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# GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| 22nd Century | 22nd Century Limited, LLC |
| AD | Alzheimer's Disease |
| ADHD | attention deficit hyperactivity disorder |
| cig or cigt | cigarette |
| CO | carbon monoxide |
| CSC | cigarette smoke condensate |
| CTM | clinical trial material |
| FDA | (U.S.) Food and Drug Administration |
| FTC | (U.S.) Federal Trade Commission |
| ELISA | enzyme-linked immunosorbant assay |
| EPA | (U.S.) Environmental Protection Agency |
| G | gram(s) |
| h or H | hour(s) |
| HHS | (U.S.) Department of Health and Human Services |
| HSD | hemodynamic shearing device |
| IARC | International Agency for Research on Cancer |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug Application |
| IOM | Institute of Medicine |
| Kg | kilogram(s) |
| KY2R4F | University of Kentucky reference cigarette 2R4F |
| KY3R4F | University of Kentucky reference cigarette 3R4F |
| LA | low alkaloid |
| LOD | Limit of Detection |
| MAO | monoamine oxidase |
| mg | milligram(s) |
| min | minute(s) |
| mL | milliliter(s) |
| $mm^3$ | cubic millimeter(s) |
| NAB | N-Nitrosoanabasine |
| NAB | N-Nitrosoanatabine |
| NCSU | North Carolina State University |
| ND | Not Done |
| ng | nanogram |
| NIDA | National Institute on Drug Abuse |
| nM | nanomolar |
| NNK | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone |
| NNN | N-9-nitrosonornicotine |

| | |
|---|---|
| NRT | nicotine replacement therapy |
| OSHA | (U.S.) Occupational Safety and Health Administration |
| P450 | cytochrome P450 enzyme |
| PD | Parkinson's Disease |
| QTP | quinolinic acid phosphoribosyltransferase |
| RTI | Research Triangle Institute International |
| TPSAC | Tobacco Products Scientific Advisory Committee |
| TSNA | tobacco-specific nitrosamine |
| μg | micrograms |
| USDA | United States Department of Agriculture |
| VLN | very low nicotine |
| WHO | World Health Organization |

# 1. BRIEF SUMMARY

22nd Century Limited, LLC (22nd Century) is developing its investigational product, X-22 Smoking Cessation Product, for the indication of smoking cessation. The product is intended to reduce cravings for cigarettes and increase the chances of successfully quitting smoking.

X-22 Smoking Cessation Product is a tobacco-based cigarette. It is a botanical drug product manufactured using very low nicotine (VLN) processed tobacco from the very low alkaloid variety Vector 21-41 as the active ingredient; consequently, the X-22 cigarette is a very low nicotine (VLN) cigarette. The inactive ingredients are the flavorings, filter and wrapper components. It is administered by combustion and inhalation of its smoke.

Like conventional cigarettes, X-22 cigarettes are toxic and pose health risks to subjects, namely cancer, cardiovascular disease, respiratory disease and reproductive effects. X-22 cigarettes have a tobacco content and tar yield per cigarette comparable to typical commercial cigarettes, but have a nicotine content and yield that are reduced more than 90% compared to typical commercial cigarettes and the University of Kentucky Reference 2R4F (KY2R4F) cigarette (the tobacco industry analytical reference standard). X-22 cigarettes are manufactured and used in the same manner as conventional cigarettes, and X-22 cigarettes have the same physical and chemical properties as conventional cigarettes, except for the reduction in nicotine and related compounds. The composition of smoke from X-22 cigarettes is similar to the composition of smoke from conventional cigarettes. Pharmacology and toxicology information will be provided by reference to the literature on conventional commercial products on which X-22 cigarettes are based.

The proposed phase II clinical trial with X-22 Smoking Cessation Product will be a prospective, randomized, double-blind, parallel-group, active-control, multi-center trial with a 6-week double-blind active treatment period in subjects who have expressed a desire to quit smoking. Subjects will receive either the X-22 cigarette or an active control cigarette with typical nicotine levels for 6 weeks. The proposed daily usage is the same as the subject's normal usage of cigarettes.

The comparison of smoke analysis demonstrates that the exposure to smoke compounds from X-22 will be similar to the exposure from conventional cigarettes and to the active control cigarettes subjects will use during the treatment phase of the clinical trial. This provides assurance that the product can be tested in human subjects without additional risks beyond those already recognized for cigarette smoking.

22nd Century believes that the scientific rationale for using a VLN cigarette alone as a smoking cessation product together with the encouraging results of the previous clinical studies with VLN cigarettes, indicate that X-22 could be a useful addition to the available therapies for the treatment of patients who desire to quit smoking, and should now be studied in a more systematic manner under an Investigational New Drug Application (IND).

# 2. INTRODUCTION

22nd Century intends to develop its investigational product, X-22 Smoking Cessation Product, for the indication of smoking cessation.

X-22 Smoking Cessation Product is a tobacco-based cigarette. It is a botanical drug product manufactured using a very low nicotine (VLN) processed tobacco as the active ingredient; consequently, the X-22 cigarette is a VLN cigarette. Like conventional cigarettes, X-22 cigarettes consist of filler, filter, and wrapper components. The filler in X-22 cigarettes is comprised of 90% cured tobacco leaf and 10% conventional tobacco additives (flavor and humectants) and does not contain other non-tobacco material. Other inactive ingredients are the filter and wrapper components, which are supplied by providers of components for conventional cigarettes. The X-22 cigarettes used in the proposed phase II clinical trial contain menthol in the filter. The active control for the trial will also contain menthol in the filter.

X-22 is administered by combustion and inhalation of its smoke. X-22 cigarettes have a tobacco content and tar yield per cigarette comparable to typical commercial cigarettes, but have a nicotine content and yield that are less than 10% of those in typical commercial cigarettes and the University of Kentucky Reference 2R4F (KY2R4F) cigarette (a tobacco industry analytical reference standard). The product is intended to reduce cravings for cigarettes and increase the chances of successfully quitting smoking.

The pharmacology and toxicology of X-22 cigarettes are provided as applicable by reference to the literature on conventional cigarettes, in accordance with guidance on botanical drug products, and since:

(1) X-22 is manufactured and used in the same manner as conventional cigarette tobacco;

(2) X-22 cigarettes are conventional cigarettes except for the use of VLN tobacco; and

(3) X-22 cigarettes have the same physical and chemical properties as the commercial products on which this literature is based.

VLN tobacco is the active ingredient in X-22 cigarettes and has been used in several other VLN cigarette formulations, data for some of which is presented in this application. The VLN tobacco is produced using a proprietary variety, Vector 21-41. VLN Vector 21-41 tobacco used in the preparation of X-22 clinical trial material (CTM) for the proposed IND clinical trial X-22-201 has also been used by 22nd Century to prepare the proprietary Magic® VLN cigarette. The Magic formulation differs from X-22 CTM in the flavoring and wrapper characteristics. A comparison of the physical and chemical characteristics of X-22 cigarette, Magic and other VLN formulations to a tobacco industry standard (normal nicotine) cigarette (KY2R4F) is presented in Table 2-1 and in the CMC Item 7 section of this IND. Data from a smoke composition study with Magic is presented in Section 3.1.2 of this Item.

VLN tobacco from the tobacco variety Vector 21-41 was also used in Quest® cigarettes sold by Vector Tobacco Inc. from December 2002 to December 2007 and in Quest 3 menthol cigarettes from November 2003 to December 2007. VLN tobacco was blended with other

tobacco in Quest 1 and Quest 2 cigarettes, and it was the only tobacco in Quest 3, which is most similar to X-22.

A comparison of the physical and chemical characteristics of Quest 3 to other VLN tobacco formulations is presented in Table 2-1. Data from a smoke composition study with Quest 3 is presented in Section 3.1.3 of this Item. A safety assessment of the genetically-modified Vector 21-14 tobacco in Quest 3 brand cigarettes (Vector Tobacco, Inc.) has been submitted to the Food and Drug Administration (FDA) by Vector Tobacco, Inc. in IND 69,185. 22nd Century has a right of reference to redacted versions of the IND documents. The United States Department of Agriculture (USDA) has deregulated Vector 21-41 tobacco in 2002 as described in Section 3.2 below.

**Table 2-1 Comparison of X-22, Magic Menthol, Quest 3 Menthol, Newport® Menthol, Marlboro® Gold, and KY2R4F Reference Cigarettes**

| **Chemical:** | | **X-22** | **Magic Menthol** | **Quest 3 Menthol** | **Newport Menthol** | **Marlboro Gold** | **KY2R4F** |
|---|---|---|---|---|---|---|---|
| **Filler Composition** | | | | | | | |
| | Nicotine (mg/g) | 0.5 | 1.9 | 1.2 | 19 | 18 | 18 |
| | Nicotine (mg/cigarette) | 0.3 | 1.2 | 0.7 | 14 | 12 | 14 |
| **Smoke yields** | | | | | | | |
| | "Tar" (mg/cigarette) | 7 | 4 | 11 | 19 | 10 | 10 |
| | Nicotine (mg/cigarette) | ≤0.05 | ≤0.05 | ≤0.05 | 1.1 | 0.7 | 0.8 |
| | Carbon Monoxide (mg/cigarette) | 13 | 5 | 15 | 20 | 10 | 12 |
| **Physical:** | | | | | | | |
| | Total Weight (mg/cigarette) | 970 | 940 | 860 | 900 | 917 | 1060 |
| | Filler Weight (mg/cigarette) | 680 | 630 | 580 | 740 | 660 | 780 |
| | Length (mm) | 83 | 83 | 83 | 80 | 83 | 84 |
| | Circumference (mm) | 24.6 | 24.6 | 25.0 | 25 | 24.8 | 24.8 |
| | Pressure Drop (mm $H_2O$) | 125 | 81 | 116 | 128 | 118 | 128 |

The information provided in this summary is organized as follows:

- Rational for the Use of Very Low Nicotine Cigarettes
- Comparison of X-22 Cigarettes to Conventional Cigarettes
- Pharmacology and Toxicology of Conventional Cigarette Smoke and Nicotine
- Safety Assessment of VLN Tobacco

## 2.1. Rationale for the Use of Very Low Nicotine Cigarettes

It has been well established that cigarette smoking poses health risks to subjects, namely cardiovascular disease, multiple cancers, pulmonary disease, adverse reproductive outcomes, and exacerbation of other chronic health conditions (1). It is the goal of the US Department of Health and Human Services (HHS), as outlined in the 2010 Topics and Objectives section on Tobacco Use of the Healthy People.gov website, to reduce cigarette smoking in the United States to 12% by the year 2020 (2).

Nicotine has been recognized as a major determinant of tobacco dependence. It was suggested that reducing nicotine to very low levels could be a means of preventing the development of tobacco addiction (3). The tobacco industry in the 1990s worked on "denicotinized" tobacco; tobacco in which nicotine levels were greatly reduced by extraction, as a potential product analogous to "decaffeinated" coffee (4). Next, a cigarette brand made with tobacco from which nicotine was extracted and having an FTC nicotine yield of 0.08 mg/cigarette and a tar yield of 9.3, was marketed on a limited scale by Philip Morris in the 1990s.

In response to the interest among tobacco researchers for a denicotinized cigarette, the National Institute on Drug Abuse (NIDA) contracted with a private firm (Ultratech Corporation, Lafayette Hill, PA) to develop and manufacture denicotinized cigarettes. These cigarettes were denicotinized by removing the nicotine with a mild alkaline (ammonium solution) wash. Four types of cigarettes were developed and tested: reduced- and full-tar cigarettes containing conventional tobacco, and identically appearing reduced- and full-tar denicotinized cigarettes that with typical yields of carbon monoxide (CO) and tar, but highly reduced yields of nicotine (5). Another set of reduced nicotine research cigarettes was made by Murty Pharmaceutical using supercritical fluid extraction (6).

Data from studies with denicotinized cigarettes, which are described in more detail in Item 9, Section 2.1.3, showed that cigarettes with a very low nicotine content consistently reduce craving for cigarettes and withdrawal in smokers, and that smoking cigarettes with very low nicotine content alters the subjective reward value of smoking (7).

While it is not clear whether any effort was made to assess the removal of substances other than nicotine or to compensate for their removal in the production of the denicotinized

research cigarettes, industry documents show that processes involved in removing nicotine from tobacco were not specific for nicotine and other components are also removed, resulting in changes in taste and other factors (8). Levels of monoamine oxidase inhibitors (MAOIs) such as β-carboline alkaloids, naphthoquinone, and acetaldehyde are also affected by extracting nicotine from tobacco. Besides nicotine, the following compounds or compound classes have been known to be simultaneously extracted from denicotinized tobacco:

- Isoprenoids - a class of compounds that are acyclic terpenes such as solanesol and neophytadiene.
- Oils and waxes - which cover a number of compound classes and a larger number of specific compounds analogous to essential oils in other plants such as citrus fruit, these compounds in tobacco are largely responsible for the characteristic "tobacco" flavor and aroma. Removal of these compounds, or even a change in the concentration ratios, can destroy the characteristic flavor or aroma of a plant, including tobacco.
- Carboxylic Acids - Tobacco contains many, however, palmitic acid, oleic acid, and a number of $C_{18}$-fatty acids were specifically identified.
- Hydrocarbons in the range $C_{27}H_{50}$ to $C_{33}H_{68}$.
- Other compounds, including cembranoids and stigmasterol.

Efforts to develop a commercial "denicotinized" cigarette with adequate palatability involved reconstitution of tobacco blends by re-addition of non-nicotine components of extracts. However, even re-addition of all components, including nicotine, resulted in cigarettes with lower consumer acceptability.

In 1998, 22nd Century undertook to develop a cigarette for use as a smoking cessation aid that has the very low nicotine content of the lowest nicotine extracted cigarettes, but that is produced without using any process other than those used in production of conventional cigarettes, thus avoiding the issues resulting from extraction of nicotine. Although low alkaloid (LA) mutants of tobacco are known, the nicotine content in these LA lines is higher than in the extracted tobacco. 22nd Century, in a sponsored research program with North Carolina State University, developed a very low alkaloid tobacco variety, Vector 21-41, in which nicotine biosynthesis is specifically suppressed. This development of this variety is described in Item 7. Tobacco from Vector 21-41 is used to produce the X-22 smoking cessation product, which is described in Section 2.2 below.

In contrast to conventional low-yield ("light" or "ultra light") cigarettes that have reduced tar and nicotine yields as measured by smoking machines mainly due to smoke dilution, VLN cigarettes deliver greatly reduced ratios of nicotine to other smoke components. The data from human studies of cigarettes made from VLN tobacco, described in more detail in Item 9, Section 2.1, indicates that VLN cigarettes that deliver the sensory and behavioral cues associated with cigarette use but do not deliver a satisfying amount of nicotine break the association of those cues with the contingent delivery of nicotine reinforcement and promotes extinction of smoking cues and facilitates smoking cessation.

NIDA in 2009 included an option to develop and produce research cigarettes with different levels of nicotine (from very low to high), in its request for proposals for a 5-year contract for Preparation and Distribution of Research and Drug Products. 22nd Century agreed, as a subcontractor to Research Triangle Institute International (RTI), in RTI's contract with NIDA for the Research Cigarette Option, to use its very low nicotine tobacco to supply 9 million modified nicotine cigarettes with 8 different nicotine levels to NIDA. These research cigarettes, Spectrum™, are expected to be delivered to RTI in July 2011.

## 2.2. X-22 Smoking Cessation Product

X-22 Smoking Cessation Product is a tobacco-based cigarette. It is a botanical drug product manufactured using VLN tobacco as the active ingredient to provide a VLN cigarette. The inactive ingredients are the filter, wrapper, flavors and adhesive. It is administered by combustion and inhalation of its smoke. X-22 cigarettes have a tobacco content and tar yield per cigarette comparable to typical commercial cigarettes, but have a nicotine content and yield that are less than 10% of those in typical commercial cigarettes and the KY2R4F cigarette (the tobacco industry analytical reference standard). The product is intended to reduce cravings for cigarettes and increase the chances of successfully quitting smoking.

X-22 cigarettes, like conventional cigarettes, consist of filler, filter, and wrapper components. The filler in cigarettes is comprised primarily of cured tobacco leaf. X-22 cigarettes are similar to conventional cigarettes except that processed tobacco from a very low alkaloid tobacco variety, which is proprietary to 22nd Century, is used in the filler. All processing of tobacco is carried out by processors of conventional tobacco. All components are supplied by providers of components for conventional cigarettes.

X-22 cigarettes contain menthol in the filter. The active control cigarette for the trial will also contain menthol in the filter. Menthol is an organic compound, either derived from natural sources or synthesized, that is widely used in consumer and medicinal products. It has cooling, analgesic, and irritative properties, reflecting its interactions with specific neuronal receptors that can modulate pain and communicate to areas of the brain concerned with taste and other sensations. It has long been used in cigarettes, and for some cigarettes it is a flavor-characterizing additive. The menthol is included as a palatability aid and is also believed to be useful in masking the nicotine sensation of the cigarettes in the mouth and throat, thus helping to maintain the blind for the study (9).

Like conventional cigarettes, X-22 cigarettes pose health risks to subjects, namely cancer, cardiovascular disease, respiratory disease and reproductive effects. Except for the use of the VLN tobacco, the growing, curing and processing of tobacco for X-22 is the same as for conventional cigarettes, and X-22 cigarettes have the same physical and chemical properties as conventional cigarettes, except for the reduction in nicotine and related compounds (minor alkaloids and TSNAs). The composition of smoke from VLN cigarettes is very similar to the composition of smoke from conventional cigarettes (10).

The VLN tobacco used in X-22 is obtained from the genetically engineered tobacco variety Vector-21-41. The same very low alkaloid tobacco variety was used to produce tobacco used in Quest cigarettes sold by Vector Tobacco Inc. from December 2002 to December 2007 and

in Quest 3 menthol cigarettes from November 2003 to December 2007. Tobacco from Vector 21-41 was blended with other tobacco in Quest 1 and Quest 2 cigarettes, and it was the only tobacco in Quest 3, which is most similar to the X-22 cigarette. In addition to being sold commercially, Quest 3 cigarettes have been used in clinical studies, including trials evaluating their usefulness as an aid to smoking cessation, as described in Item 9, Section 2.1.

The tobacco variety, Vector-21-41, and related technology to reduce nicotine biosynthesis in tobacco ("QPT Technology"), was developed at North Carolina State University (NCSU) in a 5-year research program funded by 22nd Century. 22nd Century was in turn granted an exclusive worldwide license to the QPT Technology and in 1999, 22nd Century exclusively sublicensed its rights to the QPT Technology to Liggett Group, Inc., the fifth largest cigarette company in the United States and in 2001 to Liggett Group's affiliate Vector Tobacco Inc. Liggett Group, Inc. and Vector Tobacco Inc. are both wholly-owned subsidiaries of Vector Group Ltd. Vector Tobacco Inc. used Vector 21-41 tobacco in their Quest line of cigarettes. This license agreement has been terminated, and 22nd Century now holds sole rights to the use of Vector 21-41 VLN tobacco.

### 2.3. Proposed First Clinical Trial

The first clinical trial with X-22 will be a prospective, randomized, double-blind, parallel-group, active-control, multi-center trial with a 6-week double-blind active treatment period in subjects who have expressed a desire to quit smoking. Subjects will receive either X-22 cigarettes or an active control cigarette with normal nicotine levels during a 6 week treatment phase, followed by a 4-week abstinence phase, and an 8-week follow-up phase. The proposed daily usage of X-22 or active control cigarettes during the treatment phase is the same as the subject's normal usage of cigarettes.

This study is designed to evaluate the efficacy of X-22 as a smoking cessation aid and to assess the effect of X-22 on abstinence at 2 and 3 months after the quit date, the severity of withdrawal symptoms, the effect of X-22 on cigarette consumption prior to the quit date, and to evaluate the tolerability of X-22 as a smoking cessation aid.

The full protocol is contained in Item 6 of this IND.

# 3. NONCLINICAL INFORMATION ON X-22 SMOKING CESSATION PRODUCT

## 3.1. Comparison of X-22 Cigarettes to Conventional Cigarettes

In the pre-IND consultation discussion about X-22 with the FDA, the Agency agreed that, given the extensive human experience with the use of nicotine in cigarette smoke and the botanical nature of this product, the standard supportive preclinical studies required by International Conference on Harmonisation (ICH) M3 guidelines could be waived for the Initial IND submission. The Agency requested that a comparison of the smoke generated from the variety of tobacco used in X-22 cigarettes with that from commonly used cigarette smoke be provided in the IND application, with the proviso that any novel compound(s) or increased exposure to a compound(s) in the variety of tobacco used in the X-22 cigarette or its smoke would require the identification of such compound(s) and might require further toxicological assessment including general toxicology, genetic toxicology, reproductive toxicology and carcinogenicity studies as per the ICH M3 guidelines. The results of the smoke analysis study are presented below in Section 3.1.2.

### 3.1.1. Smoke Chemistry

Tobacco is unique among commercial botanical products in that its primary use (i.e., in the form of cigarettes) is to supply, upon combustion and subsequent inhalation, an aerosolized mixture of gaseous and suspended particulate components to the consumer. As with any botanical, the naturally complex chemical composition of the tobacco leaf is increased dramatically upon combustion. In addition to nicotine, there are approximately 4800 individual smoke constituents that have been identified in currently marketed United States cigarettes. The International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) have identified over 70 compounds in the mainstream smoke of cigarettes as known, probable, or possible carcinogens. The Tobacco Products Scientific Advisory Committee of the FDA Center for Tobacco Products recently compiled a list of 107 harmful and potentially harmful components of cigarette smoke. Toxicological and analytical data for the vast majority of these constituents individually do not yet exist. Even for those components for which such data do exist, there is currently no accepted national standard for assessing individual exposure or for defining maximal permissible exposures, nor is there agreement as to either the relative chemical toxicity or biological activity for individuals exposed to these substances, alone or in combination. Currently, there is no requirement to collect data on individual smoke constituents.

Despite the lack of a cohesive and codified regimen for qualitatively and quantitatively assessing the full complement of toxic and carcinogenic substances in cigarette smoke, there is at present a generally accepted list of approximately 45-55 tobacco constituents for which sufficient evidence exists of a prominent health risk to consumers. The genesis of this list is based on the work of Dr. Dietrich Hoffmann. This list, which has been periodically revised and updated since its introduction by Dr. Hoffmann, is used as an unofficial benchmark guide to develop new testing regimens for exposure to cigarette toxins and carcinogens by several major national [i.e., the EPA and the Occupational Safety and Health Administration

(OSHA)] and international agencies [i.e., IARC and the World Health Organization (WHO)] devoted to protecting the health of the public. In addition, in North America, Canada has also passed legislation that requires the annual testing and reporting of over 40 cigarette smoke constituents for all cigarette brands sold. Most, if not all, of these constituents are contained within the 'Hoffmann' list of cigarette toxins and carcinogens or one of its variants (11,12).

### 3.1.2. Comparison of Smoke from Cigarettes Made with VLN Tobacco (Magic), Conventional Cigarettes (Marlboro, Newport) and Reference Cigarettes (KY2R4F)

In order to provide a systematic characterization of the principal combustion components of X-22 cigarettes made from Vector 21-41 tobacco, as requested by FDA at the pre-IND meeting of January 21, 2009, Filtrona Technology Centre was contracted to perform an analysis (13) of mainstream smoke constituents and assess the levels of individual toxins and carcinogens derived primarily from the 'Hoffmann' list. This analysis compared smoke from the following cigarettes:

- Magic Menthol, a cigarette manufactured by 22nd Century that had a formulation very similar to X-22 cigarettes, including the same tobacco variety (Vector 21-41) used in X-22 cigarettes,
- Newport Menthol King, a top-selling U.S. commercial cigarette style,
- Magic, a non-menthol version of Magic Menthol,
- Camel® Blue, a top-selling U.S. commercial cigarette style, and
- Marlboro Gold King, the top-selling U.S. commercial cigarette style.

Smoke was analyzed for a spectrum of well-known toxins and carcinogens typically found in combusted cigarettes.

RESULTS

The results of the mainstream smoke chemistry analysis conducted at Filtrona Technology Centre on the Magic formulation are provided in Table 3-1. The results from this independent analysis confirm that the smoke from the VLN (Magic Menthol) cigarette made with Vector 21-41 tobacco used in X-22, as shown below, is chemically similar to smoke from conventional cigarettes. Results of this smoke composition study are included in Table 3-1.

