable. This chapter discusses three common additives that affect the chemical senses—cocoa, licorice, and menthol—and the evidence of menthol's effects on the chemical senses—the olfactory, gustatory, and trigeminal systems. Menthol is added to an estimated 90% of cigarettes sold in the United States.[91] It has multiple effects on the chemical senses that may make it easier for consumers to smoke menthol cigarettes; for example, menthol can reduce the pain and irritation of tobacco smoke. These and other factors may help explain the widespread use of menthol in cigarettes, both those that are labelled as menthol and those that are not.

Studies have shown that taste perception is associated with smoking status; the ability to detect bitter taste may help protect individuals from tobacco use. Tasters, including supertasters, who make up approximately 75% of the world's population,[145,154–157] are more likely to reject the bitter taste of tobacco and nicotine. Studies also show that supertasters are more likely to smoke menthol cigarettes than medium and nontasters, and that African Americans, Asians, and women are more likely to be supertasters than whites and men. Supertasters are more likely to perceive bitter flavors, but also perceive stronger taste intensities from PTC/PROP than medium and nontasters. It is possible that menthol helps mask the bitter, irritating, and painful effects of nicotine/tobacco and in doing so, makes cigarettes and other tobacco products more palatable for supertasters.

The sensory effects of menthol could increase the risk of smoking among African Americans, who are more likely than whites to be supertasters; menthol could also contribute to TRHD if it increases the risk for nicotine dependence and the difficulty of quitting. Marketing menthol to African Americans, women, youth, and other groups, may be more than a marketing strategy. Rather, it may encourage groups with a genetic tendency to reject bitter taste to smoke a tobacco product that they are likely to find more palatable than other tobacco products.

By 2050, over 300,000 cumulative excess deaths are expected to result from menthol smoking in the United States alone.[8] The congressionally mandated 2011 FDA Tobacco Product Scientific Advisory Committee report on menthol cigarettes found that "the evidence is insufficient to conclude that it is more likely than not that smokers of menthol cigarettes have increased risk for disease caused by smoking compared with smokers of non-menthol cigarettes."[8,p.218] However, the 2011 TPSAC report also found that it "is more likely than not that the availability of menthol cigarettes increases the likelihood of addiction and the degree of addition in youth smokers," and that it "is more likely than not that the availability of menthol cigarettes results in lower likelihood of smoking cessation success in African Americans, compared to smoking non-menthol cigarettes."[8,p.216-217] These factors could contribute to the disease burden of lung cancer among groups with high rates of menthol smoking, such as African Americans.

Research Needs

The effects of menthol on TRHD should be studied in relation to the entire tobacco use continuum, smoking initiation through chronic disease outcome.[185] It has been hypothesized that menthol cigarettes increase and maintain smoking in part through menthol's sensory qualities. Further study of the chemical senses may lead to a greater understanding of smoking and quitting behaviors among menthol smokers. The hypothesis that smoking rates would be lower among groups with high rates of menthol cigarette use—such as African Americans, Asians, women, and youth——if menthol cigarettes were removed from the market requires further study. Studies are also needed to determine how other ingredients with effects similar to menthol may influence smoking behaviors, including smoking initiation and maintenance. The chemosensory effects of other flavor additives in cigarettes, such as cocoa, licorice, nutmeg, ginger, and sugar, as both non-characterizing and characterizing flavors, merits further examination. Tobacco industry documents may be a useful source of information on flavor additives and their impact on the chemical senses. It is also important to focus on flavor additives in other tobacco products, including cigars, smokeless tobacco, and electronic cigarettes, as well as those used in conventional cigarettes.

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