**Table 3-1 Mainstream Smoke Chemistry Data[1] Conducted by Filtrona Technology Centre on the Magic Formulation**

| Analyte Tested | Magic Menthol | Magic | Newport Menthol | Marlboro Gold | Camel Blue |
|---|---|---|---|---|---|
| **Tar, Nicotine, CO (mg/cigt)** | | | | | |
| Tar | 3.5 (0.2) | 3.7 (0.2) | 18.7 (0.7) | 10.1 (0.3) | 10.8 (0.9) |
| Nicotine | 0.03 (0.00) | 0.03 (0.00) | 1.07 (0.02) | 0.72 (0.02) | 0.80 (0.05) |
| Carbon Monoxide | 5.4 (0.2) | 6.3 (0.4) | 19.7 (0.7) | 10.5 (0.2) | 12.5 (0.8) |
| **Ammonia (µg/cigt)** | 24.8 (2.0) | 23.1 (2.1) | 14.0 (0.2) | 9.9 (2.0) | 9.5 (0.3) |
| **Aromatic Amines I (ng/cigt)** | | | | | |
| Aminobiphenyl, 3- | 1.50 (0.13) | 1.55 (0.09) | 0.83 (0.09) | 0.99 (0.07) | 0.91 (0.01) |
| Aminobiphenyl, 4- | 1.02 (0.07) | 0.89 (0.09) | 0.61 (0.10) | 0.69 (0.11) | 0.55 (0.08) |
| Aminonaphthalene, 1- | 7.6 (0.1) | 8.3 (0.2) | 10.5 (0.4) | 11.2 (0.4) | 9.9 (0.4) |
| Aminonaphthalene, 2- | 4.16 (0.08) | 4.38 (0.11) | 2.32 (0.12) | 2.97 (0.40) | 2.70 (0.24) |
| **Carbonyls/Aldehydes (µg/cigt)** | | | | | |
| Acetaldehyde | 283 (13) | 353 (41) | 768 (29) | 474 (11) | 563 (13) |
| Acetone | 112 (8) | 138 (19) | 265 (12) | 167 (3) | 202 (5) |
| Acrolein | 12.0 (0.9) | 14.8 (2.4) | 75.2 (1.2) | 43.6 (1.9) | 48.9 (4.3) |
| Butryaldehyde | 10.4 (1.1) | 13.2 (1.2) | 39.9 (4.3) | 26.2 (1.4) | 30.3 (0.3) |
| Crotonaldehyde | 4.6 (0.8) | 7.5 (0.8) | 16.9 (1.2) | 8.9 (0.5) | 16.4 (1.1) |
| Formaldehyde | 5.3 (1.5) | 5.7 (0.6) | 33.0 (1.0) | 17.7 (1.5) | 19.3 (2.5) |
| Methylethylketone | 23.4 (2.2) | 28.4 (2.4) | 55.5 (3.2) | 35.7 (1.1) | 45.1 (2.7) |
| Propionaldehyde | 20.0 (1.3) | 25.3 (3.0) | 53.7 (1.9) | 34.7 (0.7) | 42.4 (0.9) |
| **Hydrogen Cyanide (µg/cigt)** | 44 (5) | 60 (4) | 291 (22) | 137 (2) | 158 (12) |
| **Menthol (mg/cig)** | 0.34 (0.01) | not detected | 0.58 (0.2) | not detected | not detected |
| **Metals (ng/cigt)** | | | | | |
| Arsenic | <1.5 | <1 | 4.3 (0.3) | 3.1 (0.1) | 2.8 (0.3) |
| Beryllium | <2 | <2 | <2 | <2 | <2 |
| Cadmium | 13.8 (1.3) | 16.8 (0.4) | 63.3 (1.4) | 36.7 (1.4) | 40.8 (1.4) |
| Chromium | <10 | <10 | <10 | <10 | <10 |
| Cobalt | <2 | <2 | <2 | <2 | <2 |
| Lead | <5 | 5.3 (0.4) | 21.2 (0.1) | 14.3 (0.3) | 14.3 (0.7) |
| Nickel | <10 | <10 | <10 | <10 | <10 |
| Selenium | <2 | <2 | <2 | <2 | <2 |

| Analyte Tested | Magic Menthol | Magic | Newport Menthol | Marlboro Gold | Camel Blue |
|---|---|---|---|---|---|
| **Nitric Oxide (µg/cigt)** | 153 (3) | 200 (7) | 163 (12) | 155 (6) | 156 (5) |
| **Phenols (µg/cigt)** | | | | | |
| Catechol | 13.2 (0.3) | 14.1 (1.0) | 59.0 (0.8) | 40.8 (0.6) | 41.3 (2.2) |
| Cresol, m- & p- | 3.9 (0.2) | 4.5 (0.3) | 9.2 (0.4) | 7.0 (0.2) | 6.1 (0.4) |
| Cresol, o- | 1.5 (0.1) | 1.7 (0.1) | 3.6 (0.2) | 2.8 (0.2) | 2.3 (0.2) |
| Hydroquinone | 16 (1) | 18 (2) | 64 (2) | 38 (2) | 38 (3) |
| Phenol | 5.1 (0.3) | 6.3 (0.3) | 13.4 (0.7) | 10.6 (0.2) | 8.8 (0.5) |
| Resorcinol | <0.5 | <0.5 | 5.7 (0.3) | 3.2 (0.1) | 3.5 (0.2) |
| **Polynuclear Aromatic Hydrocarbons (ng/cigt)** | | | | | |
| Benzo[a]pyrene | 0.9 (0.1) | 2.4 (0.1) | 9.3 (0.1) | 9.7 (0.2) | 6.7 (0.7) |
| **Semi-Volatiles (µg/cigt)** | | | | | |
| Pyridine | 3.5 (0.3) | 6.0 (0.4) | 18.0 (1.2) | 12.6 (1.7) | 11.5 (1.6) |
| Quinoline | 0.04 (0.01) | 0.05 (0.00) | 0.20 (0.02) | 0.16 (0.02) | 0.11 (0.01) |
| **Tobacco Specific Nitrosamines (ng/cigt)** | | | | | |
| NAB | 1.3 (0.1) | 1.9 (0.8) | 9.7 (0.8) | 8.4 (1.4) | 7.6 (0.4) |
| NAT | 5.7 (0.4) | 9.1 (2.7) | 95.6 (2.4) | 98.9 (3.8) | 77.6 (0.4) |
| NNK | 10.9 (1.4) | 18 (4) | 57.6 (4.7) | 93.1 (4.1) | 66.8 (2.1) |
| NNN | 39.1 (0.2) | 47 (6) | 113.0 (2.8) | 102.8 (2.3) | 72.3 (2.8) |
| **Volatiles (µg/cigt)** | | | | | |
| Acrylonitrile | 5.6 (0.2) | 6.8 (0.8) | 10.4 (0.5) | 7.5 (0.2) | 9.3 (0.1) |
| Benzene | 23 (3) | 28 (3) | 53 (2) | 37 (2) | 46 (4) |
| Butadiene, 1,3- | 18 (1) | 22 (3) | 61 (2) | 42 (1) | 47 (2) |
| Isoprene | 116 (7) | 136 (24) | 494 (23) | 315 (19) | 400 (8) |
| Stryene | 3.6 (0.4) | 4.8 (0.1) | 24.6 (0.9) | 14.6 (0.4) | 16.9 (0.9) |
| Toluene | 32 (5) | 39 (4) | 79 (8) | 53 (6) | 72 (5) |

[1] Average analyte values (standard deviations) are based on 3 runs per cigarette brand tested.

CONCLUSIONS

The results from this independent, mainstream smoke chemistry analysis of Magic cigarettes, regular and menthol, demonstrate that combustion of Vector 21-41 used in the manufacture of X-22 cigarettes produces smoke that is comparable to that produced by conventional, top-selling, commercial cigarette brands currently on the market in the United States. The results also show that the presence of menthol in the filter component of the cigarettes does not significantly affect the chemical composition of the smoke. This provides support that smoke

from X-22 cigarettes is not expected to provide any exposure to novel compounds or increase the exposure to a known compound for the subjects in the proposed clinical trial.

### 3.1.3. Comparison of Smoke from Cigarettes Made with Vector 21-41 Tobacco (Quest 3), Conventional Cigarettes (Marlboro Light, and Camel 100) and Reference Cigarettes (KY2R4F)

A similar smoke composition comparison study was conducted by Vector Tobacco on their Quest 3 VLN cigarette made from Vector 21-41 tobacco (the same tobacco used in X-22) and submitted to FDA in their Initial IND 69,185. Arista Laboratories performed this study (10). The smoke analysis examined Quest 3, other conventional brands and a control reference cigarette (KY2R4F) for qualitative and quantitative-differences in a spectrum of well-known toxins and carcinogens typically found in combusted cigarettes. At the time of the study, Vector Tobacco was manufacturing Quest 3 cigarettes under a licensing agreement with 22nd Century. 22nd Century has since reclaimed all marketing rights and is now an owner of this Arista report and the data contained therein.

This comparison has recently been updated with the testing of Quest 3 Menthol by the same testing laboratory (14). Some analytes were not measured in both sets of analyses. They are indicated in Table 3-2 as Not Done (ND).

Table 2-1 in Section 2 shows the comparison between the Quest 3cigarette used in this study and the X-22 cigarette, demonstrating their comparability.

RESULTS

The results of the mainstream smoke chemistry analysis conducted at Arista Laboratories on Quest 3 menthol and non-menthol formulations are provided in Table 3-2. In addition to differing in the presence of menthol, the Quest 3 filter contains an activated carbon segment, while the Quest 3 menthol filter not (activated carbon would be expected to absorb menthol).

The results from this independent analysis confirm that the combusted smoke from Quest 3 VLN cigarettes as shown below is chemically similar to a conventional, American brand (Marlboro Lights), as well as a standard reference cigarette (Kentucky Reference, KY2R4F) tested.

The full reports of the Arista smoke composition studies are included in the study report section of this Item.

## Table 3-2 Mainstream Smoke Chemistry Data[1] Conducted at Arista Laboratories on Quest 3

| Analyte Tested | Quest 3 | Marlboro Light | KY2R4F | Quest 3 Menthol | KY3R4F |
|---|---|---|---|---|---|
| | Project 1808 Aug 2004 | | | Project 11066 Mar 2011 | |
| **Tar, Nicotine, CO (mg/cigt)** | | | | | |
| Puffs/Cigt | 6.2 (0.1) | 8.3 (0.3) | 9.1 (0.2) | 5.6 (0.2) | 8.3 (0.0) |
| Tar | 7.8 (0.3) | 10.8 (0.5) | 9.9 (0.6) | 11.0 (0.2) | 8.4 (0.1) |
| Nicotine | 0.048 (0.003) | 0.82 (0.02) | 0.81 (0.02) | 0.043 (0.001) | 0.74 (0.02) |
| Carbon Monoxide (mg/cigt) | 10.1 (0.2) | 11.5 (0.7) | 12.3 (0.9) | 15.1 (1.5) | 10.8 (0.4) |
| Water | 0.7 (0.2) | 1.0 (0.1) | 0.8 (0.2) | 2.1 (0.4) | 0.79 (0.1) |
| **Ammonia (μ/cigt)** | 41 (4) | 14 (1) | 9.6 (0.3) | 34 (3) | 7.8 (NA) |
| **Aromatic Amines I (ng/cigt)** | | | | | |
| Aminobiphenyl, 3- | 2.9 (0.2) | 2.2 (0.1) | 2.0 (0.1) | 2.7 (0.2) | 1.7 (NA*) |
| Aminobiphenyl, 4- | 2.0 (0.2) | 1.5 (0.1) | 1.3 (0.1) | 1.8 (0.1) | 1.1 (NA) |
| Naphthylamine, 1- | 8.1 (0.6) | 8.2 (0.4) | 7.2 (0.5) | 12.3 (0.7) | 9.5 (NA) |
| Naphthylamine, 2- | 4.6 (0.3) | 5.0 (0.2) | 4.6 (0.2) | 7.4 (0.5) | 6.3 (NA) |
| **Aromatic Amines II (ng/cigt)** | | | | | |
| Aniline | 208 (15) | 189 (14) | 173 (14) | ND* | ND |
| Anisidine, o- | 2.0 (0.2) | 3.0 (0.2) | 2.9 (0.3) | ND | ND |
| Toluidine, m- | 40 (3) | 38 (3) | 38 (6) | ND | ND |
| Toluidine, o- | 38 (3) | 39 (3 | 38 (2) | ND | ND |
| **Carbonyls/Aldehydes (μg/cigt)** | | | | | |
| Acetaldehyde | 345 (24) | 619 (52) | 656 (69) | 786 (20) | 758 (NA |
| Acetone | 113 (14) | 269 (23) | 294 (26) | 366 (12) | 340 (NA) |
| Acrolein | 21 (3) | 66 (7) | 66 (8) | 53 (2) | 56 (NA) |
| Butryaldehyde | 14 (2) | 32 (3) | 35 (5) | 34.4 (0.3) | 31 (NA) |
| Crotonaldehyde | 5 (1) | 21 (3) | 16 (3) | 18.9 (0.1) | 14 (NA) |
| Formaldehyde | 9.4 (0.9) | 25.6 (2.9) | 24.9 (3.9) | 11.8 (0.2) | 14.7 (NA) |
| Methylethylketone | 26 (4) | 78 (9) | 91 (8) | 93 (2) | 96 (NA) |
| Propionaldehyde | 20 (2 | 52 (5) | 54 (5) | 58 (1) | 59 (NA) |
| **Hydrogen Cyanide (μg/cigt)** | 77 (3) | 127 (8) | 111 (7) | 307 (16) | 120 (NA) |
| **Mercury (ng/cigt)** | 1.34 (0.03) | 1.90 (0.07) | 2.07 (0.12) | 3.12 (0.17) | 2.08 (0.14) |

| | **Quest 3** | **Marlboro Light** | **KY2R4F** | **Quest 3 Menthol** | **KY3R4F** |
|---|---|---|---|---|---|
| **Analyte Tested** | Project 1808 Aug 2004 | | | Project 11066 Mar 2011 | |
| **Metals (ng/cigt)** | | | | | |
| Arsenic | 2.7 (0.2) | 4.3 (0.3) | 3.4 (0.2) | 3.2 (0.1) | 2.7 (0.2) |
| Cadmium | 22 (1) | 47 (2) | 50 (3) | 76 (2) | 33 (0.1) |
| Chromium | <LOD | <LOD | <LOD | 0.7 (0.2) | <LOQ (0.5) |
| Lead | 13.3 (0.9) | 14.3 (0.8) | 12.7 (0.0 | 18.1 (1.0) | 10.4 (0.5) |
| Nickel | <LOD[2] | <LOD | <LOD | 1.4 (0.1) | 0.8 (0.1) |
| Selenium | 1.3 (0.1) | 2.1 (0.1) | 1.0 (0.0) | 5.5 (0.2) | 2.2 (0.2) |
| **Nitric Oxide (µg/cigt)** | 224 (33) | 175 (14) | 196 (9) | 301 (22) | 239 (10) |
| **Phenols (µg/cigt)** | | | | | |
| Catechol | 20 (1) | 43 (2) | 44 (2) | 25 (2) | 37 (1) |
| Cresol, m & p | 7.4 (0.5) | 6.6 (0.7) | 6.5 (0.5) | 13.2 (1.2) | 6.4 (0.2) |
| Cresol, o- | 2.3 (0.2) | 2.2 (0.2) | 2.3 (0.2) | 4.1 (0.4) | 2.3 (0.1) |
| Hydroquinone | 15 (1) | 38 (2) | 33 (2) | 22 (1) | 32 (1) |
| Phenol | 7.9 (0.6) | 8.6 (0.8) | 7.7 (0.7) | 14.9 (1.4) | 7.5 (0.3) |
| Resorcinol | 0.34 (0.02) | 1.05 (0.05) | 0.68 (0.03) | 0.61 (0.05) | 0.70 (0.02) |
| **Polynuclear Aromatic Hydrocarbons (ng/cigt)** | | | | | |
| Anthracene | 39 (1) | 54 (1) | 57 (3) | ND | ND |
| Benz-anthrazene | 9.6 (0.4) | 14.2 (0.5) | 14.1 (0.9) | ND | ND |
| Benzo[a]pyrene | 4.2 (0.2) | 6.6 (0.3) | 6.2 (0.3) | 5.6 (0.3) | 5.6 (NA) |
| Benzo[e]pyrene | 3.2 (0.1) | 4.2 (0.2) | 4.1 (0.3) | ND | ND |
| Chrysene | 9.8 (0.3) | 16.3 (0.7) | 15.9 (1.0) | ND | ND |
| Flourene | 173 (9) | 188 (11) | 210 (9) | ND | ND |
| Flouroanthene | 47 (4) | 58 (4) | 58 (4) | ND | ND |
| Indeno[1,2,3-cd]Pyrene | 2.5 (0.2) | 3.7 (0.3) | 3.2 (0.4) | ND | ND |
| Naphthalene | 349 (21) | 400 (30) | 391 (33) | ND | ND |
| Phenanthrene | 122 (6) | 152 (8) | 161 (12) | ND | ND |
| Pyrene | 28 (2) | 44 (2) | 43.(2) | ND | ND |
| **Tobacco Specific Nitrosamines (ng/cigt)** | | | | | |
| NAB | 1 (0.1) | 16.7 (1.7) | 17.0 (0.4) | 1.3 (0.2) | 15.4 (NA) |
| NAT | 6 (0.5) | 128 (10) | 132 (8) | 8 (0.4) | 120 (NA) |
| NNK | 13 (2) | 82 (5) | 144 (5) | 12 (2) | 100 (NA) |
| NNN | 79 (2) | 138 (6) | 148 (4) | 83 (4) | 111 (NA |

| Analyte Tested | Quest 3 | Marlboro Light | KY2R4F | Quest 3 Menthol | KY3R4F |
|---|---|---|---|---|---|
| | Project 1808 Aug 2004 | | | Project 11066 Mar 2011 | |
| **Semi-Volatiles (μg/cigt)** | | | | | |
| Pyridine | 3.3 (0.9) | 6.0 (0.6) | 4.9 (0.4) | 11.7 (0.8) | 4.7 (NA) |
| Quinoline | 0.22 (0.01) | 0.22 (0.02) | 0.20 (0.02) | 0.39 (0.01) | 0.22 (NA) |
| Vinylpyridine, 3- | 0.45 (0.06) | 1.47 (0.14) | 1.15 (0.05) | ND | ND |
| **Volatiles (μg/cigt)** | | | | | |
| Acrylonitrile | 4.7 (0.3) | 8.9 (0.8) | 8.5 (1.1) | 21.4 (1.3) | 9.9 (NA) |
| Benzene | 14 (1) | 42 (2) | 46 (3) | 54 (2) | 45 (NA) |
| Butadiene, 1,3- | 19 (2) | 40 (4) | 39 (2) | 49 (3) | 42 (NA) |
| Isoprene | 137 (12) | 402 (37) | 369 (35) | 401 (26) | 361 (NA) |
| Styrene | 2.7 (0.3) | 6.7 (0.7) | 6.8 (0.8) | 12.4 (0.8) | 6.3 (NA) |
| Toluene | 24 (2) | 77.(4) | 87 (7) | 98 (5) | 80 (NA) |

* ND = Not Done, NA = Not Applicable

[1] Average analyte values (standard deviations) for Quest 3, Marlboro Light, and Quest 3 Menthol are based on 5 or 6 runs per cigarette brand tested in Project 1808 and 3 runs in Project 11066.

[2] LOD - Level of Detection

CONCLUSIONS

The results from this independent, mainstream smoke chemistry analysis of Quest 3 demonstrate that combustion of the tobacco used in the manufacture of X-22 cigarettes produces smoke that is comparable to that produced by combustion of the tobacco used in conventional cigarette brands currently on the market in the United States. This provides support that smoke from X-22 cigarettes is not expected to provide any exposure to novel compounds or significantly increase the exposure to a known compound for the subjects in the proposed clinical trial.

### 3.2. Pesticide Residues

Although the EPA regulates and specifies which pesticides may be used on tobacco, it does not regulate residues of pesticides approved for use on tobacco in conventional tobacco products. The United States Department of Agriculture (USDA) established standards for imported and domestic tobacco for residues that are not approved for use by the EPA on tobacco (15). These are specified in 7 CFR §29.427.

Tobaccos to be used in manufacturing X-22 for use in the proposed clinical trial comply with standards in 7 CFR §29.427. No changes in agricultural practices necessary for growing the

Vector 21-41 tobacco used in X-22. The low leaf nicotine and total alkaloid content of Vector 21-41 tobacco did not lead to an increased susceptibility to insect pests or diseases when using a typical insect and disease management program. Therefore, existing approved amounts of pesticides labeled for use on tobacco are used to control insect, disease and weed problems. This conclusion has been supported by the USDA in its determination for the non-regulated status of Vector 21-41 tobacco (16).

Residue analysis of filler in X-22 cigarettes to be used in the proposed phase II clinical trial will be carried out to confirm that the tobaccos are in compliance with the standards in 7 CFR §29.427.

As a result of these controls, under the conditions of usage proposed in the clinical trial, X-22 cigarettes will not pose any additional pesticide exposure risk to subjects in the study beyond those already know to be attributable to smoking standard cigarettes.

# 4. PHARMACOLOGY AND TOXICOLOGY OF CONVENTIONAL CIGARETTE SMOKE, NICOTINE, AND MENTHOL

## 4.1. Tobacco Smoke and Nicotine

The pharmacology and toxicity of tobacco, nicotine, and menthol have been well documented in the literature. Since X-22 cigarettes are comparable to conventional cigarettes on the market, except for the reduction in the content of nicotine and related compounds, the data are briefly reviewed here. The information that follows was obtained from the 2010 Surgeon General's Report (HHS 2010) (17), the 2001 Institute of Medicine report, "Clearing the Smoke" (18), and the 2011 Tobacco Products Scientific Advisory Committee's (TPSAC) "Draft Report and Recommendations on Menthol in Cigarettes" (9), unless otherwise noted.

### 4.1.1. Pharmacology of Tobacco Smoke and Nicotine

Tobacco smoke consists of thousands of chemical compounds. Several of the compounds are thought to contribute to the pharmacologic activity of tobacco although nicotine, the principal alkaloid in *N. tabacum,* is the largest contributor. Nornicotine and anabasine, other alkaloids in tobacco smoke, have less potent pharmacologic properties than nicotine and are found in much lower levels. Other lesser alkaloids may also influence the activity of nicotine. They both activate the sympathetic nervous system and affect cardiovascular physiology. Additionally, acetaldehyde releases norepinephrine, which results in a pressor effect.

Nicotine is a tertiary amine composed of a pyridine and an *N*-methylpyrrolidine ring. The stereoisomer present in tobacco is (S)-nicotine, which is significantly more pharmacologically active than the synthetic, (L)-nicotine isomer. The level of nicotine in the tobacco plant varies by type, strain, position of leaf on the plant stalk and growing conditions.

The dose-response characteristics of nicotine can be considered biphasic. At low doses, such as those received through smoking, nicotine acts on the central nervous system to increase blood pressure and heart rate. At high doses, nicotine acts on the peripheral nervous system, decreasing blood pressure and heart rate. It has been shown that tolerance to tobacco smoke develops after repeated use. First time smokers report nausea, headaches and dizziness that disappear with continued smoking. This response is due largely to the development of tolerance to nicotine.

There is evidence of acute tolerance to some, but not all, actions of nicotine. Very little is known about the mechanism of acute tolerance, although it has been suggested that a nicotine metabolite or the desensitization of nicotine receptors may be involved. Chronic tolerance also occurs for some nicotine effects, shown partially by the fact that smokers increase their tobacco consumption with time. Again, the mechanism is not fully understood, however several hypotheses exist including increased nicotine metabolism or alterations to nicotinic receptors in the brain.

Nicotine has also been shown to improve attention and cognition in some cases. An article reviewed studies that demonstrated the benefits nicotine administration may have on several disease states (19). Nicotine was shown to lower the incidence of symptoms and diagnosis of Alzheimer's disease (AD). AD patients who were administered nicotine showed improvement in attention and a reduction in errors on learning tasks. Nicotine administration to patients suffering from Parkinson's disease (PD) has resulted in improvement in attention and motor skills. Schizophrenic patients also have benefited from nicotine, noted by improvements in spatial perception, memory and attention. In people diagnosed with attention deficit hyperactivity disorder (ADHD), nicotine has improved concentration and reaction time.

Constituents in tobacco inhibit both forms of the enzyme monoamine oxidase (MAO-A and MAO-B). This enzyme is important in the breakdown of the amine neurotransmitters, including dopamine, which is thought to mediate the reinforcing effects of nicotine and contribute to tobacco dependence (20).

### 4.1.2. Pharmacokinetics of Nicotine in Cigarettes

Nicotine is carried on tar droplets that are inhaled by a smoker. Once tobacco smoke reaches the small airways and alveoli in the lungs, nicotine is absorbed rapidly. Two reasons account for this: the large surface area with respect to this part of the body and the alkaline pH (approximately 7.4). Once absorbed in the lungs, nicotine passes into the blood stream and is distributed throughout the body. The spleen, lungs, liver and brain all have high affinities for nicotine, which has a distribution half-life of approximately 9 minutes (21).

Nicotine is metabolized largely by the liver, although metabolism in the lungs also occurs. The two principal metabolites of nicotine are cotinine and nicotine-N'-oxide while some free nicotine is also excreted in the urine. Cotinine is formed in the liver first by the oxidation of position 5 of the pyrrolidine ring as mediated by cytochrome P-450 to nicotine *D1*'(5')-iminium ion (22). This ion is then metabolized in a second step by cytoplasmic aldehyde oxidase to cotinine (23). Nicotine-N'-oxide is formed by the oxidation of the nitrogen atom of the pyrrolidine ring (24). The excretion of nicotine from the kidney occurs through both glomerular filtration and tubular secretion and is dependent upon the pH of urine.

### 4.1.3. Toxicology of Tobacco Smoke and Nicotine

As discussed previously, tobacco smoke exerts a wide range of pathologies. The Surgeon General reported (17) that smoking causes, or contributes to, many cancers including: lung, oral, laryngeal, esophageal, bladder, cervical, pancreatic, stomach, kidney cancer and leukemia. Smoking causes respiratory diseases including: chronic obstructive pulmonary disease, pneumonia, respiratory effects in utero and respiratory effects in childhood, adolescence and adulthood. Smoking has been linked to cardiovascular diseases with respect to causal relationships found in association with the following conditions: subclinical atherosclerosis, coronary heart disease, cerebrovascular disease and abdominal aortic aneurysm. Additionally, smoking causes reproductive and other effects including: fetal deaths and still birth, fertility, low birth weight, pregnancy complications, cataracts, diminished health status/morbidity, hip fractures, low bone density and peptic ulcer disease.

The 2010 Surgeon General Report (HHS 2010) (17) also reviewed the mechanism by which the toxicity of tobacco smoke affects the lungs. Generally, the gas phase components of smoke penetrate the small airways and alveoli and may play a role in diseases such as emphysema while the particulate phase components are deposited in the larger airways and play a role in diseases such as chronic bronchitis. Smoking over time causes a narrowing of the smaller airways. Cigarette smoke has been shown to increase epithelial permeability in all areas of the lungs, which decreases its protective function. Furthermore, smoke can increase the respiratory tract secretions and/or decrease ciliary activity, thereby decreasing the protective action of the mucociliary system in the lung.

The acute toxicity of nicotine brings about dizziness, nausea, vomiting, headache and diarrhea. More severe intoxication can occur, resulting in death, due to paralysis of respiratory muscles. Green tobacco sickness is an occupational illness due to the dermal absorption of nicotine present in the dew on tobacco leaves. The symptoms are similar to the toxic effects of inhaled nicotine.

While it is difficult to assess the direct contribution of nicotine to tobacco-related effects due to the complex mixture of chemicals in tobacco smoke, several observations have been made. Chronic exposure to nicotine in tobacco smoke affects many body systems and contributes to the progression of several diseases. It may cause atherosclerotic disease by acting on lipid metabolism and coagulation, by hemodynamic effects and/or by endothelial injury. Nicotine contributes to acute coronary events by causing increased oxygen demand, thrombosis or coronary spasm.

Furthermore, nicotine may contribute to the progression of chronic hypertension by aggravating vasoconstriction. Chronic nicotine exposure reduces skin blood flow which may slow wound healing time. Nicotine use during pregnancy increases the risk of low birth weight, prematurity, spontaneous abortion, and perinatal mortality in humans. The development of emphysema may be influenced by nicotine. Finally, nicotine is not genotoxic.

## 4.2. Menthol

### 4.2.1. Nonclinical Toxicology of Menthol in Cigarettes

The Tobacco Products Scientific Advisory Committee of the Center for Tobacco Products of the Food and Drug Administration was mandated to produce a report on the public health impact of menthol in cigarettes. The resulting "Draft Report and Recommendations on Menthol in Cigarettes" (9) was made public in April of 2011. The information contained in the section below was taken from that report.

As detailed in Chapter 7 of the TPSAC report, some information on the understanding of the differential risks posed by menthol versus non-menthol cigarettes comes from toxicological studies. The relevant studies include in vitro and in vivo approaches using menthol or smoke from cigarettes. As for toxicologic studies in general, there are questions about the relevance of animal and cell toxicology studies with respect to the potential toxic effects of menthol in cigarette smokers.

Various studies have addressed the toxicity of menthol using in vitro cellular assays that assess whether menthol damages or kills cells. One general issue in interpreting such studies is the relevance of the concentrations used and the endpoints investigated to toxicity in smokers. One study (Bernson and Pettersson, 1983, as cited in the TPSAC report) investigated the toxicity of menthol in four different bioassays. They summarize the findings as suggesting that menthol may lead to "…a deterioration of biological membranes." Other studies have shown that menthol affects cell membrane properties. Azzi et al. (2006, as cited in the TPSAC report) used a system that measures diffusion of carcinogens across porcine esophageal tissue to assess the effect of menthol on permeation and reservoir formation in the tissue for NNK and B[a]P. Menthol slowed the diffusion of these two carcinogens but increased the size of the tissue reservoir for NNK. In another cell system, menthol increased the transepithelial electrical resistance, but the decrease was not different from that observed with non-menthol cigarettes (Alakayak and Knall 2008, as cited in the TPSAC report).

Several studies summarized in the TPSAC report have addressed interactions of menthol with membrane receptors. Sidell et al. (1990) used a human neuroblastoma cell line and identified a calcium channel that was blocked by menthol. More recent studies have focused on the TRPM8 Ca2+-permeable channel. Results from various cellular systems show that activation of the TRPM8 channel by menthol induces cell death (Yamamura et al. 2008; Li et al. 2009, as cited in the TPSAC report), although one study using prostate cancer cells found that TRPM8 activation was not the mechanism of menthol-induced cell death in that system (Kim et al. 2009, as cited in the TPSAC report).

Another inhalation study was reported in the peer-reviewed literature in 1997 (Gaworski et al. 1997, as cited in the TPSAC report). In this study, Fischer 344 rats were exposed to mainstream smoke from a reference cigarette and a similar cigarette containing 5000 ppm synthetic *l*-menthol. The only difference noted between the two exposure groups was a dose-response trend with level of particulate matter for nasal discharge in the reference cigarette group but not in the menthol cigarette group.

A report on a study conducted by Reynolds Tobacco Co. of a 90-day inhalation study comparing menthol vs no menthol in heated tobacco vs. conventional cigarettes (Salgado and Glantz 2011, as cited in the TPSAC report) indicated that menthol inhalation from heated tobacco produced more severe histopathological changes in the lungs compared to conventional cigarettes.

CONCLUSIONS

The TPSAC report reached the following conclusions regarding menthol, based on the evidence reviewed:

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers inhale more smoke than non-menthol cigarette smokers. Because of methodologic issues in studying smoking topography, the generalizability of these finding to the smoking of menthol cigarettes in daily life is questionable.

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers are exposed to higher levels of nicotine and other tobacco smoke toxins, at least in regular daily smokers of more than 5 or 10 cigarettes per day. There are insufficient data to know if menthol cigarettes result in greater smoke intake and more exposure to tobacco smoke toxins among smokers of relatively few cigarettes per day.

- The evidence is insufficient to conclude that smokers of menthol cigarettes face a different risk of tobacco-caused diseases than smokers of non-menthol cigarettes. Some toxicology studies raise concern, particularly the finding that the addition of menthol is associated with greater fine particles which are suspected to contribute to cardiovascular disease. Available epidemiologic data do not demonstrate increased disease risk in people, but the data are largely limited to lung cancer. The hypothesis that menthol cigarette smoking increases the risk of cardiovascular disease is biologically plausible and needs to be investigated.

# 5. SAFETY ASSESSMENT OF VLN TOBACCO, THE ACTIVE INGREDIENT IN X-22 CIGARETTES

Cigarettes, including X-22 cigarettes, cause many serious and life-threatening conditions such as cancer, cardiovascular disease, respiratory disease and reproductive effects (1). Furthermore, X-22 is intended for smoking following combustion, as opposed to ingestion. The toxicity of cigarette smoke, in terms of disease outcomes, is well understood and is not differentiated by brand nor reduced by changes in (specifically, reduction of) tar content. The HHS reported in 2001 that changes in cigarette design, including reductions in tar, from the 1950s to the mid-l980s had no convincing effect on the disease burden caused by cigarette use, either for smokers as a group or the entire population. Thus, any change in nicotine content, a minor component of tar, as a result of the incorporation of VLN tobacco in X-22 cigarettes is not expected to be clinically relevant. Cigarettes should be considered maximally toxic, in that the thousands of unknown constituents in tobacco smoke may make X-22 cigarettes as toxic and harmful to human subjects as continuing to smoke their usual brand. However, it should be noted, unlike conventional cigarettes sold over-the-counter, X-22 cigarettes used in clinical trials with confirmed smokers or prescribed by a physician to confirmed smokers, will be used for a relatively short time period and for smoking cessation.

The genetic modification in Vector 21-41 is described in Item 7. Other than the specific reduction of expression of an endogenous nicotine biosynthesis enzyme in the roots, the only modification is the insertion of the selectable marker gene, *npt II*. The *nptII* gene was the first selectable marker for plant transformation to be approved for human consumption (25). The biosafety of the use of kanamycin resistance as a selectable marker in transgenic plants has been discussed extensively (26,27). The only new protein possibly expected in Vector 21-41 is *npt-II* protein. The *npt-II* protein has no significant homology with proteins listed as food allergens or toxins and is instable to proteolytic enzymes, heat, and stomach acid conditions. For these reasons, allergenicity or toxicity were not a concern (28). Tobacco is not consumed as a food, but rather smoked. Therefore, like other proteins in tobacco, *npt-II* would be broken down during the curing, aging, processing and burning of the tobacco prior to human exposure (29). An enzyme-linked immunosorbent assay (ELISA) test did not detect any *npt-II* protein in cured, processed Vector 21-41 tobacco leaf. Breakdown products and derivatives of proteins in tobacco Vector 21-41 would be similar to those derived from other proteins normally found in non-transgenic tobacco leaves to which humans are exposed.

## 5.1. Nonclinical Studies of Vector 21-41 Tobacco

Studies of the toxicological effects of the products of combustion from cigarettes made with VLN tobacco from Vector 21-41 have been done by Chen et al (30). A material termed cigarette smoke condensate (CSC), collected by filtering smoke from two types of cigarettes made with Vector 21-41 tobacco (Quest 1 and Quest 3) and KY2R4F cigarettes, was subjected to a battery of *in vitro* tests to determine its toxicological profile. CSC from Quest 1 (nicotine yield 0.53 mg/cig) and Quest 3 (nicotine yield 0.032 mg/cig) had less nicotine than CSC from a standard reference cigarette, KY2R4F (nicotine yield 0.80 mg/cig). The

authors reported that in addition to nicotine, some tobacco-specific nitrosamines (TSNAs), aldehydes, and volatile organic compounds were also reduced in the Quest cigarettes compared to the KY2R4F. Aromatic amines were slightly lower in CSC from Quest 1 and slightly higher in CSC from Quest 3.

CSC from all three types of cigarettes was positive for mutagenic potential in the Ames test, produced a similar concentration-dependent increase in lactate dehydrogenase in the cell culture medium of normal human bronchial epithelial cells, and increased cytoplasmic nucleosomes, the sub-G1/G0 population of cells, and the frequency of apoptotic comet tails. CSC from either of the Quest cigarettes inhibited cell growth more than CSC from the reference cigarette, and adding nicotine to the CSC from Quest cigarettes attenuated this inhibition. CSC from Quest cigarettes also decreased gap junction intercellular communication, caused cell cycle arrest, and increased proapoptotic protein Bax independent of p53 induction. The authors concluded that nicotine attenuates cytotoxicity possibly in part through inhibition of apoptotic pathways.

A study by Catanzaro et al (31) studied the effect of mainstream cigarette smoke from Quest 1, Quest 3, and KY2R4F cigarettes on juvenile apolipoprotein E-deficient mice exposed for 8 and 12 weeks. In both studies, mice exposed to smoke from all three cigarettes developed greater areas of lipid-rich aortic lesions than did non-smoking controls. Smoke from the very-low-nicotine Quest 3 resulted in smaller aortic lesions than did smoke from Quest 1 or KY2R4F cigarettes. Urinary levels of isoprostane F2 alpha VI, increased proportionally to cigarette nicotine yield, whereas induction of pulmonary cytochrome P4501A1 was proportional to tar yield. Lesion area was associated with both nicotine and tar yields, although in multiple regression analysis only nicotine was a significant predictor of lesion area. Smoke exposure did not alter systolic blood pressure (SBP), heart rate (HR), blood cholesterol, or leukocyte count. Taken together, these observations suggest that smoking may accelerate atherosclerosis and that nicotine may be one of the causative factors.

A study was performed to explore the effects of varying TSNA levels in low nicotine tobacco products (32). TSNAs are important carcinogens in smokeless tobacco products and cigarette smoke. Two of these tobacco alkaloid derived compounds, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N9-nitrosonornicotine (NNN), are consistently carcinogenic in laboratory animals, with NNK showing higher activity. TSNA levels were lower in very-low-nicotine Quest 3 cigarettes than in conventional cigarettes, although NNN was only slightly reduced (0.83 ug/g for Quest 3 vs 2.8 ug/g for Marlboro Light).

Ramachandran et al (33) studied the effect of mainstream and sidestream cigarette smoke extracts from ordinary high-nicotine cigarettes (Marlboro 100's), low-nicotine cigarettes (Quest 1), and VLN cigarettes (Quest 3) on the thrombogenic properties of platelets under flow conditions that approximately mimicked normal vascular blood flow. Extracts from low- and VLN cigarettes caused significantly greater platelet activation than extracts from high-nicotine cigarettes. That nicotine was crucial was confirmed by adding 50 nM nicotine (comparable with the nicotine level in smokers' plasma) to VLN cigarette smoke extracts and demonstrating a reduction in the shear-dependent rate of platelet activation of more than 75%. The authors conclude that although low- and very low-nicotine cigarettes may be

useful in weaning smokers from cigarettes, they also might cause a significantly increased risk of thrombotic disease in smokers and others exposed to the secondhand smoke from such cigarettes. This hypothesis can be tested only in controlled clinical trials, which is one reason that 22nd Century is proposing to develop X-22 as a prescription drug, rather than as an over the counter product.

A second study (34) employed a hemodynamic shearing device (HSD) to investigate the in vitro effects of cigarette smoke on platelet activation and endothelial cell adhesion of the activation in a combined system of platelets and cultured human umblical vein endothelial cells under physiological shear stress. The authors investigated the alteration of E-selectin expression on endothelial cells upon exposure to: (1) platelets and Quest 3 ("nicotine-free") smoke extract, (2) platelets alone, and (3) Quest 3 smoke extract alone, under physiological shear stress. They confirmed that nicotine decreases platelet activation due to cigarette smoke and found that: (i) surface expression of E-selectin on endothelial cells was significantly increased upon simultaneous exposure of endothelial cells and platelets to nicotine-free extracts relative to exposure of endothelial cells to either platelets or Quest 3 smoke extract alone ($p<0.05$), (ii) platelet activation was significantly increased in the presence of Quest 3 smoke extract ($p<0.05$) and (iii) nicotine (200 nM), when added to Quest 3 smoke extract, significantly reduced platelet activation due to Quest 3 smoke extract ($p<0.05$), an effect additionally confirmed by conventional cigarette extracts which contain more nicotine ($p<0.05$). It was concluded that: (a) "nicotine-free" smoke extract and platelets additively increase endothelial cell E-selectin surface expression, and (b) nicotine modulates platelet activation regardless of endothelial cells.

# 6. INTEGRATED OVERVIEW AND CONCLUSIONS

## 6.1. Safety of the Usage Levels in the Proposed Clinical Trial

In the proposed trial, X-22 cigarettes will be provided in a limited amount for 6 weeks only to confirmed smokers. As described in Item 9, Section 2.1, when smoking VLN cigarettes, smokers generally consume fewer cigarettes per day than when they smoke their usual brand. It is expected that the exposure of subjects to smoke components in the trial will, in general, be no greater than if they did not participate and continued to smoke their usual brand.

22nd Century believes that the product, as designed and manufactured, is not more or less harmful than conventional cigarettes when used as directed in this clinical trial.

## 6.2. Conclusions Regarding Human Safety

Cigarette smoking is the cause of many serious and life-threatening conditions. The United States Surgeon General has reported that smoking causes, or contributes to, many cancers including: lung, oral, laryngeal, esophageal, bladder, cervical, pancreatic, stomach, kidney cancer and leukemia. Smoking causes respiratory diseases including: chronic obstructive pulmonary disease, pneumonia, respiratory effects in utero and respiratory effects in childhood, adolescence and adulthood. Smoking has been linked to cardiovascular diseases with respect to causal relationships found in association with the following conditions: subclinical atherosclerosis, coronary heart disease, cerebrovascular disease and abdominal aortic aneurysm. Additionally, smoking causes reproductive and other effects including: fetal deaths and still birth, fertility, low birth weight, pregnancy complications, cataracts, diminished health status/morbidity, hip fractures, low bone density and peptic ulcer disease.

Results of the smoke composition comparison study show that the smoke from X-22 cigarettes contains no novel toxic compound(s) and that human subjects who inhale smoke from X-22 will not be exposed to greater amounts of known toxic compound(s) than when they inhale smoke from standard US cigarette brands.

The addition of menthol to the X-22 cigarette is not expected to have any impact of the relative toxicity of the cigarette smoke, based on the following conclusions reached by the TPSAC in their draft report:

- The evidence is insufficient to conclude that smokers of menthol cigarettes face a different risk of tobacco-caused diseases than smokers of non-menthol cigarettes. Some toxicology studies raise concern, particularly the finding that the addition of menthol is associated with greater fine particles which are suspected to contribute to cardiovascular disease. Available epidemiologic data do not demonstrate increased disease risk in people, but the data are largely limited to lung cancer. The hypothesis that menthol cigarette smoking increases the risk of cardiovascular disease is biologically plausible and needs to be investigated.

VLN cigarettes, including X-22 cigarettes, have been shown in nonclinical studies to demonstrate similar toxicological effects to standard cigarettes. Relatively recent nonclinical studies suggest that nicotine attenuates tobacco smoke-related cytotoxicity (possibly in part through inhibition of apoptotic pathways), that nicotine may be one factor that accelerates the development of tobacco smoke-related atherosclerosis, and that nicotine attenuates (but does not eliminate) the increased risk of tobacco smoke-related thrombotic disease. The fact that nicotine contributes in various ways to numerous tobacco smoke-related health risks is one reason that 22nd Century is proposing to develop X-22 as a prescription drug.

Based on this body of information, it is reasonable to conclude that X-22 cigarettes poses no new hazard or health risk beyond the risks known for conventional cigarettes and that, under the conditions of usage proposed in the clinical trial, X-22 cigarettes should not pose any additional risk to subjects in the study beyond those already know to be attributable to smoking conventional cigarettes.

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# ESTABLISHING A NICOTINE THRESHOLD FOR ADDICTION

## The Implications for Tobacco Regulation

On February 25, 1994, the Food and Drug Administration (FDA) released a letter to the Coalition on Smoking or Health announcing its intention to consider regulating cigarettes. The agency's premises were that the vast majority of tobacco users self-administer the product for the drug effects of nicotine and to sustain addiction and that cigarette manufacturers control the levels of nicotine in cigarettes to maintain this addiction. The FDA further raised the possibility of regulating cigarettes on the basis of their nicotine content to prevent addiction.

On February 28, 1994, the ABC news program *Day One* presented evidence that tobacco manufacturers manipulate the nicotine content of cigarettes. One way they do this is by removing nicotine from tobacco and then adding it back in controlled amounts, using tobacco extracts containing nicotine. It was suggested on the news program that the amount of nicotine in tobacco was controlled to ensure that the level was adequate to maintain nicotine addiction. In support of this idea the program quoted an internal memorandum from a Philip Morris Tobacco Company scientist that had been discovered in recent litigation: "The cigarette should be conceived not as a product but as a package. The product is nicotine. . . . Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke."[1] That the pharmacologic actions of nicotine are important determinants of why people smoke is supported by studies conducted by the tobacco industry[2,3] and by nonindustry researchers.[4]

That nicotine addiction sustains tobacco use for most smokers is well established.[4] Once a person is addicted to nicotine, quitting smoking is difficult, and more than 90 percent of the smokers who try to quit each year fail.[5] An important, if not the most important, component of a policy to reduce tobacco use in the population is to prevent the development of nicotine addiction in young people.[6] Young people do not start to smoke because they are addicted, but rather because of psychosocial and environmental influences, particularly peer influences, psychological factors, and advertising. Young people generally underestimate the addictiveness of nicotine, and most of them at first intend to smoke only for a few years.[6] However, once they begin to smoke, many become addicted to nicotine, and this addiction sustains the self-injurious behavior into adulthood. The result of nicotine addiction is a 40 percent probability of premature death from illness caused by tobacco.[7] It is difficult to prevent adolescents from experimenting with cigarettes. However, by regulating the availability of nicotine in tobacco products, it may be possible to prevent the transition from experimental or occasional smoking to addiction. This paper examines the proposition that the level of nicotine likely to produce addiction can be estimated and that mandating a nicotine content below that level is a feasible approach to tobacco regulation.

### Is There a Threshold Level of Nicotine Intake Associated with Addiction?

We define addiction according to the Surgeon General's 1988 Report on Nicotine Addiction: it is the compulsive use of a drug that has psychoactivity and that may be associated with tolerance and physical dependence (i.e., may be associated with withdrawal symptoms after the cessation of drug use).[4] For smokers, addiction is assumed to involve daily smoking of



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cigarettes, difficulty in not smoking every day, and a high likelihood of withdrawal symptoms after cessation of smoking.

Most American smokers are believed to be addicted according to these criteria.[8] However, approximately 10 percent of current smokers (a group sometimes called tobacco "chippers") regularly smoke five or fewer cigarettes per day and appear not to be addicted.[9] Most do not have withdrawal symptoms when they stop. Typically, such people smoke in specific situations, can skip smoking for one or more days, and can quit smoking without great personal distress.

The daily intake of nicotine from tobacco can be estimated from the level of cotinine, the principal metabolite of nicotine, in blood or saliva.[10] The average blood cotinine concentration in addicted smokers is about 300 ng per milliliter.[11,12] Smokers of 5 or fewer cigarettes per day have average serum cotinine levels of 54 ng per milliliter and an average consumption of 3.9 cigarettes per day.[13] The cotinine level normalized for cigarette consumption is 14 ng per milliliter per cigarette, or 70 ng per milliliter for a person who smokes five cigarettes per day. Thus, it is reasonable to estimate a level of 50 to 70 ng of cotinine per milliliter as a cutoff point for the addictive threshold. Of course, there is no sharply demarcated threshold level, and there are some people who smoke fewer than five cigarettes per day and have great difficulty in quitting and others who can smoke more than five cigarettes per day and quit with ease.

Studies involving the infusion of nicotine and cotinine into smokers indicate that the daily intake of nicotine can be estimated as 0.08 times the blood cotinine concentration.[10] A level of 50 to 70 ng of cotinine per milliliter corresponds to a daily intake of 4 to 6 mg of nicotine. Thus, 5 mg of nicotine per day is proposed as a threshold level that can readily establish and sustain addiction.

## Delivery of Nicotine from Cigarettes

On average, an American cigarette contains 8 to 9 mg of nicotine.[11] The concentration of nicotine in tobacco ranges from 1.5 to 2.5 percent.

Typically, the cigarette delivers about 1 mg of nicotine to the circulation of the smoker,[14] representing an absolute bioavailability of about 12 percent. The variation in intake per cigarette is considerable, however, ranging from 0.3 to 3.2 mg, representing a bioavailability of 3 to 40 percent, depending on how the cigarette is smoked.[14,15] The daily intake of nicotine is poorly correlated with machine-determined yields.[11,12,16] This is because smoking machines smoke cigarettes in a standardized way, whereas people can take more puffs, puff more intensively, and occlude ventilation holes in the filter or on the cigarette in order to obtain the desired dose of nicotine from most cigarettes. When the number of cigarettes available to an individual smoker is reduced from an average of 38 to 5 per day, the intake of nicotine per cigarette increases an average of threefold,[17] a figure consistent with the maximal absolute bioavailability cited, 40 percent. We emphasize that this absolute bioavailability is the percentage of the nicotine contained in the cigarette that can be absorbed systemically by the smoker; it is unrelated to the smoking-machine yield. If the design of cigarettes were to change, bioavailability would need to be reassessed in people smoking the redesigned cigarettes.

## Threshold Levels of Nicotine in Cigarettes as a Way to Avert Addiction

Although machine-measured cigarette yields are not useful in predicting a smoker's intake of nicotine, the absolute level of nicotine in a cigarette could be regulated to limit the maximal obtainable dose. Studies using cigarettes developed for research purposes to be low in nicotine have demonstrated that intake can be limited by restricting the amount of nicotine in the tobacco.[2,18]

Assuming that the estimated target daily dose of nicotine should be 5 mg or less to avert addiction and that a young person may smoke up to 30 cigarettes per day, one can conclude that a maximal available (i.e., systemic) dose of 0.17 mg of nicotine per cigarette is the threshold level for a less-addictive cigarette. Assuming a maximal bioavailability of 40 percent with intensive smoking, an absolute limit of 0.4 to 0.5 mg of nicotine per cigarette should be adequate to prevent or limit the development of addiction in most young people. At the same time, it may provide enough nicotine for taste and sensory stimulation.

## A Possible Strategy for Regulation

The rationale behind the strategy for regulating the nicotine content of cigarettes is to prevent the development of nicotine addiction in young people. To minimize the hardship to already addicted adult smokers, the level of nicotine in tobacco could be reduced gradually, with a goal of reaching a target nicotine level over perhaps 10 to 15 years. The intended result of such a strategy would be that cigarettes could still be sold, but the number of addicted smokers would be markedly reduced. In the absence of addiction, levels of tobacco consumption should decline sharply, causing a substantial reduction in the rates of tobacco-caused illnesses.

There are, of course, a number of caveats. A threshold level for nicotine addiction is a theoretical concept based on observations in current smokers and studies of the bioavailability of nicotine during smoking restriction. That restricting levels of nicotine would prevent addiction needs to be verified empirically. There is concern that for already addicted adult smokers, reducing the nicotine level in tobacco might result in more intensive compensatory smoking, with increased exposure to toxic combustion products such as carbon



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monoxide and tar. Switching from higher-yield to lower-yield cigarettes has been shown to result in smoking more cigarettes or smoking more intensively, both of which are associated with increased exposure to carbon monoxide and other toxins.[18,19] Overcompensation (i.e., inhaling more smoke from low-nicotine cigarettes than from higher-yield brands) appears, however, to persist only for days or weeks. In long-term studies of carbon monoxide exposure after subjects switched to low-yield cigarettes, compensatory oversmoking appears not to persist.[20,21] It is also conceivable that cigarettes could be manufactured to reduce the delivery of tar and carbon monoxide as well as the nicotine content. Even if there is some element of overcompensation and smokers are exposed to increased levels of toxins, their short-term (10 year) risk may be offset by the long-term benefit of a greater likelihood that they will stop smoking (as cigarettes become less satisfying) and by the enormous benefit of preventing nicotine addiction in future generations.

It should be noted that other researchers have proposed the introduction of "safer" cigarettes that are enriched with nicotine in order to reduce the ratio of tar to nicotine.[22] The rationale for such cigarettes is that smokers would need to inhale less smoke to obtain the desired dose of nicotine, and exposure to toxins would thus be reduced. A strategy involving nicotine-enriched cigarettes might reduce morbidity and mortality from cigarette smoking, but the reduction would probably be limited, because even at reduced doses, tobacco smoke is highly toxic. The goal of that approach — producing a safer cigarette for those who cannot stop smoking — is the diametric opposite of ours. Our goal is the prevention of nicotine addiction and a reduction in the prevalence of cigarette smoking, which in the long term would eliminate exposure to the toxins in tobacco smoke and reduce tobacco-induced morbidity and mortality much more.

The measures described in this proposal may seem drastic to some. However, the problem of one quarter of a billion premature deaths caused by tobacco use in developed countries[7] calls for drastic action. Tobacco use is motivated by nicotine addiction. We offer a strategy for the prevention of nicotine addiction based on recent scientific data. This approach deserves study by the regulatory authorities.

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We are indebted to Dr. Charles R. Schuster, former director of the National Institute on Drug Abuse, and Dr. John Slade, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, for their helpful comments; and to Ms. Kaye Welch for assistance in the preparation of the manuscript.

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Supported in part by grants (DA02277 and DA01696) from the National Institute on Drug Abuse.

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# A Nicotine Delivery Device Without the Nicotine? Tobacco Industry Development of Low Nicotine Cigarettes

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Joshua Dunsby and Lisa A. Bero Ph.D., "A Nicotine Delivery Device Without the Nicotine? Tobacco Industry Development of Low Nicotine Cigarettes" (2005). Tobacco Control. 13, pp. 362-369. Postprint available free at: http://repositories.cdlib.org/postprints/788

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# A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes

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*Tob. Control* 2004;13;362-369
doi:10.1136/tc.2004.007914

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RESEARCH PAPER

# A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes

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*Tobacco Control* 2004;**13**:362–369. doi: 10.1136/tc.2004.007914

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Received 24 February 2004
Accepted 28 July 2004

**Background:** Defining harm reduction and regulating potentially reduced exposure products (PREPs), including low nicotine products, are key issues in tobacco control policy. The US Congress has been considering legislation authorising the Food and Drug Administration (FDA) to regulate tobacco products.
**Objective:** To investigate tobacco industry perceptions, interests, motivations, and knowledge regarding the marketability of low nicotine tobacco products.
**Methods:** Qualitative analysis of internal tobacco industry documents identified in the Legacy Tobacco Documents Library between February 2002 and June 2004. Search terms included low-, no-, reduced-nicotine; denicotinization; low-, reduced- alkaloids; Next; de-nic; and key names of people, organisations, projects, and their common abbreviations and acronyms.
**Results:** The tobacco industry has made repeated efforts to develop low nicotine cigarettes. Reasons for doing so include consumer appeal and economic importance in a highly competitive cigarette market for "healthier" products. The industry considered the development of a new "denic" market segment a critical challenge.
**Conclusions:** The tobacco industry exploits consumer misunderstanding of the health effects of nicotine in development and marketing efforts. The industry has risked the development of a less addictive product to expand the market reach of tobacco products based on perceived health benefits and appeal to quitters.

Nicotine is the basis for tobacco addiction,[1 2] and the pharmacology of nicotine occupies a fundamental place in tobacco control. The publication of the US Surgeon General's Report, *The health consequences of smoking: nicotine addiction*, in 1988, focused attention on the health implications, as well as the policy implications, of treating tobacco as an addictive substance.[1] Subsequently, public attention seized at times on the issue of high nicotine—and presumably more addictive—tobacco. During the mid 1990s, US policymakers, the Food and Drug Administration (FDA), and the media scrutinised the possible manipulation of nicotine levels in cigarettes. Speculation followed on whether the tobacco industry was involved in developing products to keep smokers addicted.[3–5] The subsequent release of internal tobacco industry documents, moreover, affirmed that the industry considered a cigarette to be "in essence, a vehicle for delivery of nicotine".[6 7]

At odds with the logic that nicotine content is essential to cigarette sales, the tobacco industry has invested substantial resources in the development of low nicotine, *but not necessarily low tar*, tobacco products, namely, the "Next" cigarette (Philip Morris, 1989) and the "Quest" cigarette (Vector Tobacco, 2003). These low nicotine products form part of a history of "less hazardous" cigarettes—what are now called "risk reduced" or "potentially reduced exposure products" (PREPs).[2] A low nicotine cigarette alone, however, is not less hazardous.[8] In response to changing consumer markets and regulatory environments, especially evolving health concerns, numerous innovations in cigarette design have been introduced in the last half century. Although public health goals shifted to cessation during the 1970s, industry research and development programmes continued on the path of PREPs.[2 9–13]

Harm reduction is one approach to reduce death and disease from tobacco use; however, smoking cessation has been the dominant strategy since the early 1980s. It is defined by the Institute of Medicine (IOM) report, *Clearing the smoke: assessing the science base for tobacco harm reduction*, as a product that "lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants".[2] It includes a diverse and complex array of treatments and products; a recent review identified 19 approaches,[8] with supporters often emphasising the centrality of nicotine pharmacology in efforts to reduce the amount an individual smokes.[2 14–16]

A wave of new products has been or is soon to be marketed,[8 17] but the public health value of harm reduction is controversial.[2 18–20] These products may not actually reduce harm; they may hinder quitting, which would be preferable, or they may encourage new smokers. In particular, reduced tar products, marketed to consumers as healthier alternatives, have been found to be just as harmful.[12 21–23] Further influencing the market for these products is the growing availability of smoking cessation products, especially, nicotine replacement products.[24] The IOM *Clearing the smoke* monograph, industry activities, conferences, and lawsuits, have renewed attention to the issue. Notably, on 3 June 2003, Congress held hearings regarding FDA regulation of tobacco, which highlighted the public health implications of "reduced risk" products.[25] Although previously opposed, Philip Morris is now publicly supporting FDA regulation of tobacco products.[26] With FDA approval, tobacco companies could market their products based on health claims. Policies proposing to give FDA authority over tobacco products must contend with how to regulate the health claims of such products and how to define harm reduction in regulatory terms.

With tobacco regulation again on the public policy agenda, research on past industry activities is critical for evaluating current arguments, especially the tobacco industry's declarations of a new era of transparency and openness.

**Abbreviations:** ART, alkaloid reduced tobacco; FDA, Food and Drug Administration; PREPs, potentially reduced exposure products

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Furthermore, little policy research has been done on low nicotine tobacco: a recent review of tobacco harm reduction product categories has stated that the ''mechanism and intention'' and ''regulatory status'' of nicotine-free cigarettes are ''unclear''.[8] The objective of this study is to investigate intention and rationale—that is, why has the tobacco industry invested heavily in the development of low nicotine cigarettes? Using evidence from internal documents, the study describes the tobacco industry's perceptions, interests, motivations, and knowledge regarding the marketability of low nicotine cigarettes, particularly within the USA. The focus on the tobacco industry's consumer research on low nicotine cigarettes is used to gain insight into how and why the industry might make health claims related to low nicotine tobacco, claims with important implications for regulation.

## METHODS

Tobacco industry documents were retrieved from the Legacy Tobacco Documents Library Internet site (http://legacy.library.ucsf.edu), as well as industry websites and Tobacco Documents Online (http://tobaccodocuments.org/), from February 2002 to June 2004. Primary search terms were: low-, no-, reduced-nicotine; denicotinization; low-, reduced- alkaloids; Next; de-nic; and key names of people, organisations, projects, and their common abbreviations and acronyms. A ''snowball'' search, a selective expansion of the search based on relevant results, including searching documents filed ''nearby'' according to accession or Bates number, was also used. Over 7500 documents were screened for relevance to the tobacco industry's interests and rationale, with emphasis given to the most recent documents. Additional searches were conducted using the Lexis-Nexis and PubMed databases to identify relevant news stories, scientific publications, and government reports and using the Pollay advertising collection on Tobacco Documents Online to identify marketing materials. The documents were analysed inductively to identify, through repetition and context, subjective themes as well as to develop a factual narrative of events.

## RESULTS

The results are organised into three sections: processes for denicotinising tobacco; Philip Morris' low nicotine—alkaloid reduced—tobacco research programme; and lastly the tobacco industry's ongoing incorporation of biotechnology into research programmes to genetically modify tobacco. We focus on Philip Morris activities for several reasons. First, Philip Morris went the furthest in commercialising a specifically low nicotine tobacco product with the exception of the very recent product introductions of Vector Tobacco. Second, and reflecting the first, the majority of documents relevant to the analysis of interests and rationale were from Philip Morris, allowing a more complete narrative to be produced. The activities of RJ Reynolds are discussed as they relate to the activities of Philip Morris. Furthermore, the technological feasibility and implications of tobacco denicotinisation processes are not evaluated; we describe research programmes to the extent that they establish a substantial commitment to, and contextualise, a new market.

### Denicotinised tobacco

Attempts to remove or reduce the nicotine content of tobacco have been around for much of the history of tobacco cultivation. Plant breeding was the first method, and in the 20th century, solvents, steam, microbes, and gases have all been used to extract nicotine. In 1986, Philip Morris researchers identified over 100 patents for the denicotinisation of tobacco (table 1). Very early patent applications suggest that there was interest in removing nicotine because it was considered ''a volatile poisonous alkaloid''.[27] Most recently, researchers have experimented with ways to genetically modify tobacco to block nicotine biosynthesis. None of these methods completely eliminates nicotine, but reductions have been in the range of 80–98%.

**Table 1** Selected US denicotinisation patents[110 111]

| Year | Patent description |
|---|---|
| 1901 | Hydrocarbon solvent extraction |
| 1908 | Superheated steam, nicotine recovery |
| 1926 | Steam/ammonia, extract recombined |
| 1977 | Microbial extraction |
| 1979 | Supercritical gases extraction |
| 1993 | Genetic modification |

Historically, nicotine has been associated with the perceived strength, or harshness, of cigarette smoke. Advertising indicates that as early as the 1930s lower nicotine was associated with a milder, less irritating taste—for example, Camels in the early 1940s and Old Gold in the 1950s.[28 29] King Sano cigarettes were the dominant and oldest brand of ''denicotinised'' cigarettes although they were always a small fraction of the market. With popular health concerns giving rise to filtered cigarettes in the 1950s, for a period King Sano claimed to filter the nicotine from the smoke, and also the tobacco.[30 31]

A 1994 report by Philip Morris reviewing the issue of denicotinisation stated: ''As far back as the early 1950's through the late 1960's, Philip Morris and other companies were experimenting with various means to reduce the nicotine level of tobacco.''[32] The report identifies King Sano specifically and mentions it was marketed in Germany and Switzerland. Table 2 lists tobacco industry denicotinisation research programmes, dating from the late 1960s, for which evidence from the documents could be found. A 1973 RJ Reynolds report on a ''No-Nicotine Project'' discussed a potential market in Germany, where at the time more attention was being given to nicotine than to tar.[33] The company also explored a 90% denicotinised tobacco product for the domestic market under the name ''Project NL'' or ''project nicoless'' from about 1974 to 1976.[34–36] In 1976, Lorillard received a marketing report from Infometre on the ''low nicotine concept'', but did not seem to do anything further.[37] By 1976, Philip Morris was explicitly examining the ''smoker psychology'' and pharmacological effects of low nicotine cigarettes as part of its larger psychological research efforts.[38–40]

### Alkaloid reduced tobacco (ART) programme

As indicated in the tobacco industry documents collection, explicit discussion of *marketing* a low nicotine cigarette picked up again in the early 1980s, when Philip Morris started on a research programme that would lead eventually to the ''Next'' brand of cigarette—the name was a reference to ''nicotine extracted''.[41] Robert Seligman, a vice president who had worked for Philip Morris in research and development for nearly 30 years, was sceptical of revisiting low nicotine tobacco. In a November 1982 response to Frank E Resnik, then president of the Tobacco Technology Group, he argued:

> Anytime we conducted a consumer acceptance test, using very low nicotine-containing cigarettes, we had a great many problems maintaining our smoking population. People did not want to smoke cigarettes with a minimum of nicotine over a long period of time… From this, I am forced to conclude that a nicotine-free cigarette would be most unacceptable.[42]

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**Table 2** Selected low nicotine tobacco programme names identified in the documents

| Project name | Approximate dates | Notes |
|---|---|---|
| *Philip Morris* | | |
| Alkaloid Reduced Tobacco (ART)[112] | 1980s–early 1990s | Project leading to test marketing of "Next" brand |
| Low Nicotine Tobacco (LNT)[90] | Mid 1980s–mid 1990s | Research programme to develop low nicotine tobacco primarily through genetic means[113] |
| *RJ Reynolds* | | |
| No-Nicotine Project (NN)[33] | Early 1970s | Product development for German market |
| Project Nicoless (NL)[34 35] | 1974–1976 | Exploration of domestic market |
| Genetically Low Alkaloid Tobacco Product (GLA)[82] | 1980s | Agricultural research programme |
| Low Nicotine Tobacco Program[83]; Nicotine Reduction Program[83–85] | 1989– | Research and development programmes rekindled following Philip Morris marketing. Subprojects: Project Low Nicotine (LN); Project Lowest Nicotine Available (LNA); Project Lowest Nicotine Available For Marketing (LNAM)[83–85] |
| *Vector Tobacco* | | |
| "Quest" cigarettes[100] | Late 1990s– | Genetically modified tobacco packaged in three nicotine levels, test marketed beginning January 2003 |

About eight months later, a memorandum from Seligman to Resnik indicated that Philip Morris continued to give the idea of a low nicotine cigarette "serious consideration", but noted that the earlier efforts had achieved only an 80–90% nicotine removal rate.[43] Counter to Seligman's evaluation, Philip Morris executive management chose to explore—and eventually heavily invest in—a low nicotine tobacco research programme. The plan to produce alkaloid reduced tobacco (ART)—nicotine being an alkaloid—involved supercritical extraction, an adaptation of a patented process to decaffeinate coffee beans that Philip Morris acquired in 1985, when they purchased General Foods.[32 44]

Consumer interest and competitive pressures, primarily from RJ Reynolds, encouraged Philip Morris to develop and market a low nicotine cigarette. Evidence of consumer interest in a "healthier" cigarette is found in Philip Morris' 1985 internal new product concept study:

> The concepts of most interest included cigarettes that: would have a light smoke aroma, *would be nicotine free*, had no ashtray odor, had a supplement (a vitamin or something to reduce tooth decay), had no visible smoke, and were ultra low tar versions… of popular full flavor brands.[45] (Emphasis added)

The company's research showed what public health research later confirmed[12]: the public often misunderstands the nature of nicotine by assuming it is one of the more harmful components of cigarettes. Although it is toxic in high dosages, generally smokers are not exposed at these levels, and many other components of smoke are considered a greater health risk.[1 46 47] The tobacco industry was aware of the consumer misconceptions from the start of the project. An earlier 1984 report on consumer interest in a possible low-nicotine Merit brand found:

> There is little consumer distinction between the effects of tar and nicotine, which are bracketed together in the consumer's mind.[48]

Recognition of consumer confusion is also found in RJ Reynolds discussions as well.[49 50]

In 1986, Philip Morris had further discussions about producing a denicotinised cigarette, which it was careful to keep confidential for reasons of competitive advantage.[51–53] The marketing strategy aimed to build on awareness of the forthcoming Surgeon General's report on nicotine addiction[1] to "launch a nicotine-extracted product with the potential of mainstream acceptance".[54 55] One handwritten comment on a product position report noted that the Surgeon General had "paved the way to provide a solution/benefit easily communicated to consumers—he's done the educating—condition—cure"[54] The goal appeared to be minimising nicotine only, not carcinogenic compounds, while maintaining smoking behaviour. The staff proposed experiments to gauge smokers' sensory reaction to cigarettes with half the nicotine. John Tindall—a statistical and economic analyst working on research and development issues—explained this kind of study would be easy because "smokers don't know what the sensory effects of nicotine are and the existence of low-caffeine coffee makes the concept believable".[56]

Without considering health consequences, one proposal from a senior associate scientist wondered whether "it may be necessary to increase the tar" for flavour to make the nicotine trade-off acceptable to consumers.[57] One group of Philip Morris scientists believed it was important to determine a "sufficient" dose to maintain smoking behaviour and still claim reduced nicotine.[58] Of the proposals, Philip Morris apparently proceeded with the focus group studies that probed the relation between health and social pressures.[59] Between 1985 and 1989 Philip Morris collected responses from 2988 smokers in 11 studies.[60] By 1987, a prototype cigarette was being tested.[61]

## Consumer appeal for a low nicotine cigarette

Focus groups that reviewed marketing materials for the potential ART product demonstrated a strong interest in no-nicotine products. The interest, moreover, was based on the perception that such a product would be healthier[62–64] and "a way to quit smoking".[65 66] Philip Morris conducted new product concept studies in 1983, 1985, 1987, and 1993.[64] A summary of the focus groups reported:

> The benefits they saw were directly linked to nicotine removal. The first was a general health benefit… Even if they didn't know exactly what nicotine and its effects were, people assumed it was bad for them. The second reason for interest was that the product would allow smokers to cut down or quit.[67]

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Some smokers appeared to recognise that nicotine was addictive. Page Callaham, who worked on qualitative research for Philip Morris' Product Evaluation Division, reviewed the issue of "smokers' perception of nicotine-free cigarettes" based on Philip Morris focus group studies. In 1987, Callaham reported to Ed Gee, a director of consumer research, that some consumers might smoke *more* low-nicotine cigarettes:

> Some consumers view this product as healthier while others see it [as a way] to quit smoking. However, others commented that it would be self-defeating because they would smoke more to get the same taste satisfaction.
>
> Consumers saw themselves as either habitual smokers or 'addicted' to nicotine. People who smoke because of a habit felt that they could adjust to the taste of a nicotine-free cigarette.[68]

Corroborating the earlier results, smokers from a 1989 focus group ranked the concept first because: "The cigarette would be healthier (43%) and it would not be addictive (24%). Also cited by 14% of the smokers was that it might be easier to quit smoking." The report identified four attitudinal groups: "resigned smoker", "proud smoker", "image smoker", and "potential quitter": "The Potential Quitter was the only group to rank Nicotine Free first."[69] The product seemed to appeal to older, female, and ultra low tar smokers.[66] Thus, from Philip Morris' perspective, a smoker's likelihood of "quitting" was a way of segmenting the market.[53] Furthermore, the marketing primarily sought to address concerns about the social pressures of smoking—those who did not "feel positive about smoking"[66] or "ritual smokers" who were anxious about addiction[70]—rather than actual health consequences.

## Creating a new low nicotine market segment

An October 1987 internal marketing analysis from Susan Alter, brand manager, to Louis Suwarna, a new products director, synthesised qualitative studies for Philip Morris' new product launch planned for late 1988.[71] The low nicotine market was assessed to have the highest potential for growth, and the report reiterated the opportunity presented by the fact that "much confusion exists in smokers' minds about the different effects of tar and nicotine…".[71]

The potential for quitting, however, posed a particular problem for how best to market a low nicotine product:

> The potential, then, for ART is that fully one-third of smokers may perceive of ART as a useful tool for quitting. This raises the question of whether it is more desirable to have 'returning smokers' come back to established brands like Merit Ultra Lights, or B&H Deluxe Ultra Lights, for example, or try ART. Will it be perceived as a 'less-harmful' way to continue smoking over the long-term, or a less enjoyable product which will be easier to give up, and finally quit?[71]

"[T]he greatest potential and challenge" for their new ART product, according to Alter, was the creation of a new market category. Because brand switching was down 15% from 10 years before and the "new smokers to low tar" category included a high percentage of "returning" smokers, Alter reasoned that there was less growth potential in convincing smokers to switch brands than in creating a new product category that would capture "returning" smokers and "quitters".[71] Moreover, the company did not believe that users of the product would actually quit but instead, according to one marketing document, "smokers will feel they can better control consumption with an ART product".[72 73] The expected market was older, female smokers "as these are the people who most often express health concerns", but also potentially "young adults who may only smoke occasionally".[72] A competitive analysis by Analytic Insight, Inc, prepared for Brown & Williamson Tobacco Corporation in January 1990, reflects this marketing logic as well.[74] The economic benefit of creating a new category, a free standing brand, over the more conservative strategy of a brand line extension was reiterated in a 1989 ART planning document by David Dangoor, vice president of marketing for Philip Morris: "The most important part of this direction is that we will concentrate on 'creating' the de-nic and de-nicotined category."[75] Frank Resnik was "firmly convinced" of this strategy as well.[76] In 1988, a marketing memo had estimated the potential market share of free standing denicotinised cigarette brand at 1.5–2%, or "9–12 billion units".[72]

A document—probably from around 1992—containing the handwritten note, "John Tindall's Ryebrook presentation", provides candid insight into Philip Morris' counterintuitive decision to market low nicotine cigarettes.[77] In an overview to cigarette marketing personnel, Tindall, who had a 30 year career with Philip Morris research and development, notes that a cigarette is the most effective "nicotine delivery device". In revisiting the history of the cigarette market from 1945 to 1992, he concludes that the 25 year run of the delivery segment (filters), menthol segment, and length segment—the main technological innovations that had translated into market segments—had become unproductive by 1980. The market was "saturated with brands and extensions addressing consumers' needs in the area of health perceptions by lowering tar and in the area of price through greater length". The female demographic segment was no longer growing, and the anti-smoking movement was shifting to the more effective tactic of "making smokers feel guilty about the effect smoking might have on nonsmokers around them". The concept studies, begun in the early 1980s, suggested that future success would be based less on flavour, promotion, and packaging than on providing a feature of enough perceived benefit (for example, health). In 1988, Philip Morris' eight year forecast had estimated a 2.8% per year decline in cigarette sales in the USA.[78]

Tindall considered the ART project in light of this market analysis:

> ART was a very attractive combination of consumer need and technological capability. *The consumer attraction was expected because ART addresses smokers' health concerns, and that has been the most powerful driving force in the cigarette market since 1954.* What was technologically important about ART was the potential proprietary position it could give us. [p 24–25, emphasis added]
>
> ART started out as a controversial project. We don't actually know, by direct tests, how important nicotine is in smoking, since nothing has ever been available to smoke which comes close to having just the sensory properties of tobacco, without having nicotine… Obviously, there was concern that *a low-nicotine cigarette might put the cigarette industry out of business.* The long-term management philosophy prevailed, though; *we would compete in any category that had a chance for success.*[77] [p 25, emphasis added]

For reasons of competitive secrecy, Philip Morris avoided any outside market research at first. When the company

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finally did, it found ''very large perceived benefits''; however, it ''learned that ART also ha[d] very large sensory costs…''.[77] In Tindall's view, the reason was not ART's poor taste, but the sensory loss of the accustomed ''throat impact'' produced by nicotine. The challenge, he explained, is to ''balance sensory costs and perceived health benefits''.[77]

According to company documents, Philip Morris invested $300 million dollars on the ART project including a new product facility, the Bermuda 100 facility, which was subsequently shutdown around 1993. A ''capital appropriations request'' from Frank Resnik to vice chairman, R William Murray, stated that the production plant would cost approximately $194 million and that it would ''produce twenty-one million pounds of denicotinized tobacco per year, a quantity sufficient to support the production of twelve billion cigarettes''. At the time the return on investment was estimated at 20%.[79] The project achieved a 95–98% reduction in nicotine[80] and was marketed as a ''natural'' process akin to decaffeinated coffee.[81] Test marketing under the new brand name ''Next'' began in July 1989, around the time of the release of the Surgeon General's report on nicotine addiction, in three markets (Omaha, Hartford, and Toledo).[32 55] The test marketing of Philip Morris' free standing brand, Next, produced disappointing sales (less than 0.2 market share) and was withdrawn by the end of 1989.

Notably, RJ Reynolds considered Philip Morris' efforts to be a competitive threat and revisited its own low nicotine tobacco research efforts in 1989. In the ''Nicotine Reduction Program'' or ''Project LN'', the company proposed using genetically low nicotine tobacco it had been developing in conjunction with various extraction processes to produce cigarettes of certain nicotine reductions, probably under the brand name Vantage LN.[82–86] In efforts more than a decade earlier RJ Reynolds expressed the same market motivations as Philip Morris when it set the research objective of producing a reduced nicotine cigarette that would ''provide the Company with a unique entry capable of establishing a new category of cigarettes''.[35]

Additional test marketing of Next was conducted by Philip Morris in Tampa in May 1990. Beginning in October 1990, the company test marketed a reduced nicotine line extension of Benson and Hedges (''B&H De-Nic'') into 1992 (a Merit brand line extension had also been tested in August 1989).[32] By 1993, a Philip Morris ''concept study'' found that interest in a nicotine-free cigarette had fallen in relation to other surveyed concepts—for example, a cigarette with an adjustable filter.[64] Because of poor sales, Philip Morris pulled the product line from the market. Public health commentators presumed the product failed because it lacked addictive qualities[2]; Philip Morris, however, offered different reasons in a document drafted for a web page: (1) very low nicotine brands were already available; and (2) poor taste.[44 80]

Nonetheless, Philip Morris continued to explore the potential for its technology to produce reduced nicotine cigarettes. In 1992, a report by the Operational Planning Committee, Philip Morris discussed the company's desire to develop a technology to produce a fuller flavoured, ultra low tar cigarette. The company had made some innovations in this arena with filter and paper technology that advanced this objective. Furthermore, the product market for smokers was changing. The report explained:

> Several interesting things have happened both within and outside the tobacco/cigarette industry. *We are seeing competition for our consumers from outside our industry, primarily from the drug industry*. The ''competing'' products are, for example, nicotine chewing gum, nicotine patches and inhalers.[87] [emphasis added]

**Table 3** Philip Morris aims for genetic modification of tobacco research[91 92]

- Development of a no-nicotine tobacco that still had the flavour of major brands
- Reduce the formation of tobacco specific nitrosamines
- Produce experimental tobacco for subjective investigations of smoke
- Reduce the costs of nicotine disposal
- Better control nicotine content in variable agronomic conditions

Thus, the tobacco industry assessed the marketability of low nicotine cigarettes in the context of an expanded product market, including nicotine gum and patches. As corroborated by previous document research,[88] cigarette manufacturers competed with the drug industry to sell all kinds of nicotine products to smokers. Marketability based on health claims was the primary concern: the 1992 report described the ART technology as ''a means for lowering nicotine delivery of our products *while maintaining tar delivery*'' (emphasis added).[87] As of 1994, Phillip Morris had considered test marketing a ''De-Nic'' cigarette on the Island of St. Kitts in the Caribbean.[89]

The major failing of low nicotine tobacco products, according to the industry, had been their subjective taste. Research had already begun at Philip Morris to tackle these limitations and produce a low nicotine tobacco using their second strategy: genetic modification.

## Genetically modified tobacco

The ART programme, with its reliance on supercritical extraction technology, was only one means of achieving low nicotine tobacco.[90] A report by Philip Morris scientist, Walter Hempfling, entitled ''How can biotechnology be useful to Philip Morris's cigarette business?'' discussed the potential of genetic engineering for the tobacco industry as a whole, namely the ''dramatic reduction of the biological activity [that is, carcinogenicity] of smoke…, elimination of tobacco-specific nitrosamines, *precise control of nicotine content and delivery*, reduction of carbon monoxide and stabilization and controlled release of flavorants'' (emphasis added).[91] Hempfling noted that earlier attempts using plant breeding had often produced inferior tobacco; presumably nicotine synthesis was genetically linked to other desirable traits. Around 1985, numerous possibilities for genetic modification were identified, as shown in table 3.

The first practical application of biotechnology by Philip Morris was, in fact, the development of low nicotine tobacco in the mid 1980s.[91] First contracting to Calgene and then bringing the research in-house for reasons of competitive secrecy, Philip Morris sought to use anti-sense biotechnology to disrupt enzymes involved in nicotine biosynthesis.[92–94] The available documents do not make it entirely clear how the project progressed; nonetheless, on 4 November 1997, a patent was issued to Philip Morris for an anti-sense DNA method for altering nicotine in tobacco plants.[95] According to an internal email, the research programme achieved tobacco with an 80% reduction in nicotine.[94] Other inventors also recognised the value of biotechnology for developing low nicotine tobacco for cigarettes that would be less addictive or that could be ''used in a smoking cessation program''.[96]

By the late 1990s Philip Morris, as well as RJ Reynolds,[97] had embarked on major efforts to utilise biotechnology for commercial purposes, often with the goal of eliminating nicotine and other harmful compounds. As of 1998, documents indicate that genetically modified, low nicotine tobacco continued to receive consideration by Philip Morris.[98] Although the current status of the Phillip Morris low nicotine research programme is unclear, its history is still relevant to settling FDA authority over tobacco products.

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Furthermore, in January 2003, Vector Tobacco, the smallest of the five major tobacco companies, began to market a new cigarette, ''Quest'', that is produced from tobacco genetically modified to contain only trace amounts of nicotine[99] and that is all but marketed as a smoking cessation device.[100–103]

## DISCUSSION

Although counter to the conventional logic that the profitability of cigarettes depends on the addictive qualities of nicotine, the tobacco industry pursued, since at least the 1950s, the development of a presumably less addictive product. The explanation is exploitation of consumer misconceptions about nicotine and product diversification in a changing cigarette market.

Philip Morris played on consumer ignorance in its marketing strategy, and the industry's timing was intended to take advantage of the awareness of nicotine's addictive properties produced by the 1988 Surgeon General's report.[1 54 83] As the internal industry documents show, their goal was to make a reduced nicotine health claim, even if other harmful components were increased.

In the context of a saturated low tar cigarette market, low nicotine cigarettes were an attempt to market to consumer health concerns. The tobacco companies sought to define and lead a *new* market for ''healthier'' cigarettes that might appeal to ''quitters''. For industry management, the risk that low nicotine cigarettes might put the industry ''out of business'' was outweighed by the benefit of creating a new market segment. The highly competitive and secretive research and development efforts, including a long term commitment to genetic research, are evidence of the economic importance of this new market to the tobacco industry. The documents suggest that the tobacco industry is developing these products to maintain profitability, not protect health. Thus, the industry's motives for developing and gaining acceptance for a new segment of ''harm reduced'' products are different than the interests of the public health community. Furthermore, our findings suggest the need for an external body to review product claims and to be particularly cautious about claims that may confuse consumers.

Our study has several limitations. First, we cannot be sure that we have identified all documents on our topic. Furthermore, time and financial constraints do not allow all depositories and websites to be comprehensively investigated,[104] and additional documents are still being added. Nonetheless, numerous analyses have shown that the tobacco industry documents offer unprecedented insights into the industry's motives, interests and knowledge.[105]

The tobacco industry is remaking its image, and the concept of harm reduction is its rallying cry. By discussing its current developments for PREPs, it hopes to live up to its purported goal of transparency.[106] Following the release of the IOM report and the accompanying media attention, Philip Morris lawyers drafted a series of message points to be used by employees emphasising the company's commitment to ''the development of cigarettes that have the potential to reduce the harm caused by smoking'' and a ''rational'' regulatory environment that respects ''the principle of adult choice''.[107] Philip Morris is open about the fact that FDA regulation would now benefit the company because only with FDA approval can the industry make health claims about tobacco products[26]:

> We believe FDA regulation would provide greater consistency in tobacco policy, more predictability for the tobacco industry and an effective way to address issues that are of concern to our Company and society.[108]

### What this paper adds

The issue of tobacco harm reduction has recently received increased interest among tobacco researchers, policymakers, and the tobacco industry. Tobacco products that claim to reduce the risks of smoking are controversial because product effectiveness is uncertain and marketing practices are questioned. Attempts to regulate tobacco in the USA are dependent on resolving regulatory issues related to harm reduction.

The tobacco industry documents provide insight into the motivations, interests, and strategies of the tobacco industry in developing low nicotine products. This source of data explains why a low nicotine product is not a contradiction to tobacco industry interests. Previous document research has focused primarily on the issue of low tar cigarettes. By examining this atypical product, but one that the tobacco industry has invested heavily in, we better understand the overall market development of tobacco products that claim to be less harmful. The industry's development of low nicotine products has been market rather than health driven.

The industry knows that without the public trust embedded in FDA approval, its health claims, which could lead to greater market shares, will be dismissed and criticised. While it is too early to evaluate the genuineness and form of the new industry openness, past activities suggest that health claims will be based on perceived rather than actual health benefits. Earlier institutional cultures and organisation objectives tend to persist well into a change of rhetoric.[109]

## ACKNOWLEDGEMENTS

California Tobacco-Related Disease Research Program Grant 9RT0193 and the Legacy Foundation provided research support. The authors wish to thank Pam Ling for research materials and the Institute for Health Policy Studies writing group for comments on a draft of this paper.

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*Nicotine & Tobacco Research* (1999) **1**, 357–364

# Pharmacodynamic effects of new de-nicotinized cigarettes

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**The effects of cigarette smoking result from the delivery of nicotine, other components of smoke, and sensory stimulation. In the present study, pharmacological effects of new tobacco-derived de-nicotinized cigarettes (controls) were compared with standard cigarettes. The de-nicotinized cigarettes had the appearance, draw and taste of standard cigarettes but contained and delivered virtually no nicotine (< 0.06 mg), but delivered tar and carbon monoxide (CO). They were compared with cigarettes that delivered nicotine, CO and tar. Subjects ($n = 20$: 10 men, 10 women) participated in four experimental sessions in which they smoked either a standard cigarette or a de-nicotinized cigarette after either 3 or 12 h of tobacco deprivation. Heart rate, blood pressure, and EEG were recorded before, and for 1 h after, *ad lib* smoking. Plasma nicotine concentrations verified that de-nicotinized cigarettes did not deliver nicotine. The de-nicotinized cigarettes did not increase heart rate or activate the EEG. The subjects preferred the cigarettes that delivered nicotine compared to the de-nicotinized cigarettes. However, both types of cigarettes reduced subjective measures of tobacco craving and withdrawal. These data extend previous research that suggested the process of smoking and components of tobacco smoke other than nicotine mediate some effects of cigarette smoking. The de-nicotinized cigarettes may prove useful in evaluating effects of smoking independent of the delivery of nicotine.**

## Introduction

As described in the US Surgeon General's Report (US-DHHS, 1988), cigarette smoking is a process that involves both pharmacological and behavioral factors. The reinforcing and discriminative stimulus effects of cigarette smoking depend on the occupation of nicotine receptors (Stolerman, Kumar, Pratt, & Reavill, 1987) and sensory factors such as taste, heat, odor, and pharyngeal stimulation (Pritchard, Robinson, Guy, Davis, & Stiles, 1996). Systematic study of non-nicotine factors has been confounded by the lack of a suitable control cigarette. For the control smoking condition in previous smoking studies, investigators have used lettuce cigarettes (Butschky, Bailey, Henningfield, & Pickworth, 1995; Goldfarb, Jarvik, & Glick, 1970), herbal cigarettes (Wesnes & Warburton, 1983; West & Hack, 1991), or puffing on an unlighted cigarette (Morris & Gale, 1994). An ideal control cigarette would have the taste, look, feel, draw and smell of a commercial cigarette, but would not deliver pharmacologically active doses of nicotine.

Philip Morris Inc. (Richmond, VA) tested the market acceptability of a de-nicotinized cigarette (Next®) in 1990. Although the cigarette was not well accepted in the retail market, it proved useful in clinical studies to estimate the effects of smoking with minimal nicotine delivery. For example, the Philip Morris de-nicotinized cigarette did not increase heart rate and plasma levels of nicotine (Robinson, Pritchard, & Davis, 1992). Butschky *et al.* (1995) found that these cigarettes decreased subjective measures of tobacco withdrawal. Hasenfratz, Baldinger, & Bättig (1993) used the de-nicotinized cigarettes to study the relative importance of tar and nicotine delivery to the smoking process. Thus, these cigarettes could be used to study the role of

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nicotinic and non-nicotinic determinants of the effects of cigarette smoke intake. However, the Philip Morris de-nicotinized cigarette is no longer commercially available.

In response to the need among tobacco researchers for a de-nicotinized cigarette, the National Institute on Drug Abuse contracted with a private firm (Ultratech Corporation, Lafayette Hill, PA) to develop and manufacture de-nicotinized cigarettes. The de-nicotinized cigarettes were to have similar characteristics as commercial cigarettes, but to contain and deliver virtually no nicotine. Four types of cigarettes were developed and tested: reduced- and full-tar standard cigarettes and identically appearing reduced- and full-tar de-nicotinized cigarettes that delivered CO and tar, but not nicotine. The purposes of the present study were to assess the pharmacodynamic properties of these cigarettes, to evaluate their potential as control cigarettes for tobacco research and to distinguish the effects of nicotine from other components of tobacco smoke in an experimental setting.

## Methods

### *Subjects*

Twenty research volunteers (10 males, 10 females) who were regular smokers participated in the study. Subjects were randomly assigned to two groups of 10 subjects each (five males, five females). Subjects were excluded from the study if they reported any chronic physical or mental health conditions requiring medication, current drug or alcohol addiction (except tobacco or caffeine dependence), use of tobacco products other than cigarettes, and current treatment for smoking cessation. Mean age of the subjects was 34.1 years (range = 22–41). The subjects reported smoking an average of 31 cigarettes per day (range = 20–40) and reported having smoked for an average of 18.3 years (range = 5–27). Their current brand of cigarettes was labeled as delivering an average of 1.2 mg of nicotine (range = 0.9–1.4). Sixteen of the subjects smoked mentholated cigarettes. Their mean score on a revision of the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was 8.0 (range = 6–10); scores above 6 on this test indicate a high degree of dependence. Prior to participation in the study, the subjects signed a consent form that had been approved by the local institutional review board and met US Department of Health and Human Services guidelines for the protection of human research participants. Subjects were paid approximately $300 for their participation.

### *Experimental cigarettes*

Four types of cigarettes were developed and tested: reduced- and full-tar standard cigarettes and identically appearing reduced- and full-tar de-nicotinized cigarettes that delivered CO and tar, but not nicotine (Table 1). The cigarettes were filtered, king size (85 mm overall; 25 mm cork tip overwrap). The cigarettes were produced from a mixture of shredded tobacco: 25% burley blend, 55% flue cured, 15% stems, 5% sheet tobacco) prepared at 32 cuts per inch. The cigarettes weighed an average of 1.0 g and had a moisture content of 13–15%. A cellulose acetate filter was placed on all cigarettes. The cigarettes had similar draw levels equal to a pressure drop of 8 cm of water. Nicotine was removed from the tobacco of the de-nicotinized cigarettes with a mild alkaline (ammonium solution) wash. The tobacco was steamed, air-dried and the final pH was adjusted with a citric acid solution. Full-tar cigarettes were designed to deliver $>15$ mg tar estimated by methods of the Federal Trade Commission (FTC; Federal Register, 1967; Pillsbury, 1996); reduced-tar cigarettes were designed to deliver about 11 mg of tar. Aeration holes (single column) were placed around the cork tip overwrap of the reduced-tar cigarettes; no holes were used in the cork tip overwrap of the full-tar cigarettes. The nicotine content of the dried tobacco from de-nicotinized cigarettes (reduced- and full-tar), determined by gas chromatography methods, indicated that the de-nicotinized cigarettes contained no measurable quantity of nicotine (personal communication, Peter Crooks, University of Kentucky). The de-nicotinization process also reduced tobacco-specific nitrosamines including: nitrosonornicotine (NNN), nitrosoanatabine (NAT), nitrosoanabasine (NAB) and 4- (methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK; personal communication, William Rosen, Ultratech Incorporated).

**Table 1.** Characteristics of experimental cigarettes

| | | FTC Nicotine (mg/cig) | FTC Tar (mg/cig) | Nicotine content (mg/cig) |
|---|---|---|---|---|
| Full Tar | Standard | 1.10 | 15.9 | 7.17 |
| | De-nicotinized | 0.07 | 17.3 | 0 |
| Reduced Tar | Standard | 0.60 | 10.0 | 5.58 |
| | De-nicotinized | 0.07 | 12.1 | 0 |

FTC nicotine and tar estimates were obtained by the Cambridge filter method by a commercial laboratory (Labstat Inc, Kirchner Ontario, Canada). Analysis of the nicotine content of dried tobacco made by Peter Crooks, University of Kentucky, College of Pharmacy (Lexington, KY).

*Dependent measures*

*Biochemical markers.* Biochemical markers of smoke and nicotine exposure were exhaled carbon monoxide (CO) and plasma nicotine and cotinine. Exhaled CO was measured with a breath carbon monoxide detector (Vitalograph, Lexena, KS) before, and 15 and 60 min after smoking. Plasma nicotine and cotinine were measured using a high-performance liquid-chromatography method (Hariharan, VanNoord, & Greden, 1988). The lower limit of detection was 1 ng/ml. Blood samples (10 ml) were collected before smoking and 2, 5, 10, 15, 30 and 60 min after smoking. Blood samples were kept on ice until they were centrifuged and the plasma withdrawn. Plasma was stored frozen (–20°C) until the time of analysis.

*Smoking behavior.* The time taken to smoke *ad libitum* the experimental cigarettes and the number of puffs was recorded.

*Physiological markers.* Blood pressure and heart rate were measured with an automated instrument (IVAC, San Diego, CA) at the same times that blood samples were drawn. Scalp EEG recordings (2 min resting, eyes closed) from Fz, Cz and Pz were recorded before and 5 min after smoking with an automated computer-based acquisition and analysis system (BioLogic, Chicago, IL). Analog EEG signals were digitized (256 Hz) and a fast Fourier transform algorithm converted data to the power and frequency domain. The power and peak mean frequency were derived for the typical clinical frequency bands (delta, theta, alpha, beta1, beta2) as described elsewhere (Pickworth, Herning, & Henningfield, 1988, 1989).

*Subjective measures.* Standardized tests for the quantification of tobacco withdrawal symptoms including: the Minnesota Withdrawal Scale (MWS) (Hughes & Hatsukami, 1986); Questionnaire on Smoking Urges (QSU), short version (Tiffany & Drobes, 1991), and a drug-liking question (Fraser, Van Horn, Martin, Wolbach, & Isbell, 1961) were presented on a computer before smoking, 2, 30 and 60 min after smoking. Cigarette characteristics (strength, taste, satisfaction, harshness, ease of draw, good effects, and bad effects) were measured 20 min after smoking with computerized visual analog scales. The subjects used the computer mouse to place a line on a 100-mm horizontal line to index their endorsement of the adjectives describing the cigarette. Anchors for the lines were appropriate for the adjectives; for example 'ease of draw' was scored between 'very easy' and 'very hard'.

*Procedure*

This double-blind study was performed on an outpatient basis at NIDA, Division of Intramural Research (DIR). Subjects were randomly assigned to two experimental groups (five men, five women) of 10 subjects each. Subjects in Group 1 smoked full-tar standard and de-nicotinized cigarettes; those in Group 2 smoked reduced-tar standard and de-nicotinized cigarettes.

All subjects reported to the laboratory for an orientation session (where the procedure was described and practiced) and for four experimental sessions. On two experimental days, subjects refrained from smoking for 3 h prior to the beginning of the experiment; on the two other experimental days, subjects were overnight ($>12$ h) abstinent from cigarettes and were required to have CO $<13$ ppm. The order of the abstinence days and the cigarette conditions was randomized. Each subject smoked the de-nicotinized and standard cigarettes after 3 h and overnight abstinence.

On the study day, an in-dwelling catheter was placed in a forearm vein. Baseline physiologic, subjective, and biochemical measures were collected. Then, subjects smoked an experimental cigarette *ad libitum* to a line drawn on the tobacco rod 50 mm from the tip. The number of puffs and the time taken to smoke the cigarette were recorded. For 60 min after smoking, experimental measures were repeated as indicated above.

*Data analysis*

Data was analyzed using standard analysis of variance (ANOVA) techniques for repeated measures design (Winer, Brown, & Michels, 1991). An initial ANOVA on each dependent variable was performed using five main factors: group (reduced- or full-tar), gender (two levels), cigarette type (standard or de-nicotinized), time of abstinence ($>3$ and $>12$ h), time after smoking (one, two, three or seven levels depending upon the variable). These analyses indicated that there were no significant effects of gender, group, or time of abstinence. The data were collapsed across gender and separate ANOVAs for the full- and reduced-tar cigarettes were completed using cigarette type (standard or de-nicotinized), abstinence and time after smoking as the main factors.

## Results

*Biochemical markers of smoking*

As shown in Figure 1 (upper panel), both the reduced- and full-tar standard (nicotine delivering) cigarettes increased venous plasma nicotine concentrations. After the full-tar standard cigarette, plasma levels of nicotine increased from 3.1 to 13.7 ng/ml. After the reduced-tar standard cigarette, plasma levels of nicotine increased from 3.3 to 15.5 ng/ml. The highest plasma levels occurred at 2 min after smoking. In contrast, de-nicotinized cigarettes did not increase plasma levels of nicotine. The ANOVA for the full-tar cigarette indicated that there was a significant effect of cigarette [$F(1,9) = 32.5$; $p < 0.001$]; time [$F(54,6) = 22.3$; $p < 0.001$]; and a significant cigarette by time interac-

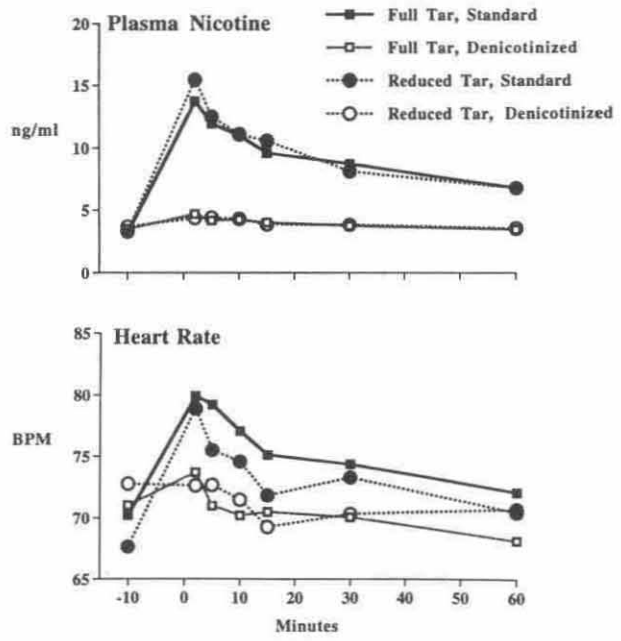



**Figure 1.** Upper panel: Mean ($n = 10$) venous plasma nicotine concentration before and up to 60 min after smoking experimental cigarettes. Time = 0 minutes when subjects finished smoking the experimental cigarette. Lower panel: Mean ($n = 10$) heart rate (beats per minute, BPM) before and up to 60 min after smoking experimental cigarettes.

tion [$F(6,54) = 19.4$; $p < 0.001$], Similarly, the ANOVA for the reduced-tar cigarette indicated that there was a significant effect of cigarette [$F(1,9) = 17.0$; $p < 0.003$]; time ($F(6,54) = 24.4$; $p < 0.001$]; and a significant cigarette by time interaction [$F(6,54) = 21.1$; $p < 0.001$].

Plasma venous cotinine levels before smoking the experimental cigarettes averaged 257.5 ng/ml in subjects that were at least 3-h tobacco-deprived and 229.2 ng/ml in subjects that were at least 12-h tobacco deprived. Plasma cotinine levels did not significantly change as a function of cigarette type, abstinence, or time after smoking.

Baseline exhaled CO averaged 13 ppm in subjects that were $> 3$ h tobacco-abstinent and 8.3 ppm in subjects that were $> 12$ h tobacco abstinent. After smoking, exhaled CO increased to 19.5 ppm at 15 min and 17.9 ppm at 60 min in subjects that were $> 3$ h tobacco-abstinent. In subjects that were 12-h tobacco abstinent, CO averaged 15.3 and 13.9 ppm at 15 and 60 min after smoking. The ANOVA for the full-tar cigarette indicated a significant effect of abstinence [$F(1,9) = 8.6$, $p < 0.02$) and time [$F(2,18) = 48.8$, $p < 0.001$]. Similarly, the ANOVA for the reduced-tar cigarette indicated that there was a significant effect of abstinence [$F(1,9) = 9.1$, $p < 0.001$] and time [$F(2,18) = 50.2$, $p < 0.001$]. There were no significant differences between the standard and de-nicotinized cigarettes on the exhaled CO levels.

*Smoking behavior*

The time to smoke the full-tar cigarettes averaged 238 and 249 s for the standard and de-nicotinized, respectively. The time to smoke the reduced-tar cigarettes averaged 272 and 274 s for the standard and de-nicotinized, respectively. The ANOVAs for both the reduced- and full-tar cigarettes indicated there was no significant effect of cigarette or abstinent condition and no significant interaction.

The number of puffs per cigarette averaged 12.3 and 12.8 for the standard and de-nicotinized full-tar cigarettes and 15.3 and 16.7 for the standard and de-nicotinized reduced-tar cigarettes, respectively. The ANOVA for the regular indicated no significant effect of cigarette (standard vs. de-nicotinized) but a significant effect of abstinence [$F(1,9) = 6.4$, $p < 0.05$]. In the 3-h abstinence condition, 12.1 puffs were taken: in the 12-h abstinence condition, 13.2 puffs were taken. The ANOVAs for the reduced-tar cigarettes indicated no significant effect of cigarette or abstinence on number of puffs per cigarette.

*Physiological measures*

As illustrated in Figure 1 (lower panel), both standard (nicotine delivering) cigarettes increased heart rate by 10 beats per minute. The biggest increase occurred 2 min after smoking. Neither de-nicotinized cigarette type significantly changed heart rate. The ANOVA of the full-tar cigarette indicated a significant effect of cigarette [$F(1,9) = 22.8$, $p < 0.001$]; time [$F(6,54) = 14.5$, $p < 0.001$]; cigarette by abstinence interaction [$F(1,9) = 10.6$, $p < 0.01$]; and cigarette by time interaction [$F(6,54) = 6.4$, $p < 0.001$]. The ANOVA of the reduced-tar cigarette indicated a significant effect of time [$F(6,54) = 7.0$, $p < 0.001$]; and a significant cigarette by time interaction [$F(6,54) = 6.3$, $p < 0.001$].

Immediately after smoking the standard cigarettes ($> 3$ h abstinence) there was an increase in systolic blood pressure of 9 mm Hg. The change in systolic blood pressure after de-nicotinized cigarettes was smaller and the ANOVAs indicated that there was no significant effect of either cigarette type on systolic blood pressure. Diastolic pressure increased immediately after smoking.

The ANOVA for the full-tar cigarette indicated a significant difference between standard and de-nicotinized cigarettes on this measure, [$F(1,9) = 8.04$, $p < 0.02$] and a significant effect on time [$F(6,54) = 2.5$, $p < 0.05$]. Full-tar cigarettes that delivered nicotine increased diastolic blood pressure more than the de-nicotinized cigarettes. There was no significant effect of the reduced-tar cigarettes on diastolic pressure.

The effects of the experimental cigarettes on two measures of EEG activity, theta power and alpha frequency, were assessed. Theta power decreased after smoking full-tar standard cigarettes to an average of 88% of the baseline value; conversely, after smoking

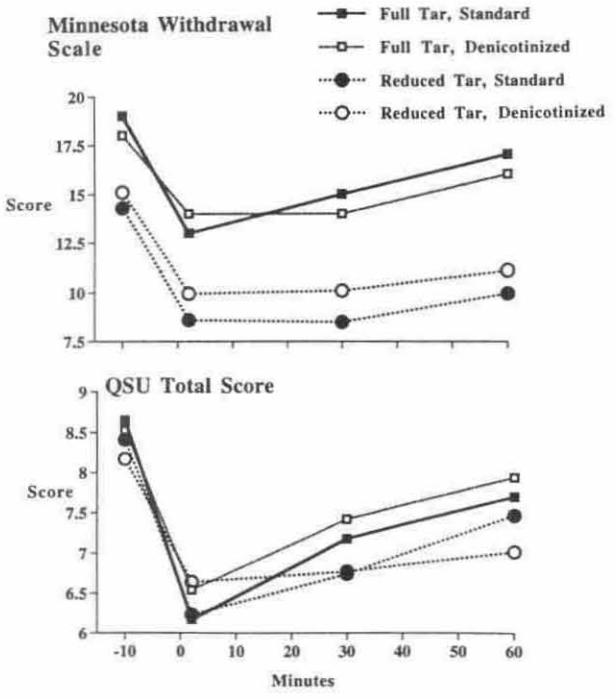



**Figure 2.** Upper panel: Mean ($n = 10$) score on the Minnesota Withdrawal Scale before and up to 60 min after smoking experimental cigarettes. Lower panel: Mean ($n = 10$) score on Questionnaire on Smoking Urges before and up to 60 min after smoking experimental cigarettes.

full-tar de-nicotinized cigarettes, theta power increased to 127% of baseline values. The ANOVA for the full-tar cigarettes indicated a significant effect of cigarette [$F(1,9) = 12.62$, $p < 0.006$] and a trend toward a significant effect of abstinence [$F(1,9) = 4.3$, $p < 0.07$]. The reduced-tar cigarettes did not significantly affect measures of theta power. The EEG alpha frequency was not significantly affected by any of the experimental cigarettes.

*Subjective measures*

The Minnesota Withdrawal Scale (MWS) was used to measure the effects of the experimental cigarettes on tobacco abstinence symptoms. As shown in Figure 2 (upper panel), all of the experimental cigarettes (standard and de-nicotinized) immediately reduced scores on the MWS. Baseline scores that averaged 18.8 for the full-tar cigarettes and 17.3 for the reduced-tar cigarettes were reduced to 13.3 and 10.5 respectively immediately after smoking. Even 60 min later, the scores of tobacco withdrawal remained reduced below baseline levels. The ANOVA of the full-tar cigarette indicated there was a significant effect of time [$F(3,27) = 3.1$, $p < 0.05$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions. Similarly, the ANOVA for the reduced-tar cigarettes indicated a significant effect of time [$F(3,27) = 4.8$, $p < 0.01$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions.

A short form of the Questionnaire on Smoking Urges (QSU) was used to assess cigarette craving. The total QSU score is illustrated in Figure 2 (lower panel). All of the experimental cigarettes reduced cigarette craving immediately after smoking and scores were reduced for as long as 60 min after smoking. The ANOVA for the full-tar cigarette indicated there was a significant effect of time [$F(3,27) = 6.6$, $p < 0.01$], but no significant effect of cigarette (standard vs. de-nicotinized) and no significant interactions. Similarly, the ANOVA for the reduced-tar cigarettes indicated a significant effect of time [$F(3,27) = 5.0$, $p < 0.01$], but no significant effects of cigarette (standard vs. de-nicotinized) and no significant interactions. The ANOVAs on both Factor 1 and Factor 2 of the QSU also indicated a significant effect on time but no significant effects of cigarettes (or interactions).

Responses on the visual analog scales measured cigarette characteristics and smoking satisfaction (Table 2). The ANOVAs indicated that for both reduced- and full-tar cigarettes there was no significant difference between standard and de-nicotinized cigarettes on 'draw', 'good effects', or 'strength'. There were no significant main effects of abstinence and no abstinence by cigarette interactions. On some measures there were significant differences between the standard and de-nicotinized cigarettes. For example, the full-tar cigarettes showed significant differences between the de-nicotinized and standard cigarettes on measures of: 'bad effects' [$F(1,9) = 5.03$, $p < 0.05$]; 'satisfaction' [$F(1,9) = 6.44$, $p < 0.05$]; and 'taste' [$F(1,9) = 5.88$, $p < 0.05$]. Standard and de-nicotinized full-tar cigarettes also differed on the responses on the drug-liking question of the Single Dose Questionnaire [$F(1,9) = 4.81$, $p < 0.05$]. The reduced-tar cigarettes showed significant differences between the de-nicotinized and standard cigarettes on measures of: 'bad effects' [$F(1,9) = 11.7$, $p < 0.01$], 'harsh' [$F(1,9) = 20.1$, $p < 0.01$], and 'taste' [$F(1,9) = 6.62$, $p < 0.05$]. Standard and de-nicotinized reduced-tar cigarettes also differed on the responses on the drug-liking question of the Single Dose Questionnaire [$F(1,9) = 22.1$, $p < 0.01$].

## Discussion

Although the importance of a control condition in clinical research is well recognized, smoking research has been hampered by the unavailability of a de-nicotinized control cigarette. The rapid delivery of nicotine is an integral part of cigarette smoking (Henningfield, Stapleton, Benowitz, Grayson, & London, 1993). Furthermore, in smoking, more than after other forms of drug ingestion, sensory stimuli evoke responses that are highly conditioned and reliably associated with the onset of drug action (Rose, Behm, & Levin, 1993). Thus, a tobacco-based, nicotine-free, control cigarette could be used to distinguish the effects of smoke-delivered nicotine from the effects of other components of tobacco smoke and the process of smoking *per se*.

**Table 2.** Evaluations of experimental cigarette characteristics

| VAS Measure | Full tar standard | Full tar de-nicotinized | Reduced tar standard | Reduced tar de-nicotinized |
|---|---|---|---|---|
| Strength | 37 ± 10.8 | 30 ± 3.8 | 37 ± 5.7 | 32 ± 11.8 |
| Harsh | 61 ± 12.5 | 42 ± 8.6 | 35 ± 9.5 | 68 ± 9.7 |
| Taste | 17 ± 5.8 | 14 ± 1.8 | 38 ± 6.4 | 13 ± 5.9 |
| Satisfaction | 12 ± 3.8 | 17 ± 2.9 | 35 ± 6.2 | 17 ± 9.6 |
| Good effects | 25 ± 4.9 | 23 ± 2.9 | 44 ± 10.6 | 23 ± 10.0 |
| Bad effects | 47 ± 10.3 | 36 ± 8.1 | 41 ± 9.1 | 66 ± 7.7 |
| Draw level | 46 ± 10.3 | 32 ± 4.9 | 39 ± 9.4 | 39 ± 10.3 |

Visual Analog Data for seven measures of cigarette characteristics. Numbers are mean (SEM on 100 mm scale ($n = 10$); data are collapsed across the two abstinence conditions ($> 3$ and $> 12$ h).

The present study was an evaluation of a new de-nicotinized cigarette. The results of the study indicated that the de-nicotinized cigarette met many of the criteria for a suitable control and may be useful in smoking research.

The de-nicotinized cigarettes used in the study contained negligible levels of nicotine. In contrast, the tobacco in so-called 'light' and 'ultra light' commercial cigarettes contained substantial amounts of nicotine that are typically similar to those found in standard nicotine-delivering cigarettes. For example, the nicotine content (per cigarette) of six brands of 'light' cigarettes averaged 11.75 mg; three brands of 'ultra light' cigarettes was 10.94 mg; and of six brands of 'full flavor' cigarettes was 12.19 mg (Massachusetts Department of Public Health, 1998). The FTC smoking machine estimates of nicotine and tar delivery differ among cigarette types because the smoke from 'light' and 'ultra light' cigarettes is diluted through filter ventilation—the more the ventilation, the lower the yield of nicotine and tar (Kozlowski, Mehta, Sweeney, Schwartz, Vogler, Jarvis, & West, 1998). In practice, the delivery of nicotine to the smoker is determined by how the cigarette is smoked (Kozlowski *et al.*, 1998; Herning, Jones, Benowitz, & Mines, 1983). Nicotine absorption as measured by plasma levels of cotinine in smokers of low FTC nicotine yield cigarettes ($< 0.4$ mg) were similar to the levels of cotinine in high-nicotine yield cigarettes (Benowitz, Hall, Herning, Jacob, Jones, & Osman, 1983). In spite of the low FTC estimates of nicotine and tar delivery in 'ultra light' cigarettes, they are unacceptable as a control condition for tobacco research because substantial amounts of nicotine can be obtained. The de-nicotinized cigarettes used in this study contained virtually no nicotine; thus, regardless of how they were smoked, no nicotine was available for delivery.

Venous plasma nicotine concentrations verified that neither the reduced- nor the full-tar de-nicotinized cigarette delivered measurable levels of nicotine to the volunteers. However, reduced- and full-tar standard cigarettes increased plasma nicotine by 10.6 and 12.2 ng/ml, respectively. These increases were similar to those reported after smoking a commercial cigarette (Pickworth, Fant, Nelson & Henningfield, 1998).

The de-nicotinized cigarettes failed to cause the physiological effects ordinarily seen after smoking cigarettes that deliver nicotine. For example, heart rate increased after the standard cigarettes were smoked, but not after de-nicotinized cigarettes. Others have reported that smoking nicotine-free cigarettes did not increase heart rate (Butschky *et al.*, 1995; Rose & Behm, 1991). Furthermore, EEG activation, indicated by a decrease in theta power (Ulett & Itil, 1969), occurred after smoking the standard cigarettes but not after the de-nicotinized cigarettes. In fact, after smoking de-nicotinized cigarettes, theta power increased, a sign of tobacco abstinence (Herning, Jones, & Bachman, 1983; Pickworth *et al.*, 1989; Ulett & Itil, 1969). The increase in theta power was especially evident after subjects smoked the full tar de-nicotinized cigarettes. This EEG change may result from the exposure of cues associated with smoking without the delivery of nicotine. Tiffany & Hakenewerth (1991) reported that cigarette craving increased when smokers listened to audio tapes of situations where smoking occurred.

Measures of smoking behavior did not appear to be related to the nicotine content of the cigarette. The time to smoke and the number of puffs to smoke the cigarette did not differ between the de-nicotinized and standard cigarettes. The boost in exhaled CO was similar after standard and de-nicotinized cigarettes. In the present study, as in an earlier study in which cigarettes were smoked through a tar- and nicotine-trapping occlusive filter (Pickworth *et al.*, 1998), the fact that only one cigarette was smoked may have prevented demonstration of the compensatory changes in smoking that are typical when nicotine dosing levels are varied (Hurt & Robertson, 1998; Djordjevic, Fan, Ferguson, & Hoffmann, 1995). In the present research, the short period of tobacco abstinence, unfamiliar and unsatisfactory cigarette taste, and the subject recognition that they could smoke their own cigarette in 1 h may have diminished efforts to change smoking behavior to obtain more nicotine. Further studies will be needed to characterize the possible changes in smoking that could develop across sequential cigarettes smoked within a test session, as well as across days, weeks, or even months of smoking. It would also be interesting to determine the possible interaction of nicotine by different instructional sets, e.g., 'smoke as you desire' vs. 'gradually reduce your smoking'.

Experimental cigarettes were assessed after >3 and >12 h of tobacco abstinence. We expected that subjective liking of the cigarettes, ability to relieve tobacco withdrawal symptoms and cardiovascular effects would be greater after 12-h than after 3-h abstinence. For reasons that are not clear, this was not observed. Compliance to the 12-h abstinence was verified by lower levels of plasma nicotine, cotinine and exhaled CO. However, significant baseline differences in tobacco abstinence measures (QSU and MWS) in the 3- and 12-h conditions were not observed. Furthermore, the standard cigarettes did not have greater effects on subjective measures of tobacco abstinence, change in heart rate, measures of smoking behavior in the longer abstinence condition. Neither did the longer abstinence enhance the subjective responses to the de-nicotinized cigarettes. These findings have theoretical and practical implications. The effects of the standard cigarettes on physiological responses should be enhanced with longer abstinence as the smokers lose tolerance to nicotine (Fant, Schuh, & Stitzer, 1995; Schuh & Stitzer, 1995). If de-nicotinized cigarettes were used to facilitate smoking cessation through extinction, they would need sufficient acceptability to sustain continued administration.

De-nicotinized and standard cigarettes reduced acute measures of tobacco withdrawal. Scores on the MWS and QSU decreased immediately after smoking. Similar results were reported in other laboratory studies after another de-nicotinized cigarette, Next® (Butschky *et al.*, 1995; Gross, Lee, & Stitzer, 1997; Rose & Behm, 1991). In a field study that compared subjective and physiological effects of standard and de-nicotinized cigarettes, both cigarettes reduced subjective craving (Baldinger, Hasenfratz, & Bättig, 1995). On the other hand, it has been well established that substitution of nicotine-free cigarettes leads to withdrawal (Finnegan, Larson, & Haag, 1945) as well as dissatisfaction and inability to sustain the addiction (Hurt & Robertson, 1998). The persistence of nicotine-associated subjective effects and withdrawal symptom relief in acute settings is not surprising in light of the massive conditioning histories of subjects prior to the study. For example, in this study, assuming our subjects typically took 10 puffs per cigarette and that they smoked 31 cigarettes per day, then they had averaged smoking more than 200,000 cigarettes and taken more than 2 million nicotine-associated puffs prior to our study. Even assuming that subjects smoked fewer cigarettes in their first few years of smoking, the conditioning opportunities are massive.

Scores on scales of liking indicated that subjects enjoyed cigarettes that deliver nicotine more than cigarettes that did not. Other measures of product satisfaction were less for the de-nicotinized than the standard cigarettes. For example, after smoking the reduced tar cigarettes, ratings of taste, satisfaction, and good effects were higher than after the de-nicotinized cigarettes; conversely, ratings of bad effects were lower. In other studies comparing a commercially prepared de-nicotinized cigarette, Next® (Butschky *et al.*, 1995; Gross *et al.*, 1997), with cigarettes that deliver nicotine, subjects reported less liking for the de-nicotinized cigarette. Smokers apparently find the characteristic taste and smell of nicotine appealing and cigarettes without those qualities are rated as less satisfactory.

The present study was an initial evaluation of new de-nicotinized cigarettes. Some of the non-significant effects of gender, time of tobacco abstinence and cigarette type on the physiological and subjective measures of the study may be due to the small sample size of the comparison groups. Furthermore, since 80% of the subjects ordinarily smoked menthol cigarettes, their subjective ratings of the non-mentholated experimental cigarettes may have been influenced. It is also important to emphasize that the effects of smoking a single experimental cigarette in a laboratory session may not reflect the effect of these cigarettes smoked chronically in the natural environment. Nevertheless, the de-nicotinized cigarettes in the present study met several important criteria: tobacco product, no nicotine content or delivery, levels of tar comparable to commercial cigarettes, and draw similar to nicotine-containing cigarettes. These features led to similar smoking behavior in both control and standard cigarettes indicating that the de-nicotinized cigarettes may be a useful control cigarette in smoking studies.

## Acknowledgments

The authors gratefully acknowledge the technical and research support of Marianne Chenoweth, RN, Khem Bissessur and Janeen Nichels. Allison Spires and Tanyifor Tohnya assisted in the data analyses. Alla Paskovaty, PharmD, and Maria Giannas, PharmD, provided valuable editorial help.

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Pharmacology, Biochemistry and Behavior 71 (2002) 55–61

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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# Sensory and physiologic effects of menthol and nonmenthol cigarettes with differing nicotine delivery

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Received 22 February 2001; received in revised form 10 June 2001; accepted 10 July 2001

**Abstract**

Many smokers choose menthol-flavored cigarettes, however, the influence of menthol on the effects of smoke-delivered nicotine is unknown. Research and commercial cigarettes, menthol and nonmenthol, that delivered a wide range of nicotine were evaluated. Menthol ($n=18$) and nonmenthol ($n=18$) cigarette smokers participated in a single session during which three cigarettes were smoked 45 min apart, in random order. Federal Trade Commission (FTC) nicotine yields of the three cigarettes were: research, low yield, 0.2 mg, commercial cigarettes (average), 1.2 mg; research, high yield, 2.5 mg. Commercial and high-yield cigarettes increased heart rate (HR) and blood pressure more than low-yield cigarettes; although, no differences in exhaled carbon monoxide (CO) occurred. Participants smoked commercial cigarettes faster and with fewer puffs than either of the research cigarette indicating production differences can affect topography. There was a significant group by cigarette interaction on satisfaction, and relief from cigarette craving. High-yield nonmenthol cigarettes reduced craving and were rated as more satisfying than high-yield menthol cigarettes. No differences between menthol and nonmenthol cigarettes on other subjective measures (strength, psychological reward, negative effects) were observed. Our findings indicate that nicotine delivery, but not mentholation, influences cardiovascular and most subjective measures. These results illustrate the importance of threshold levels of nicotine on subjective responses to cigarette smoking. © 2002 Elsevier Science Inc. All rights reserved.

*Keywords:* Placebo cigarettes; Menthol; Denicotinized; Smoking; African Americans

## 1. Introduction

Smoking is a complex behavior that involves the delivery of nicotine, a pharmacologically active substance, and as many as 4000 other compounds and constituents of tobacco smoke (U.S. Department of Health and Human Services, 1988). Although the reinforcing and discriminative stimulus effects of cigarettes depend upon the occupation by smoke-delivered nicotine of specific brain acetylcholine receptors (Rose et al., 2000; Stolerman et al., 1987), the role of the other compounds in cigarette smoke is unknown. Additionally, sensory cues evoked by the heat and feel of smoke, the sight and smell of the burning cigarette rod and the behavior of lighting, holding and inhaling a cigarette appear to be involved in the effects of cigarette smoking (Pritchard et al., 1996; Robinson et al., 2000). Cigarettes that contain and deliver components of tobacco smoke at and various levels of nicotine could be used to distinguish the nicotine-induced effects from those engendered by the behavior of smoking (Robinson et al., 2000). In fact, several research studies have demonstrated that cigarettes that contain and deliver little or no nicotine decrease desire to smoke, cigarette craving and other subjective signs of tobacco withdrawal (Gross et al., 1997; Pickworth et al., 1999; Robinson et al., 2000).

Although nearly 25% of Caucasian smokers and 70–80% of African American smokers in the United States choose menthol-flavored cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979), the effect of mentholation on sensory and physiologic effects of cigarettes has not been systematically studied. Recently, Pritchard et al. (1999) reported that denicotinized menthol cigarettes had no effect on EEG, cardiovascular and subjective responses. Those data suggested that menthol flavoring itself had no physiologic effects, however, the effects of mentholation on cigarettes that deliver different amounts of nicotine have not been studied. In cooperation with the National Institute on

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0091-3057/01/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0091-3057(01)00623-2



PM3003733237

Drug Abuse, Murty Pharmaceutical (Lexington, KY) recently developed four new research cigarettes (menthol and nonmenthol) that deliver very high and very low levels of nicotine. In the present study, the interaction of menthol and nicotine delivery of these new research cigarettes and commercial cigarettes on cardiovascular effects, smoke delivery factors and cigarette taste and satisfaction were assessed. This study was designed to independently determine how nicotine and menthol interact to influence the physiologic and subjective effects of smoking and to assess the acceptability of these new cigarettes for tobacco research. To control for novelty effects of smoking cigarettes of differing flavor, a group design was chosen. Subjects that ordinarily smoked menthol cigarettes received menthol cigarettes in the experiment and nonmenthol smokers received nonmenthol cigarettes.

## 2. Methods

### 2.1. Subjects

Thirty-six (36) research volunteers participated in the study. Subjects were selected based on good health and a smoking history of at least 2 years, smoking 15 or more cigarettes per day. Prior to their participation, subjects signed an informed consent document that had been approved by the local Institutional Review Board and met U.S. Department of Health and Human Services guidelines for the protection of human research participants. They were paid US$60 for their participation.

Subjects were assigned to two groups (18 subjects each) based on the characteristics of their usual cigarette—menthol or nonmenthol. The menthol group was composed of 13 men and 5 women; 17 were African American, 1 was Caucasian. The nonmenthol group was composed of 14 men and 4 women; 3 were African American, 15 were Caucasian. The groups did not significantly differ as a function of gender; they differed significantly by ethnic composition (Pearson $\chi^2 = 22.1$, $P < .001$) The groups were similar for age (mean = 32.6 years), weight (75.4 kg), nicotine dependence, Fagerström (Heatherton et al., 1991) score = 5.8, cigarettes per day = 23.1 and years smoked = 15.9. The nicotine yield as determined by the methods (Federal Register, 1967; Pillsbury, 1996) of the Federal Trade Commission (FTC) of their usual brands of cigarettes differed between groups. The FTC nicotine yield of the brands smoked by the menthol group averaged 1.26 mg, whereas the FTC nicotine yield of the brands in the nonmenthol group averaged 1.02 mg [$F(1,34) = 18.95$, $P < .001$].

### 2.2. Experimental cigarettes

Four research (Murty Pharmaceutical) cigarettes were made (FTC yield: nicotine mg, tar mg, puffs/cigarette): nonmenthol, high yield (2.5, 20.9, 12.2); menthol, high yield (2.5, 20.8, 12.6); nonmenthol, low yield (0.2, 12.4, 8.3); and menthol, low yield (0.2, 11.2, 8.3). Nicotine was removed from the tobacco of the low-yield cigarettes by supercritical fluid extraction techniques. The research cigarettes were all 85 mm in length (king size) and filtered with cellulose acetate filters and commercially available citrate paper. The pressure drop for the research cigarettes ranged from 11.2 to 13.8 cm water. The commercial cigarettes (FTC yield: nicotine mg, tar mg, puffs/cigarette) were: Newport (1.3, 17, 10.9), Kool (1.1, 16, 8.2), Winston (1.1, 16, 10.9) and Marlboro (1.1,16. 11.9).

On the study day, the cigarettes were dispensed from the pharmacy in vials labeled as Cigarettes 1, 2 and 3. A band of white opaque tape was wrapped around the tobacco rods of all cigarettes to obscure the trademarks of the commercial cigarettes. Subjects smoked 50 mm of the tobacco rod to the edge of the tape.

### 2.3. Dependent measures

Before and after smoking each cigarette, systolic (SBP) and diastolic (DBP) blood pressure (seated) and heart rate (HR) were measured using an automated cardiovascular monitor (Datascope, Paramus, NJ). Before and after smoking exhaled carbon monoxide (CO) was measured in parts per million (ppm) with a CO sensor (Vitalograph, Lenexa, KS). Time to smoke the cigarette to a defined length (50 mm of tobacco rod) and the number of puffs were recorded. After each cigarette, subjects completed a Duke Sensory Questionnaire (Behm and Rose, 1994) and a Cigarette Evaluation Scale (Westman et al., 1992). The Duke Sensory Questionnaire has nine items: (1) How much did you like the puffs? (2) How satisfying were the puffs? (3) How high in nicotine were the puffs? (4) How similar to your own brand (cigarette) were the puffs and rate the strength of the puffs on (5) tongue, (6) nose, (7) back of mouth and throat, (8) windpipe and (9) chest? All questions were answered on a scale of 1 to 7, anchored at the extremes with *not at all* and *extremely*. To avoid multiple comparisons and to distinguish the effects of nicotine from menthol on measures of "strength" responses to Questions 5–9 were summed. The Cigarette Evaluation Scale is an 11-item questionnaire that evaluates the cigarette for: (1) satisfying; (2) tastes good; (3) makes you dizzy; (4) calms you down; (5) makes you concentrate; (6) feels more awake; (7) reduces hunger for food; (8) makes you nauseous; (9) feels less irritable; (10) did you enjoy the sensations of the smoke in your throat and chest; and (11) did it immediately reduce your craving for cigarettes. These questions were answered on a 1 to 7 scale as described above. For data analyses, Question 1 (Satisfaction) and Question 11 (Craving Relief) were analyzed alone, and Questions 2 and 10 (Peripheral Sensation), Questions 4, 5, 6, 7 and 9 (Psychological Reward) and Questions 3 and 8 (Negative Effect) were summed (Rose et al., 2000).


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### 2.4. Procedure

This double-blind study was performed on an outpatient basis at NIDA, Intramural Research Program. Subjects were assigned to the two groups on the basis of their usual flavor of cigarettes (menthol or nonmenthol). This assignment was chosen to decrease the influence of novelty of cigarette flavor on the subjective evaluations of the cigarettes. Subjects participated in a single experimental session where they smoked three cigarettes separated by 45 min. Subjects were not required to be tobacco abstinent on the study day. The first cigarette of the experimental session was smoked about 45 min after the subject had smoked their last cigarette before reporting to the lab. The presentation of cigarettes was determined by a Latin-square design. Each subject smoked a research low- and high-yield cigarette and a commercial cigarette. Subjects who ordinarily smoked menthol cigarettes smoked only menthol cigarettes in the experimental session; whereas subjects that ordinarily smoked nonmenthol cigarettes smoked nonmenthol cigarettes in the experiment. However, the commercial cigarette was never the usual brand that the subject smoked.

### 2.5. Data analyses

Repeated-measures analysis of variance (ANOVA) was used to compare continuously distributed variables with between- and within-subjects factors (Winer et al., 1991). The between-subjects factor had two levels: menthol and nonmenthol cigarette; the within-subjects factors had three levels: commercial cigarette, research high and low nicotine yield. Significance was evaluated using the Greenhouse–Geisser epsilon adjustment. Post hoc comparisons between cigarettes were performed by adjusting $P$ values to the number of comparisons (Bonferroni's method). Categorical data were compared by the chi-square test. Differences were considered significant at $P<.05$. Data are presented as means ± S.D. unless otherwise indicated. Data were analyzed using SPSS statistical software (Version 10; SPSS, Chicago IL).

## 3. Results

### 3.1. Physiologic measures

Commercial and high-yield cigarettes increased HR more than the reduced-yield cigarettes (Fig. 1). There was a significant effect of cigarette [$F(2,68)=6.92$; $P<.01$] but no main effect of group (menthol vs. nonmenthol) and no significant group by cigarette interaction. Post hoc tests indicated that HR increase after smoking commercial and high-yield research cigarettes differed significantly from the low-yield cigarettes, but not from each other.

Commercial and high-yield research cigarettes increased SBP by 4.1 and 2.2 mm Hg; but low-yield nicotine cigarettes decreased SBP by 0.6 mm Hg. The analyses indicated a significant effect of cigarette [$F(2,68)=4.3$; $P<.02$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc tests indicated that SBP did not differ after the high-nicotine-yield research and commercial cigarettes. The SBP response to the low-yield research cigarettes differed significantly from the other cigarettes.

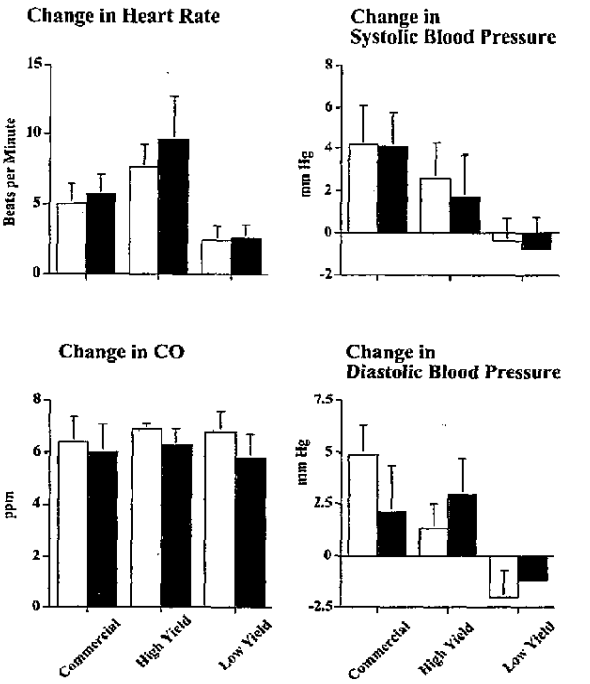



Fig. 1. Average differences between pre- and postsmoking HR, blood pressures and CO for menthol (open bars, $n=18$) and nonmenthol (closed bars, $n=18$) cigarettes. All cigarettes for the menthol group were menthol; and nonmenthol for the other group. Commercial cigarettes were not the usual brand that the subjects smoked. Research cigarettes were low yield (0.2 mg nicotine) and high yield (2.5 mg).

The commercial and high-nicotine-yield research cigarettes caused a small but significant increase in DBP. DBP increased by 3.5 and 2.1 mm Hg after commercial and high-nicotine-yield cigarettes, respectively. DBP decreased by 1.5 mm Hg after the low-yield research cigarette. The analyses indicated a significant effect of cigarette [$F(2,68)=5.8$; $P<.01$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc tests indicated that DBP increased significantly more after smoking the commercial and high-yield research cigarettes than the low-yield cigarette.

Changes in exhaled CO are illustrated in Fig. 1. All cigarettes increased exhaled CO by amounts that did not significantly differ as a function of the cigarette type or mentholation. There was no significant interaction between cigarette type and group.


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### 3.2. Smoking variables

The number of puffs to smoke the 50 mm tobacco rod is illustrated in the upper panel (Fig. 2). The average number of puffs was 8.4, 11.9 and 12.8 for the commercial, high-yield and low-yield cigarettes, respectively. The analyses indicated a significant difference between cigarettes [$F(2,68)=53.7$, $P<.01$]. Post hoc analyses confirmed that significantly fewer puffs were taken to smoke the commercial cigarette than either of the research cigarettes. The mean number of puffs to smoke the high-yield and the low-yield research cigarettes did not significantly differ.

Time to smoke the cigarettes is illustrated in the lower panel of Fig. 2. Time to smoke the commercial cigarettes averaged 284.4 s, whereas the time to smoke the high- and low-yield research cigarettes averaged 426.6 and 407.1 s, respectively. The analyses indicated there was a significant effect of cigarette [$F(2,68)=49.8$; $P<.01$] and a significant cigarette by group interaction [$F(2,68)=3.9$; $P<.05$]. There was no significant main effect of group. Post hoc tests indicated that the average time to smoke the commercial cigarette was significantly less than the times to smoke either the high- or the low-yield research cigarettes. Because 17 of the 18 subjects in the menthol group were African American, the analyses were also run using ethnicity as the between-subjects factor. This analysis indicated no significant effect of ethnic group.

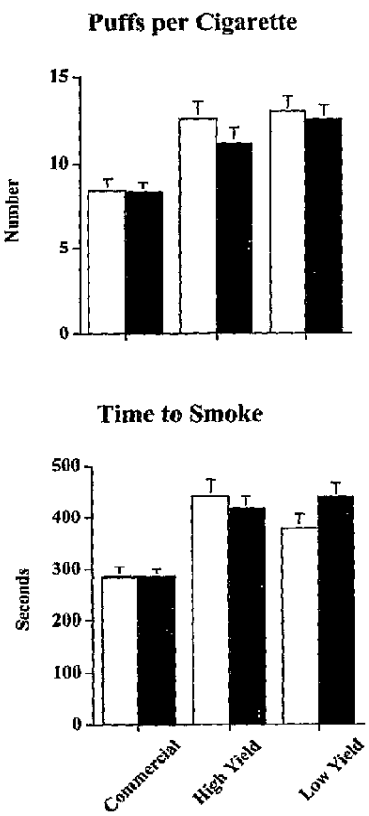



Fig. 2. Average puffs per cigarette and time to smoke for menthol (open bars, $n=18$) and nonmenthol (closed bars, $n=18$) cigarettes. Cigarette and group description are given in Fig. 1.

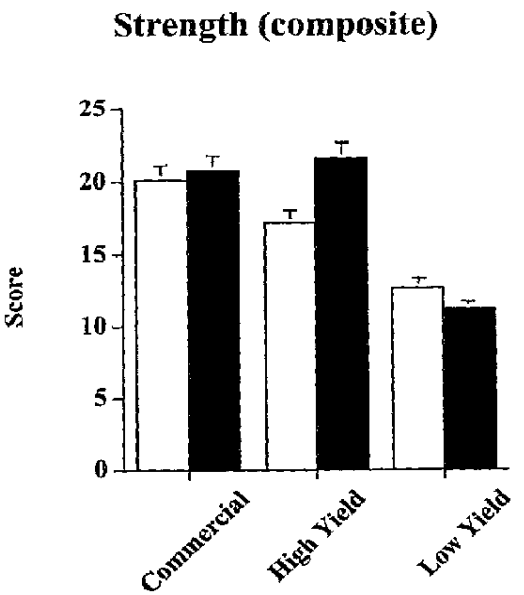



Fig. 3. Average overall rating of strength at nose, tongue, throat, wind pipe and lung (total possible score=35) for menthol (open bars, $n=18$) and nonmenthol (closed bars, $n=18$) cigarettes. Cigarette and group description are given in Fig. 1.

### 3.3. Subjective measures

Data from the Duke Sensory Questionnaire (Behm and Rose, 1994) are illustrated in Fig. 3 and the top half of Table 1. As shown in Table 1, there was no main effect of group (menthol vs. nonmenthol) and no significant interaction between group and cigarette. However, there was a significant main effect of cigarettes on questions of like puffs, satisfaction with puffs, high in nicotine and similar to own brand. In general, participants preferred commercial and high-yield research cigarettes (cigarettes C and H) to low-yield research cigarette (cigarette L). Compared to their own brand the commercial cigarette was rated as significantly more similar than either of the research cigarettes.

Fig. 3 illustrates the perceived strength of the cigarettes in five areas of the respiratory tract: nose, tongue, mouth, windpipe and lung. The ANOVA indicated that there was a main effect of cigarettes [$F(2,68)=15.6$; $P<.01$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc pairwise comparisons showed that the commercial and high-yield research cigarettes were rated significantly stronger than the low-yield research cigarette.


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Table 1
Subjective responses to commercial, research high- and low-yield cigarettes

| | Main effect of group (menthol vs. nonmenthol) | Group × cigarette interaction | Main effect of cigarette | Pairwise comparisons |
|---|---|---|---|---|
| *Duke Sensory Questionnaire* | | | | |
| Like puffs | 0.6; ns | 3.0; ns | 6.1; $P<.01$ | C>L; H=L; C=H |
| Puff satisfaction | 0.7; ns | 2.4; ns | 11.9; $P<.01$ | C>L; H>L; C=H |
| High in nicotine | 0.6; ns | 2.3; ns | 11.2; $P<.01$ | C>L; H>L; C=H |
| Similar to own | 0.8; ns | 0.3; ns | 13.5; $P<.01$ | C>H; C>L; H=L |
| *Cigarette Evaluation Scale* | | | | |
| Satisfaction | 0.7; ns | 3.1; $P<.05$ | 14.9; $P<.01$ | C>L; H>L; C=H |
| Craving Relief | 0.6; ns | 4.8; $P<.02$ | 11.6; $P<.01$ | C>L; H>L; C=H |
| Peripheral Sensation | 0.1; ns | 2.0; ns | 6.4; $P<.01$ | C>L; H=L; C=H |
| Psychological Reward | 0.3; ns | 1.7; ns | 6.8; $P<.01$ | C>L; H=L; C=H |
| Negative Effects | 0.4; ns | 0.8; ns | 4.2; $P<.02$ | C>L; H>L; C=H |

Values of $F$ of repeated-measures ANOVA are shown; where there was a significant main effect, post hoc pairwise comparisons (Bonferroni) between cigarettes were made. C=commercial; H=research, high yield, L=research, low yield, ns=nonsignificant.

Data from the Cigarette Evaluation Scale (Westman et al., 1992) are shown in the lower half of Table 1. On the cigarette satisfaction question, there was a significant effect of cigarette and a group by cigarette interaction; there was no significant main effect of group (menthol vs. nonmenthol). Satisfaction scores were significantly greater after smoking commercial or high-yield nicotine research cigarettes than the low-yield research cigarette. There was no difference between the commercial and the high-yield research cigarettes. The nonmenthol high-yield cigarette was rated higher than the menthol high-yield cigarette. An ANOVA using ethnicity and cigarette as main factors revealed that there was no significant effect of ethnicity or significant interaction between ethnicity and cigarette type.

The Craving Relief question indicated a significant effect of cigarette and a significant group by cigarette interaction; there was no significant main effect of group. The craving relief score was significantly higher after smoking commercial and high-yield research cigarettes than after low-yield research cigarettes. There was no significant difference between the commercial cigarette and the high-yield research cigarette. The high-yield research cigarette was more effective at reducing craving among the nonmenthol group. An ANOVA using ethnicity and cigarette as main factors revealed a significant effect of cigarette [$F(2,33)=13.8$, $P<.01$], no significant main effect of ethnicity but the interaction between ethnicity and cigarette type was significant [$F(2,68)=7.0$; $P<.01$]. African Americans obtained more craving relief from the low-yield and less from the high-yield cigarettes than white subjects.

On scales that measured Peripheral Sensation, Psychological Reward and Negative Effects, a similar pattern of results occurred. There were significant main effects of cigarette but no significant main effect of group and no significant group by cigarette interaction. On all scales, the scores after smoking the commercial cigarette were significantly higher than after the low-yield research cigarette. Scores after smoking the commercial and the high-yield research cigarettes did not differ. On the scales of Peripheral Sensation and Psychological Reward, the high- and low-yield research cigarettes were not different; but on the negative effects scale, scores after smoking the high-yield cigarette were significantly higher than after the low-yield cigarette.

## 4. Discussion

The principal aim of this study was to determine how nicotine delivery (assessed by FTC methods) and menthol flavoring of cigarettes interact to influence physiologic and subjective effects of smoking. Since a large portion of smokers in the United States choose mentholated cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979), it is important to assess research cigarettes that meet the flavor preferences of this population of smokers.

Consistent with previous research, cigarettes that contained nicotine increased HR and SBP and DBP compared to the low-yield nicotine cigarettes (Butschky et al., 1995; Pickworth et al., 1999; Rose and Behm, 1991). Additionally, the present study showed that the menthol condition did not significantly affect cardiovascular parameters. This lack of effect of mentholation in the low-yield cigarettes replicates the recent findings by Pritchard et al. (1999) who reported that menthol in a denicotinized cigarette had no subjective or physiologic effects. The results of the present study extend those findings to indicate that mentholation does not significantly change the effects of smoking cigarettes that deliver average and higher amounts of nicotine.

The study population reflected the consumption preferences of adult US smokers. African American smokers frequently choose menthol cigarettes, whereas white smokers frequently choose nonmentholated cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979). However, ethnic differences in group composition (i.e., the overrepresentation of African American smokers in the menthol group) may have impacted the present results.


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For example, ethnic differences in nicotine metabolism could have been operative. Caraballo et al. (1998) reported higher levels of cotinine, the major metabolite of nicotine, in African Americans compared with white and Mexican Americans, at all levels of cigarette consumption. Sellers (1998) suggested that the differences in cotinine could be due to ethnic differences in the distribution of polymorphic varieties of *CYP2A6*, a gene that controls the production of the enzymes involved in nicotine metabolism. Where significant differences between the cigarettes were revealed, the analyses were repeated using ethnicity as a main factor. No main effects of ethnicity were significant, but there was a significant interaction between ethnicity and cigarette type on the craving relief measure where African Americans obtained more craving relief from the low-yield and less from the high-yield cigarettes than white subjects.

Smoke delivery factors such as time to smoke and puffs per cigarette were different for the research cigarettes compared to the commercial cigarettes. These results indicate that the manufacturing process of the research cigarettes, and not their nicotine delivery or mentholation, affected the way the cigarettes were smoked. Manufacturing characteristics (e.g., density of tobacco packing, paper porosity) that influence physical characteristics of cigarettes could affect the texture and draw from cigarettes (Pickworth et al., 1998; Scherer, 1999) resulting in longer time to smoke and more puffs to smoke.

The effects of the cigarettes were assessed on subjective measures of satisfaction, perceived strength, craving relief, peripheral sensation, psychological reward and negative effects. The overall trend was that nicotine delivery, but not menthol flavoring, determined subjective ratings of strength. Nicotine has been shown to play an important sensory role in cigarette taste and sensory impact (Pritchard et al., 1996). Subjective measures likely reflect nicotine and tar content and cigarette properties (air dilution, draw, taste, heat). The interaction between nicotine and tar delivery must be evaluated in studies where plasma levels of nicotine and smoking topography measures are collected.

Some of the peripheral sensations induced by smoke-delivered nicotine may be mediated at nicotine receptors exist along the airways (Grant et al., 1986; Lee et al., 1993). The peripheral effects of nicotine were demonstrated in a recent study that distinguished the nicotine from the non-nicotine components of tobacco smoke (Rose et al., 2000). Nicotine activated sensory nerves in animal (Ginzel, 1975) and human studies (Rose et al., 1993). Chronic nicotine administration is known to increase the number of brain nicotine receptors (Marks et al., 1992; Benwell et al., 1988), but the effects of chronic nicotine administration on the number of nicotine binding sites in peripheral tissue lining the airways is unknown. It is likewise uncertain whether the subjective effects of cigarettes (e.g., taste, strength, satisfaction) differ as a function of the level of nicotine tolerance.

The high-yield research cigarettes in the study delivered (by FTC machine estimates) about twice the nicotine and considerably more tar than commercial cigarettes. Nevertheless, the responses to the high-yield research cigarettes and the commercial cigarettes were similar and usually differed from the low-yield cigarette. Evidently, subjective evaluations of cigarette taste and strength may depend upon a threshold level of nicotine or other components of tobacco smoke. Very low levels of delivery are regarded as unsatisfactory, but higher (than usual) delivery does not increase satisfaction and, at some level, may have been aversive.

McCarthy et al. (1995) reported an exhaled CO and cardiovascular effects were similar after nonmenthol and menthol cigarettes but when nonmenthol smoking was associated with larger puff volumes and more puff per cigarette. In the present study, exhaled CO and HR changes were similar in menthol and nonmenthol cigarettes. However, in the present study, topography measures were not related to nicotine or menthol but appeared dependent on the manufacturing differences between research and commercial cigarettes.

Further studies of these research cigarettes are warranted. Plasma nicotine levels after smoking the research and commercial cigarettes would indicate whether differences between cigarettes are due to pharmacologic or manufacturing components. The present study compared commercial and research, menthol and nonmenthol cigarettes using groups that ordinarily smoke either menthol or nonmenthol cigarettes. This experimental design led to ethnic differences in group composition. Although statistical corrections were applied to correct for ethnic differences, it would be desirable to also study the cigarettes in ethnically homogenous groups or using a within-subjects design. Nevertheless, using the new high- and low-yield research cigarettes, it was determined that nicotine content, but not mentholation, importantly determined the physiologic and subjective effects of smoking. The research cigarettes used in the present study may prove useful in smoking studies where a wide range of nicotine delivery is needed.

## Acknowledgments

The editorial and technical assistance of Jennifer L. Malson, Tara Fackett, Karen Baumgarner and Stacey Steckley are gratefully acknowledged.

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PM3003733243

*Nicotine & Tobacco Research* Volume 6, Number 3 (June 2004) 523–532

Taylor&Francis
healthsciences

# Extinguishing the rewarding value of smoke cues: Pharmacological and behavioral treatments

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[Received 14 April 2003; accepted 13 October 2003]

**The present study examined several pharmacological and behavioral treatments designed to promote extinction of the responses to rewarding cigarette smoke cues. Pharmacological treatments comprised nicotine skin patches (21 mg/24 hr) and the nicotinic acetylcholine receptor antagonist mecamylamine (10 mg/day), administered separately or in combination. Behavioral manipulations included switching to denicotinized cigarettes, to cigarettes having different menthol flavor, or to ventilated-filter (low tar and nicotine) cigarettes. Smokers were assigned to the various treatments for 2 weeks before they quit smoking. During weekly test sessions, subjects rated the rewarding effects of their usual brands of cigarettes or cigarettes with different menthol content (mentholated vs. nonmentholated). Over the 2-week treatment period, all pharmacological treatments reduced ratings of reward for the usual-brand test cigarettes. Switching to smoking denicotinized cigarettes for 2 weeks similarly decreased rewarding effects of the usual-brand test cigarettes. Subjects also strongly preferred cigarettes with the same menthol content to which they were accustomed. However, manipulating the menthol content of the cigarettes smoked during the 2 weeks of treatment had different effects, depending on whether smokers habitually smoked mentholated or nonmentholated cigarettes. For menthol smokers, removal of the menthol cue hampered extinction of reward ratings for the usual-brand (mentholated) test cigarette. For nonmenthol smokers, addition of the menthol cue did not affect the progress of extinction of nonmenthol smoke cues. These findings demonstrate the importance of sensory cues in determining subjective reward and show that the reward value of these cues can be altered by removal of nicotine from tobacco or by pharmacological manipulations that interfere with the reinforcing effects of nicotine.**

## Introduction

Studies have shown that a smoker's reaction to cigarettes is affected by distinctive smoking cues, as well as by the delivery of nicotine (Herskovic, Rose, & Jarvik, 1986; Rose, 1988; Rose & Behm, 1995). For example, blocking the sensations produced by smoking, either with local airway anesthesia or by administration of a peripheral nicotinic antagonist, reduces ratings of smoking satisfaction (Rose, Tashkin, Ertle, Zinser, & Lafer, 1985; Rose, Westman, Behm, Johnson, & Goldberg, 1999b; Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984). Smokers also rate intravenous administration of nicotine in the absence of smoke cues as less desirable than cigarette smoking (Westman, Behm, & Rose, 1996). In this paper the term *smoke cues* refers to the stimulus aspects of cigarette smoke (as opposed to environmental cues), which elicit sensations via taste, olfactory, or other respiratory tract nerve fibers.

Smoke cues are important in affecting cigarette reward, and may be important in clinical treatment, if, for example, devaluing smoke cues were to lead to a decrease in smoking behavior or more successful smoking cessation. Despite the potential significance of such cues, there has been little investigation of how the rewarding value of smoke cues might be altered by pharmacological or behavioral treatments. The present study examined the effects of several such manipulations. Pharmacological treatments included nicotine and the nicotinic acetylcholine receptor antagonist mecamylamine, administered separately and in combination. In previous studies, the administration of nicotine alone or mecamylamine alone reduced ratings of the subjective enjoyment of

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ISSN 1462-2203 print/ISSN 1469-994X online © 2004 Society for Research on Nicotine and Tobacco

*DOI: 10.1080/14622200410001696501*

smoking (Levin et al., 1994; Rose et al., 1994a,b; Rose, Behm, & Westman, 1998). Moreover, we have reported promising results in smoking cessation treatment with the use of the mecamylamine in conjunction with nicotine replacement therapy (Rose et al., 1994b, 1998; Rose, Westman, & Behm, 1996).

Nicotine or mecamylamine administration is thought to interfere with the reinforcing effects of nicotine in cigarette smoke; over time, this attenuation of the effects of inhaled nicotine, and resultant breaking of the association between smoking and nicotine reinforcement, should lead to a reduction in the conditioned reinforcing effects of smoke cues (i.e., extinction; Bouton & Swartzentruber, 1991). The present study was conducted to study the effects of 2 weeks exposure to treatment with nicotine, mecamylamine, or both to ascertain whether the subjective reward associated with familiar smoke cues would be attenuated. In addition, we sought to compare the results of pharmacological treatment with an unconventional behavioral extinction treatment approach designed to reduce cigarette reward (i.e., having subjects switch to smoking denicotinized cigarettes for 2 weeks). Assuming that subjects would comply with this treatment, the removal of nicotine from the cigarettes should have had an effect similar to the pharmacological blockade of the effects of nicotine, in terms of promoting the extinction of smoke cues.

To evaluate these hypotheses, participants were periodically presented with test cigarettes to rate for rewarding properties, during 2 weeks of exposure to one or more of several pharmacological and behavioral treatments. At each session, subjects smoked one of their usual brand of cigarettes. By observing a reduction in the subjective reward associated with the same cigarette across sessions, we could assess the time course of extinction. A second type of cigarette that was smoked at each session differed from the other test cigarette in menthol flavor (i.e., mentholated vs. nonmentholated cigarettes) but delivered the same nicotine dose. Based on the extinction hypothesis, we predicted that pharmacological blockade treatment would attenuate the reward associated with the usual brands of cigarettes. We also predicted that changing the cigarette cues during the treatment period would retard extinction of responses to the usual-brand cigarette cues. This prediction was based on the well-established finding in studies of conditioning that the degree of extinction measured during a given test stimulus shows a generalization gradient depending on how similar the test stimulus is to the stimulus that has been extinguished (Rilling, 1977). Finally, we hypothesized that pharmacological blockade would reduce the acquisition of conditioned rewarding properties by a relatively novel cue (i.e., menthol) paired with nicotine reinforcement.

## Method

Participants were recruited for a quit-smoking study and exposed to various experimental manipulations for 2 weeks before a target quit-smoking date. Different groups of participants were asked either to switch to other brands of cigarettes during these 2 weeks or to continue smoking their usual brands, as summarized in Table 1, which also shows the pharmacological treatments received by each group. Subjects were randomly assigned to each group, and pharmacological treatments were administered double-blind. Because the data in the present study were collected prior to the quit-smoking date, the postcessation treatments are not described in detail here.

The precessation treatments comprised administration of nicotine skin patches, mecamylamine, or both; and cigarette brand-switching, as follows:

- Nicotine skin patches. Nicotine skin patches (Habitrol), delivering 21 mg of nicotine in 24 hr, and placebo patches were donated by Ciba Self-Medication, Inc. (Woodbridge, New Jersey).
- Mecamylamine. Mecamylamine (Inversine) was purchased from Merck & Co., Inc., (West Point, Pennsylvania), and capsules containing 5 mg of mecamylamine or placebo (lactose) capsules were prepared by the Duke Medical Center Pharmacy. Subjects were instructed to swallow one capsule in the morning and one at night (10 mg/day total dose).
- Cigarettes. Nicotine-containing cigarettes (menthol and nonmenthol) of various brands were purchased locally; subjects' usual brands or brands differing in menthol content (but having the same nicotine yield) were used as test cigarettes. The terms *mentholated* and *nonmentholated* are based on package labeling, inasmuch as nonmenthol cigarettes contain a small amount of menthol. Denicotinized cigarettes were donated by Philip Morris, Inc. (Richmond, Virginia). These cigarettes contained tobacco from which the nicotine had been extracted by high-pressure carbon dioxide. The tar delivery, when smoked by U.S. Federal Trade Commission (FTC) criteria, was 9 mg, whereas the

**Table 1.** Number of subjects in each condition.

| Brand switch | NIC/MEC | NIC only | MEC only | Placebo |
|---|---|---|---|---|
| Usual brand | 30 | 8 | 43 | 12 |
| Denicotinized cigarette | 31 | 12 | – | 7 |
| Menthol cigarette | 32 | – | – | 13 |
| Low tar and nicotine cigarette | 28 | 9 | – | 8 |
| Total *n* | 121 | 29 | 43 | 40 |

MEC, mecamylamine; NIC, nicotine; NIC/MEC, nicotine plus mecamylamine.

nicotine delivery was extremely low (approximately .08 mg). Hasenfratz, Baldinger, and Battig (1993), and Rose, Behm, Westman, and Coleman (1999) measured nicotine intake after subjects smoked these cigarettes and found that plasma nicotine levels increased less than 2 ng/ml.

*Subject recruitment*

A total of 233 healthy male and female smokers interested in quitting smoking were recruited from the community by newspaper and radio advertisements and by word of mouth. These subjects were randomly selected from a larger subject sample ($n = 454$) that received identical pharmacological and behavioral treatments for 2 weeks; however, the other 221 subjects participated in a different study and were asked to smoke different types of test cigarettes, having different nicotine deliveries, to evaluate hypotheses regarding nicotine tolerance (in contrast to the present study, which assessed reactions to test cigarettes of equal nicotine delivery but that differed in menthol flavor). Results from the other study sample are not presented here.

Study participants were between the ages of 18 and 65 years. To be included in the study they had to smoke at least 20 cigarettes per day on average; express a desire to quit smoking within the next 30 days; and be in general good health, based on physical examination, electrocardiogram, serum chemistries, complete blood count, and urinalysis. Additionally, subjects had to express a willingness to switch to a mentholated brand of cigarettes from their usual brand (or vice versa) if assigned to that experimental condition. The following criteria were bases for exclusion: Hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg); hypotension (systolic blood pressure < 90 mmHg, blood pressure diastolic < 60 mmHg); coronary artery disease; cardiac rhythm disorder; history of urinary retention; prostatic hypertrophy; glaucoma; impaired renal function; history of skin allergy; active skin condition (psoriasis) within the past 5 years; other major medical condition; current psychiatric disease; pregnancy or nursing; current alcohol or drug abuse; or current smokeless tobacco use, nicotine replacement therapy, or other smoking cessation treatment.

*Procedure*

During the 2 weeks of the study, subjects applied a skin patch daily, swallowed capsules twice daily, and smoked cigarettes; the content of each varied according to the group assignment. In addition, subjects attended three laboratory sessions, 1 week apart, conducted after overnight (12-hr) abstinence from smoking. Compliance with the smoking abstinence requirement was assessed at the beginning of the session by expired-air carbon monoxide (CO) measurement. At these three laboratory sessions, subjects were given two test cigarettes to smoke, mentholated and nonmentholated, 30 min apart (order counterbalanced). The FTC nicotine and tar delivery of the two cigarettes was similar and was chosen to be as close as possible to each subject's usual brand of cigarette. Each cigarette was smoked through a controlled puff delivery apparatus (Levin, Rose, & Behm, 1989), which regulated the volume of each puff. The number of puffs and interpuff interval also were controlled, so that the same amount of smoke was delivered from each test cigarette. This procedure ensured that changes in reward ratings induced by the various treatments were not confounded with changes in smoke dose. The puffing parameters were individualized based on the measurement of each subject's ad libitum smoking of a single cigarette (of his or her usual brand) at the screening session.

Subjects were supplied with sufficient quantities of cigarettes of the appropriate type (according to the brand-switch condition to which they were assigned) to last until the following week (a 9-day supply, based on self-reported consumption at screening). They were instructed to begin the following day smoking only the assigned brand and to take capsules (containing 5 mg of mecamylamine HCl or placebo) twice daily (morning and evening) and to apply skin patches (21 mg/24 hr vs. placebo) daily. They also were given diary cards and asked to record the study medications taken, as well as the number of cigarettes smoked (including slips, which were defined as smoking of their usual brand if they were in a different brand-switch condition).

*Dependent measures*

*Cigarette evaluation questionnaire.* This questionnaire, used in several previous studies (e.g., (Rose, Behm, & Westman, 2001; Westman, Levin, & Rose, 1992), was administered immediately after smoking during the test sessions, to measure the subjective rewarding effects of smoking. Each item was rated using a seven-point scale ranging from "not at all" to "extremely." A composite reward score was computed by averaging responses on the following items: "Was it satisfying?", "Was there a good taste?", "Did it calm you down?", "Did it make you feel more awake?", Did it reduce your hunger for food?", "Did it make you feel less irritable?", "Did it immediately reduce your craving for cigarettes?", and "Did you enjoy the sensations in your throat and chest?"

*Plasma nicotine and cotinine concentrations.* At each session, venous blood samples (10 cc) were collected

and centrifuged to separate plasma. For a subset of smokers, plasma samples were packed on dry ice and shipped from Durham, North Carolina, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay by gas chromatograph, modified for use with a capillary column.

*Expired-air carbon monoxide.* Subjects' expired-air CO concentrations were measured at each session to verify overnight abstinence and to measure smoke intake during the test sessions, using a portable CO monitor (Vitalograph, Inc., Lenexa, Kansas). The criterion for assessing overnight abstinence was derived on both theoretical and empirical grounds and was implemented using a formula that assigned a threshold CO for each subject, which took into account that individual's CO level measured in the afternoon, the estimated accumulation of CO during smoking the remainder of the day, and the half-life for elimination during the night (assumed to be 6 hr). For a subject with an afternoon CO level of 30 ppm, a morning measurement of less than or equal to 20 ppm was required.

*Self-reported cigarette smoking.* Subjects were asked to record the number of cigarettes smoked daily; separate counts were conducted for the cigarette type to which subjects were assigned and for their usual brand (reflecting noncompliance in the brand-switch conditions).

*Nicotine dependence.* Subjects completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) at the baseline session and at 2 weeks after initiating treatment.

### *Statistical analysis*

All statistical analysis was performed using SUPER-ANOVA and STATVIEW (SAS Institute, Cary, North Carolina). In analyzing subjective reward evaluation, we entered test cigarette (usual brand vs. menthol-switch) and session (1, 2, or 3) into the analysis as repeated factors. A multivariate approach to repeated-measures analysis of variance (ANOVA) was used, which appropriately took into account the correlation pattern among repeated measurements. Additional between-subjects factors were included as described below. To interpret significant interactions, we analyzed the simple effects of one factor for different levels of the other factor (Keppel, 1982).

The experimental design of the clinical trial from which participants were selected was nonorthogonal, with unequal numbers of subjects receiving different combinations of nicotine and mecamylamine treatment, and not all treatment combinations being represented. Type III sums of squares were calculated in the statistical analyses to deal with this nonorthogonal design (Maxwell & Delaney, 1990). In addition, the analyses were conducted in two phases. The first set of analyses addressed whether nicotine skin patch and mecamylamine treatment, alone or in combination, affected the subjective reward associated with smoking. In these analyses, results were averaged across the brand-switching manipulation that took place during the first 2 weeks of the study. The results described below showed that active treatment, comprising nicotine skin patch, mecamylamine, or both, attenuated the reward of the usual brands of cigarettes.

In the second phase, the analysis included the between-subject factors of treatment (active vs. placebo) and brand-switch condition (usual brand, menthol-switch, denicotinized, or low tar and nicotine). Active treatments comprised nicotine, mecamylamine, or both. As before, the within-subject factors were test cigarette and session.

Finally, we compared smokers whose usual brands of cigarettes were nonmentholated with those who smoked mentholated brands, in terms of how they responded to being switched to cigarettes of different menthol content. To obtain sufficient sample sizes for this analysis, we pooled data from all active treatments that had been shown to reduce the rewarding value of smoke cues (the active pharmacological treatments and the behavioral extinction treatment of switching to denicotinized cigarettes).

## Results

### *Subject characteristics*

Table 2 shows characteristics of the subject sample, including age, race, gender, and information about cigarette smoking habits. No significant differences were found in demographic or smoking history variables across treatment groups, with the exception

**Table 2.** Demographic information ($n = 233$).

| Characteristic | Mean (*SD*) |
|---|---|
| Sex | |
| Males | 119 |
| Females | 114 |
| Race | |
| White | 199 |
| Black | 27 |
| Other | 4 |
| Age (years) | 44.2 (10.1) |
| Number of cigarettes per day | 27.8 (10.7) |
| Years smoked | 24.8 (10.2) |
| Federal Trade Commission nicotine (mg) | 0.75 (.32) |
| Fagerström Test for Nicotine Dependence score | 6.4 (2.1) |
| Baseline carbon monoxide (ppm) | 32.8 (13.9) |

of sex. A slight but statistically significant difference was found in the proportion of females across the different pharmacological treatment conditions (nicotine-only, 58%; mecamylamine-only, 53%; combination, 55%; and placebo, 45%). However, when sex was included as a covariate in the analyses discussed below, none of the conclusions was affected. Another issue to be noted in the analyses of menthol vs. nonmenthol smokers is the strong correlation between menthol preference and race (Clark, Gautam, & Gerson, 1996). However, the results presented below were not affected when the analyses were restricted to the subset of White smokers.

### *Effects of nicotine patch and mecamylamine treatment on reward ratings*

A significant interaction of nicotine, mecamylamine, session, and test cigarette was found, $F(2, 366) = 4.06$, $p = .02$, on the composite reward ratings of the test cigarettes. As shown in Figure 1, this interaction could be characterized as follows: Ratings of the usual-brand test cigarettes decreased across sessions in conditions in which active pharmacological treatments (i.e., nicotine patch, mecamylamine, or combination treatments vs. placebo) were presented. In each of the three active pharmacological treatment conditions a significant decrease was found across sessions in the ratings of the usual-brand test cigarettes, $F(2, 52) = 1.41$, $p = .0002$, for nicotine patch; $F(2, 72) = 21.06$, $p = .0001$, for mecamylamine; $F(2, 182) = 13.18$, $p = .0001$, for the combination). Ratings during placebo treatment did not change significantly across sessions, $F(2, 64) = .67$, $p = .51$. Ratings of the menthol-switch test cigarettes were low and remained relatively constant across sessions regardless of pharmacological treatment (all $p$ values $> .1$).

### *Effects of the 2-week brand-switch manipulation*

Given the similar effects of the three active pharmacological treatment conditions, we averaged ratings across these conditions in examining the effects of the brand-switching manipulation, comparing active and placebo pharmacological treatment conditions. In exploring possible interactions of pharmacological treatment with brand switching, we first examined compliance with smoking the assigned brand (assessed by self-report). The number of usual-brand cigarettes smoked during the brand-switching period was significantly related to reward ratings, $F(2, 164) = 3.74$, $p = .03$, for the interaction between number of usual-brand cigarettes smoked, test cigarette, session, and treatment. Therefore, we restricted the analyses to the subgroup of participants who reported minimal smoking of their usual brands when instructed to smoke a different brand. Because a histogram of the amount of usual-brand smoking showed a breakpoint at 50 cigarettes (total for the 2-week period), only subjects who reported smoking less than 50 cigarettes of their usual brands during the 2 weeks were included

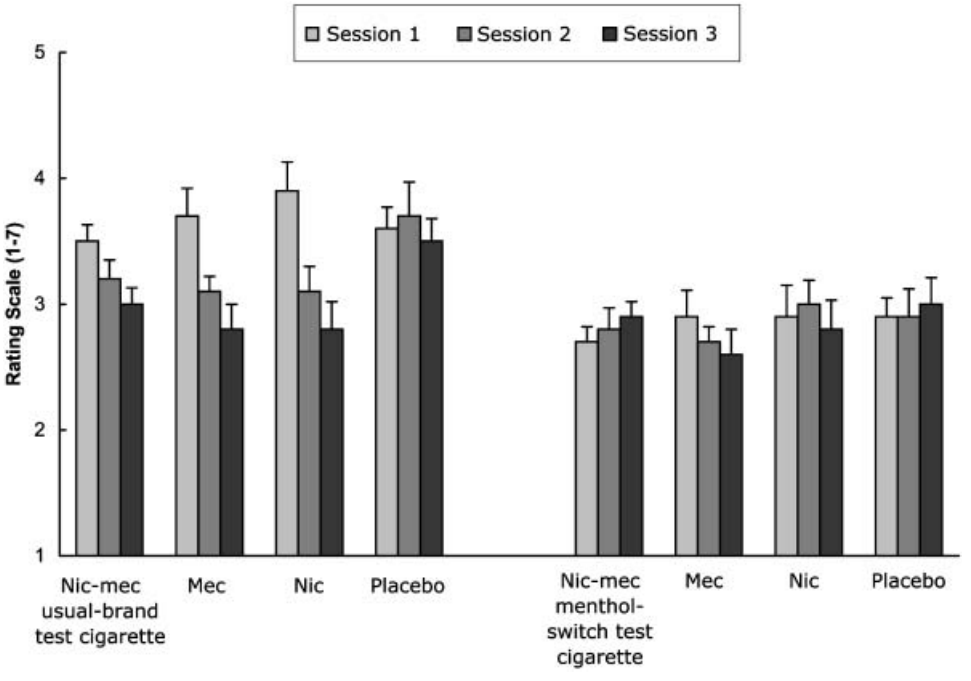



**Figure 1.** Mean ($\pm$ *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three test sessions. Session 1 was conducted before drug treatment, and sessions 2 and 3 were held weekly after initiation of treatment with nicotine plus mecamylamine (NIC/MEC), mecamylamine (MEC), nicotine (NIC), or placebo (PLAC).

(however, all subjects assigned to the usual-brand groups were included). This approach resulted in retaining most of the subjects (189/233). For subjects who met that compliance criterion, a significant interaction was observed between brand-switch condition, session, pharmacological treatment, and test cigarette, $F(6, 308) = 2.14$, $p = .048$. This interaction was interpreted by conducting analyses for each of the brand-switch conditions separately. For all brand-switch conditions except the denicotinized cigarette condition, pharmacological treatment attenuated the reward ratings of the usual-brand test cigarette across sessions relative to placebo treatment (Figure 2). For the session × treatment interaction, $F(2, 52) = 5.46$, $p = .007$, in the low tar and nicotine cigarette condition; $F(2, 150) = 4.01$, $p = .02$, in the usual-brand condition; and $F(2, 54) = 2.34$, $p = .1$, in the menthol-switch condition. In the denicotinized cigarette condition, no effect of pharmacological treatment was detected, and reward ratings dropped across sessions in both active and placebo conditions, $F(2, 56) = 5.02$, $p = .01$, including active and placebo conditions. However, with only five subjects in the placebo condition, the decrease in reward ratings for that subgroup considered separately failed to reach statistical significance.

### *Comparison of menthol and nonmenthol smokers*

We further explored the effects of the cue manipulation of switching the mentholation of the brands of cigarettes smoked during the 2-week treatment period, by comparing smokers whose usual brands were mentholated cigarettes at the outset with smokers of nonmentholated brands. This analysis included only subjects who were assigned to conditions in which the cigarettes smoked for 2 weeks were opposite in mentholation to their usual brands (including subjects in the menthol-switch condition and menthol smokers assigned to the nonmenthol denicotinized-switch condition). Moreover, we pooled the results from subjects in active pharmacological treatment conditions with those in the denicotinized-cigarette extinction regimen, because both types of treatment had

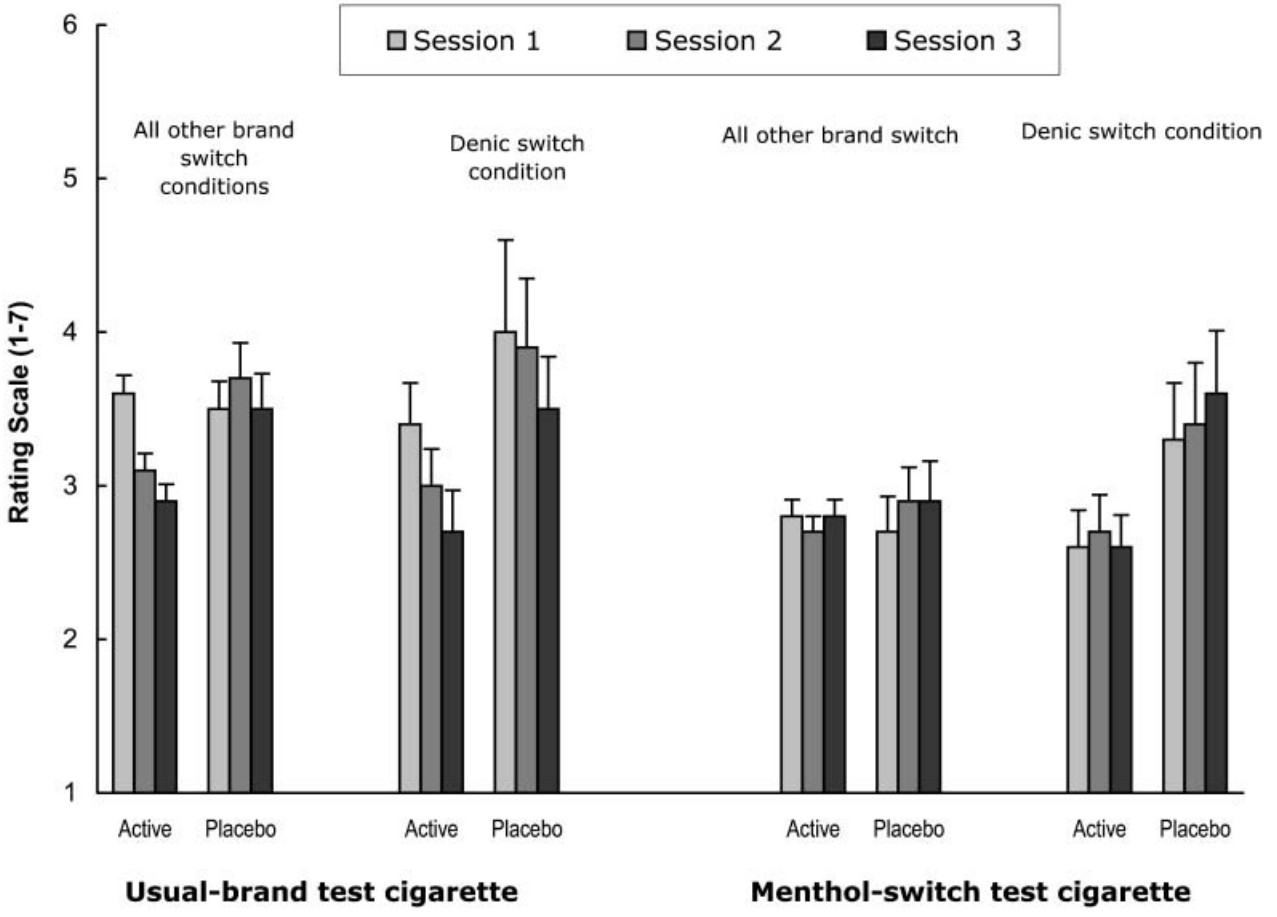



**Figure 2.** Mean (± *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three test sessions. Session 1 was conducted before drug treatment, and sessions 2 and 3 were held weekly after initiation of active treatment (ACT, comprising nicotine plus mecamylamine, mecamylamine, or nicotine) or placebo (PLAC). Results for subjects switched to denicotinized cigarettes for 2 weeks (DENIC SWITCH) are plotted separately from results for subjects in the other three brand-switch conditions (usual-brand, low tar and nicotine, and menthol-switch conditions).

been found to attenuate the rewarding effects of the usual-brand test cigarettes. With respect to ratings of the usual-brand test cigarettes (left side of Figure 3), a significant interaction was found between smoker (menthol or nonmenthol) and the effect of treatment, $F(2, 44) = 7.19$, $p = .002$. Menthol smokers on active treatment, who were switched to nonmenthol cigarettes for 2 weeks ($n = 7$), did not show a reduction in reward ratings of their usual-brand (menthol) test cigarettes across sessions, $F(2, 12) = .42$, $p = .67$, whereas habitual smokers of nonmentholated brands, who were switched to menthol cigarettes while receiving active treatment ($n = 17$), showed a significant decrease in ratings of reward of their usual-brand (nonmenthol) cigarettes, $F(2, 32) = 16.04$, $p = .0001$.

A further analysis was conducted on data from menthol smokers who continued to smoke their usual mentholated brands during the 2-week treatment period and who received active pharmacological treatment ($n = 15$); these smokers, like their nonmenthol counterparts, showed a significant decrease in reward over sessions, $F(2, 28) = 8.54$, $p = .001$ (not shown in Figure 3). Reward ratings of the menthol-switch test cigarettes, which were mentholated for habitual smokers of nonmentholated brands, and

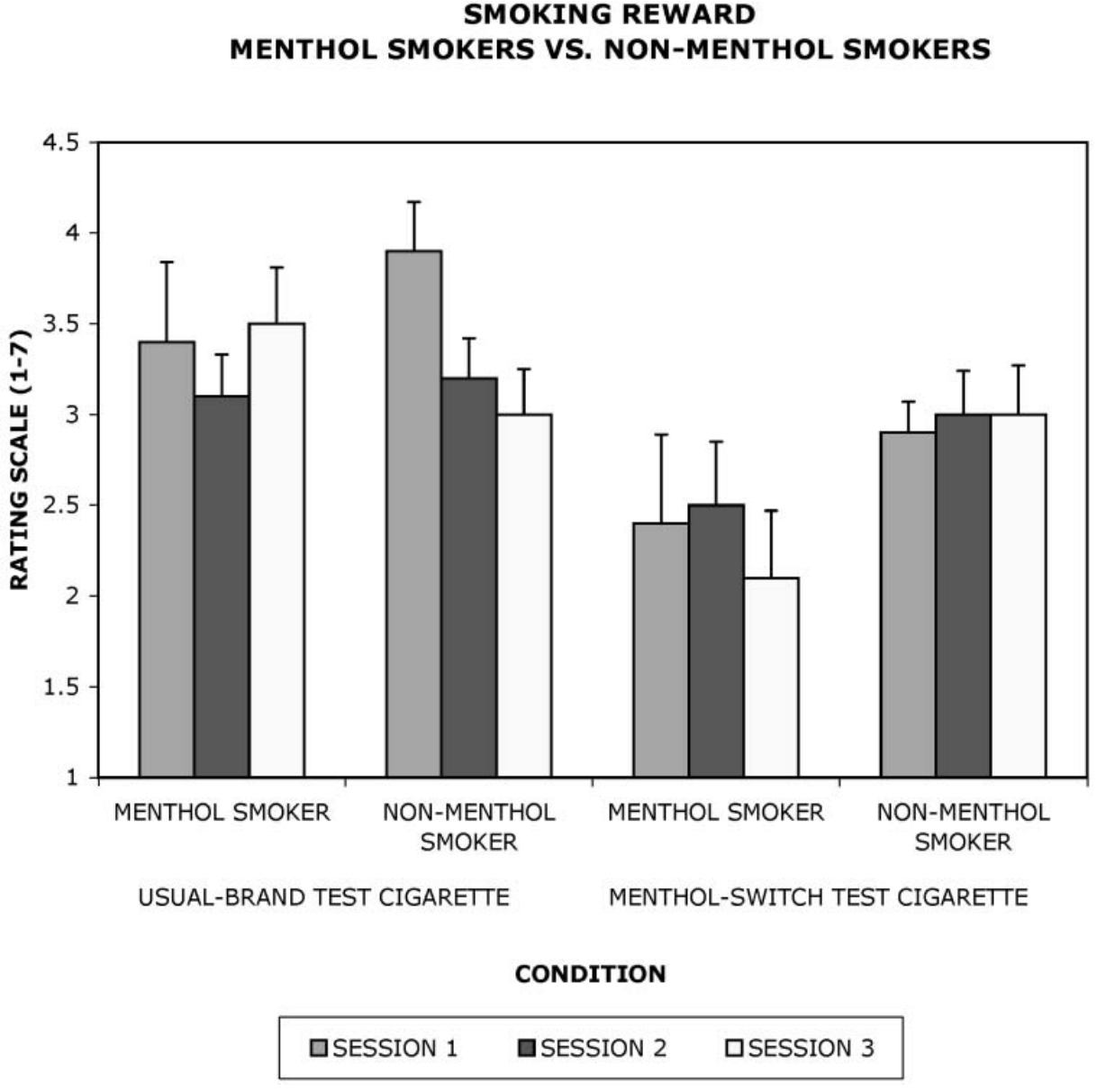



**Figure 3.** Mean ($\pm$ *SEM*) subjective reward ratings of usual-brand test cigarettes and test cigarettes for which the menthol content was different (menthol-switch test cigarettes), in three weekly test sessions. After session 1, all subjects received active treatment (either pharmacological treatment with nicotine, mecamylamine, or both, or behavioral extinction treatment entailing switching to smoking denicotinized cigarettes for 2 weeks). The cigarettes smoked for 2 weeks had a different menthol content than the usual brands (i.e., menthol smokers were switched for 2 weeks to nonmenthol brands, and nonmenthol smokers were switched for 2 weeks to menthol brands).

nonmentholated for habitual smokers of mentholated brands, were uniformly low and showed no change over sessions (right side of Figure 3).

### *Relationship between subjective reward and other measures*

For subjects in active behavioral or pharmacological treatment conditions, the change in subjective reward evaluation of the usual-brand test cigarettes over the 2 weeks of treatment was positively correlated with the change in FTND score from baseline to week 2, $F(1, 138) = 7.54$, $r = .2$, $p = .007$. This correlation remained significant when the change in cigarette consumption was entered as a covariate in a multiple regression model, $F(1, 135) = 4.71$, $p = .03$.

## Discussion

The main result of the present study was that nicotine-patch treatment, nicotine blockade, and removal of nicotine from cigarettes similarly affected the ratings of the usual-brand test cigarettes. The subjective reward associated with these cigarettes was significantly attenuated by 2 weeks of exposure to the active treatments.

The effects of mecamylamine treatment were generally in accord with previously published results. In those studies, 2 weeks (Rose et al., 1994b) or 4 weeks (Rose et al., 1998) of treatment with 5–10 mg of mecamylamine, nicotine skin patches, or both substantially reduced smoking behavior as well as subjective measures of smoking reward. In the present study, however, treatment with nicotine alone or mecamylamine alone was as effective as combined nicotine-mecamylamine treatment; in fact nicotine-only treatment showed a trend to attenuate reward to a greater extent (Figure 1). Of the two previous small-scale studies, one found that the effect of nicotine patch alone was comparable with combined nicotine-mecamylamine treatment; the other study found greater effects of the combination treatment (Rose et al., 1998). The present results, based on a much larger subject sample, suggest that nicotine administration from a skin patch can function in a manner analogous to that of blockade treatment. One mechanism by which this may happen is receptor desensitization (Quick & Lester, 2002), whereby steady administration of nicotine causes receptors to shift into an inactive conformation. If receptor desensitization were substantial, then mecamylamine administration would have little or no added effect. An alternative possibility is that nicotine, via an agonist action, partially satisfied the desire to smoke, indirectly rendering cigarettes less rewarding.

A second observation was that changing one cigarette cue, menthol, had a profound influence on ratings of reward. Although this result is not surprising, little published literature has examined the role of mentholation in cigarette preference or reward. Despite having comparable nicotine delivery, the mentholated cigarettes were substantially less rewarding to smokers of nonmentholated brands; conversely, removing the menthol cue for smokers accustomed to mentholated brands led to a decrease in reward. This result is in keeping with previous research showing that sensory attributes have a major influence on smoking reward, often overshadowing the immediate effects of nicotine (Pritchard, Robinson, Guy, Davis, & Stiles, 1996; Rose, 1988; Westman et al., 1996).

The prediction that altering the menthol cue during the 2-week pharmacological treatment period would attenuate the effect of treatment received partial support. For menthol smokers, changing to a nonmenthol cigarette during either extinction (i.e., switching to denicotinized cigarettes) or pharmacological treatment (with nicotine or mecamylamine) prevented the decrease in ratings of reward for the usual-brand test cigarettes, as assessed in the weekly laboratory test sessions. However, for smokers of nonmentholated brands of cigarettes, changing to a menthol cigarette during treatment did not appear to affect the course of extinction. That is, the reward ratings of the usual-brand (nonmenthol) test cigarettes still declined. This asymmetry in results for menthol vs. nonmenthol smokers might be accounted for when we consider that, for nonmenthol smokers, adding the menthol cue to cigarettes did not alter the fact that other smoke cues were presented without the usual nicotine reinforcement (i.e., reinforcement was attenuated by the pharmacological treatments). Hence, the reward value of these nonmenthol smoke cues should have declined.

In contrast, for a habitual smoker of mentholated cigarettes, a treatment involving switching to nonmenthol cigarettes (i.e., removing the menthol cue), would be expected to prevent the menthol cue from extinguishing, although the reward value of nonmenthol smoke cues would be expected to extinguish. However, to the extent that menthol is a major component of the conditioned reward, as it appears to be, then the overall reward value of the usual-brand test cigarettes (mentholated cigarettes) for this subgroup would tend to be maintained.

This result, while needing confirmation in larger studies, has potential implications for the use of treatments designed to devalue smoke cues. Specifically, extinction might be facilitated by ensuring that salient smoke cues are kept as similar as possible to those of the usual brand of cigarette during treatment. Some of the treatments tested in this study, including mecamylamine, have been shown to modify the

sensory properties of cigarette smoke, in that nicotine functions as a sensory cue as well as having direct central nervous system actions (Rose et al., 1999b). To the extent that this nicotine sensory cue has conditioned reinforcing value, extinction might be retarded when mecamylamine or use of denicotinized cigarettes, either of which modifies sensory cues, is employed in treatment. One approach to avoid this potential problem would be to develop nicotinic antagonists that target central nervous system receptors but do not block nicotine-related peripheral cues. In a similar vein, when using denicotinized cigarettes as an extinction treatment, nonaddictive constituents that mimic the nicotine cue might be added to the cigarettes to make them indistinguishable from nicotine-containing cigarettes, potentially facilitating extinction.

Thus far, we have discussed the decrease in ratings of reward for the usual-brand test cigarettes across sessions in terms of extinction. However, other mechanisms may have been involved in the active pharmacological treatment conditions. For example, nicotine and mecamylamine treatments may have directly interfered with the rewarding effects of nicotine delivered in the test cigarettes. However, the results from smokers in the denicotinized cigarette condition who received placebo treatment are not susceptible to this interpretational problem. In addition, for subjects receiving active pharmacological treatments, direct effects of treatment on nicotine reward would have been expected to reduce ratings of reward for the menthol-switch test cigarettes; however, no change was observed. Moreover, the results from menthol smokers, which showed that cue-change determined whether reward ratings declined over sessions, controlling for pharmacological treatment, argue in favor of an extinction hypothesis. Nonetheless, to further evaluate the extinction hypothesis, it might be advantageous in future studies to measure smokers' reactions to test cigarettes after discontinuing pharmacological treatment, to avoid any direct effects of these treatments on cigarette evaluations. In addition, studies that determine whether a reduction in the rewarding value of smoke cues is related to nonreinforced presentations of smoke cues, as opposed to being related to a reduction in nicotine dependence that follows withdrawal from nicotine, would be informative. If the reduction in ratings of reward in the present study was indeed related to a weakening of the learned association between smoke cues and nicotine reinforcement, then it is remarkable that as little as 2 weeks of treatment could significantly modify the subjective evaluation of the usual-brand smoke cues, which had presumably been reinforced thousands of times over many years. This is especially true given that some studies of evaluative conditioning have suggested that evaluations of subjective liking are relatively resistant to extinction (DeHouwer, Thomas, & Baeyens, 2001), although those studies were of much shorter duration.

Interestingly, no evidence was obtained for a conditioning effect (i.e., an increase in ratings of reward for the menthol-switch test cigarettes in the menthol-switch condition, during 2 weeks of nicotine reinforcement in the condition without pharmacological treatment). Possibly the duration of the study was insufficient to reveal an acquisition of reward associated with the menthol cue. It would be interesting to study longer exposure periods to determine whether the reward ratings would eventually reach the levels of usual-brand preference. The presence of cues already associated with nicotine reward may have retarded the acquisition of conditioning to the menthol cue, analogous to the blocking effect documented in animal learning paradigms (Kamin, 1969; Williams, 1999). If so, acquisition of conditioned reinforcing value to a menthol (or other) cue might be facilitated by presenting that cue alone (i.e., outside of the context of other smoke cues), followed by nicotine.

It is intriguing that the reward ratings of the usual-brand test cigarettes reached a "floor" that was similar to ratings of the menthol-switch test cigarettes, and that ratings of the menthol-switch test cigarettes were not affected by any of the experimental manipulations. This finding implies that the measured changes in reward value were related to the unique sensory properties of the preferred cigarettes and, therefore, involved cue-related incentive properties rather than direct central nervous system effects of nicotine. The magnitude of these changes was nevertheless substantial, resulting in a decrease in ratings by approximately one point.

Also noteworthy is the finding that pharmacological treatment apparently had little effect during 2 weeks of exposure to the denicotinized cigarette condition, in which ratings of reward decreased equivalently in active and placebo pharmacological treatment conditions. Although this conclusion is tentative in view of the limited statistical power for that comparison, the result is nonetheless plausible when we consider that pharmacological manipulations designed to attenuate the effects of nicotine would have been superfluous when subjects smoked cigarettes containing insignificant amounts of nicotine.

One limitation of the present study was the nonorthogonal design, in which not all combinations of cigarette brand-switch manipulations and pharmacological treatments were represented equally. For example, in the mecamylamine-only treatment condition, all subjects continued to smoke their usual brands of cigarettes, instead of being switched to other brands for 2 weeks. Hence, any interaction between this specific pharmacological treatment and the brand-switching manipulation would not have been detected.

Conceivably, a bias in assessing the effects of pharmacological treatments could result from pooling data from different brand-switch conditions; however, the pattern of means for subjects who continued smoking their usual brands for 2 weeks (in which all pharmacological treatments were represented, as shown in Table 1) was virtually identical to those for the entire subject sample. Similarly, the differential impact of pharmacological treatment in the denicotinized cigarette-switch condition was apparent in an examination of the means for the nicotine-mecamylamine combination treatment, in which all brand-switch conditions were represented. The comparison of menthol and nonmenthol smokers also yielded similar results when restricted to the nicotine-mecamylamine combination treatment condition. Nonetheless, the conclusions reached based on pooling results from different conditions should be regarded as preliminary, and confirmation should be sought in future studies that have adequate samples representing treatment cells missing from the current design.

In conclusion, the present study showed that pharmacological and nonpharmacological manipulations can influence the rewarding properties of cigarettes. Changes in reward value were modestly correlated with decreases in dependence, as measured by the FTND. To the extent that changes in the rewarding effects of cigarette smoking affect dependence or the propensity to relapse after quitting smoking, manipulations that affect reward might be put to clinical use. The efficacy of these treatments demonstrates the importance of the precessation period as an opportunity to provide treatment interventions that may affect the outcome of smoking cessation treatment (Rose et al., 1998). Further studies will continue to explore the therapeutic potential of these methods.

## Acknowledgments

This research was supported by National Institute on Drug Abuse grant 1-RO1-DA-02665 and by the Medical Research Service of the Department of Veterans Affairs. The authors gratefully acknowledge the assistance of Eric C. Westman, Prity Patel, Tiffany Ticinelli, Benjamen Isbell, Suzanne Schweitzer, Joanne Schaeffer, and Sarabeth Dermer for their assistance in completing the study.

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## PREFACE

This report was written by the Tobacco Products Scientific Advisory Committee (TPSAC) of the Center for Tobacco Products of the Food and Drug Administration (FDA). TPSAC was mandated by the Family Smoking Prevention and Tobacco Control Act to deliver a report to FDA on the public health impact of menthol in cigarettes within a year of the committee's formation establishment. The report was written within the requirements of the Federal Advisory Committee Act, which governs the committee's meetings. During 10 meetings, from March 30-31, 2010 through March 17-18, 2011 (see Appendix B for dates), TPSAC and Menthol Report Subcommittee developed its approach to the task of writing the report, wrote and reviewed draft chapters, and reached conclusions and drafted recommendations. Chapters were discussed in meetings by the full committee and there was opportunity for comment.

Over the course of the 10 meetings of the TPSAC or Menthol Report Subcommittee, TPSAC received valuable input from many public commenters, including researchers, tobacco industry, consultants to the tobacco industry, representatives of the public health sector, and others. The tobacco industry also responded to requests from TPSAC for specific materials. The voting members of TPSAC received useful comments from the non-voting members of the committee; TPSAC acknowledges their collegial input.

Many others provided materials that were considered by TPSAC in writing the report. TPSAC is grateful to contractors to FDA from the University of California, San Francisco, and RTI International who reviewed various sources and prepared reports for TPSAC on a very timely basis. David Mendez, PhD, from the University of Michigan School of Public Health, executed modeling to assist TPSAC in characterizing the public health impact of menthol cigarettes. Lisa Henriksen, PhD, from Stanford University, made a strong and timely contribution to the development of chapter 5. TPSAC appreciates the efforts of these two scientists, which were made on a very demanding schedule. TPSAC also thanks Denise Gellene, who edited this report and met the challenges posed by the deadline.

In submitting this report, TPSAC has met the requirement of the Family Smoking Prevention and Tobacco Control Act with regard to developing this report and making recommendations on the public health impact of menthol in cigarettes. Of course, TPSAC would be pleased to offer further guidance to FDA on this topic in the future, if needed.

# CHAPTER 1: OVERVIEW: WHAT THIS REPORT IS ABOUT

## INTRODUCTION

Menthol is an organic compound, either derived from natural sources or synthesized, that is widely used in consumer and medicinal products. It has cooling, analgesic, and irritative properties, reflecting its interactions with specific neuronal receptors that can modulate pain and communicate to areas of the brain concerned with taste and other sensations. It has long been used in cigarettes and for some cigarettes it is a flavor-characterizing additive. Menthol is also an active pharmaceutical ingredient in many products. In medical products, whether menthol is the sole pharmaceutical ingredient, as in throat lozenges or one among many such ingredients as in a cold or cough medicine, menthol is regulated as a drug with restrictions on allowable doses and uses, and requirements with respect to instructions for use and warnings. When used in cigarettes, menthol—like most other ingredients in tobacco products—is not regulated according to the safety standards applied to food and drugs.

The Family Smoking Prevention and Tobacco Control Act (the "Act") charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "the issue of the impact of the use of menthol in cigarettes on the public health including such use among children, African Americans, Hispanics, and other racial and ethnic minorities." The Act has the overall purpose of protecting "…the public health by providing the Food and Drug Administration with certain authority..." The issue of menthol in cigarettes was the first brought to TPSAC by the Food and Drug Administration (FDA); under section 907(e) TPSAC is to complete its report and recommendations on menthol in cigarettes within one year of its establishment, that is, by March 23, 2011.

This report addresses the use of menthol in cigarettes as called for by the Act. The goal is to cover the evidence related to the public health impact of the use of menthol in cigarettes and to offer evidence-based recommendations to FDA. As this is the first report prepared by TPSAC, it also describes the principles and practices by which TPSAC has developed this report, offering a precedent that will be followed, as appropriate, for future reports. This chapter and Chapter 2 introduce the methods that TPSAC has used and the basis for their selection.

## THE CHARGE TO TPSAC FROM THE FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT

The Act gives TPSAC a specific but broad charge with regard to the use of menthol in cigarettes. The report is to address the public health impact and to make recommendations on menthol in cigarettes. Under section 907 (a)(3)(B)(i),TPSAC is requested to address the following with regard to menthol:

- The risks and benefits to the population as a whole, including users and nonusers of tobacco products;
- The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- The increased or decreased likelihood that those who do not use tobacco products will start using such products.

If a standard were to be implemented in regard to menthol, under section 907 (b), the Secretary needs to consider additional matters, including technical achievability of the standard and any countervailing effects on the health of adolescent and adult users and non-tobacco users. Such effects could include the creation of a significant demand for contraband.

**WHAT IS A MENTHOL CIGARETTE?**

Under the Act, menthol is an additive, as defined in Section 900 (1). Menthol is reported to be present in most cigarettes in the United States (Henningfield et al. 2003; Giovino et al. 2004). However, TPSAC did not identify any systematic and recent data on menthol content in cigarettes. Those cigarettes marketed as menthol have sufficient menthol content for menthol to become a "characterizing flavor." A submission to TPSAC from the Lorillard Tobacco Company identified menthol levels of around 1000 ppm (wt/wt) of cigarette tobacco or higher as providing a characterizing flavor (Lorillard 2010). R.J. Reynolds Tobacco Company "...typically characterizes a cigarette as a menthol cigarette when the cigarette's menthol level is 0.3 percent or greater" by weight (R. J. Reynolds Tobacco Company 2010, p.1). Heck (2010) in a literature review noted that the menthol content of some cigarette tobaccos reaches two percent by weight. Celebucki et al. (2005) analyzed 48 menthol brands, finding an average value of 2.64 mg per cigarette. For the purpose of this report, TPSAC has not adopted a quantitative definition for a menthol cigarette, but instead relies on the brand designation.

In the brands not marketed as menthol, the amount of menthol is much lower—about 0.03 percent of the tobacco weight (Giovino et al. 2004). In response to questions from TPSAC, the R.J. Reynolds Tobacco Company submitted written comments, which included the statements below (R.J. Reynolds Tobacco Co. 2010, p.3).

> "When menthol is found in non-menthol cigarettes, the levels are extremely low —usually at a level of 50 ppm (0.005 percent) or less."
>
> "Menthol might be detected at trace levels in a non-menthol cigarette as an incidental byproduct of various tobacco processes, such as the manufacture of reconstituted tobacco."
>
> "Non-menthol cigarettes sometimes use small amounts of commercial flavorings, and these flavorings as prepared by the suppliers may use incidental amounts of menthol as a flavor component."
>
> "Some non-menthol cigarettes are made with extremely small quantities of menthol added to provide a fresh taste without imparting a characterizing menthol taste, or to brighten the tobacco flavor."

In response to the same questions from TPSAC, Altria Client Services commented in its June 30, 2010 submission for Philip Morris USA Inc. that: "PM USA does not include menthol as part of the flavor recipes used in non-menthol cigarettes," (Altria Client Services 2010, p.14). While TPSAC has been given the charge of addressing menthol in cigarettes generally, it has focused this report on menthol cigarettes. This focus is consistent with the language of the Act which refers to menthol in Section 907 (a)(1)(A) in discussing constituents or additives that are "…a characterizing flavor of the tobacco product or tobacco smoke."

**THE TPSAC FRAMEWORK FOR ASSESSING THE IMPACT OF MENTHOL CIGARETTES ON PUBLIC HEALTH**

In general, determining the public health impact or population harm of a tobacco product involves assessment of multiple factors. As described in the 2001 Institute of Medicine report, *Clearing the Smoke*, based on a harm reduction conceptual framework described by MacCoun and Reuter (2001), population harm is associated with the toxicity of the product (per use), the intensity of its use (per user) and the prevalence of use (Stratton et al. 2001). With regard to population impact, prevalence needs particular emphasis as it defines the size of the population at risk from a product. Menthol cigarettes could increase prevalence by increasing the rate of initiation and subsequent addiction and by more strongly maintaining addiction and reducing successful cessation.

TPSAC has formulated a framework that is specific to its charge related to the public health impact of menthol cigarettes. As TPSAC evaluates the available information on menthol cigarettes, it will do so within an overall conceptual framework or "model" for cigarette smoking that defines points at which the presence of menthol cigarettes could harm either the health of the individual smoker or of the public generally (Figure 1). TPSAC is charged with addressing "...the issue of the impact of the use of menthol in cigarettes on the public health..." and with further considerations related to population impact and users and non-users under section 907 (a)(3)(B)(i). The framework in Figure 1 is useful for both levels—individual and population. The model set out in Figure 1 begins with experimentation with cigarette smoking on the part of children, adolescents, and young adults and ends with the development of disease and death caused by smoking cigarettes. The model is not inclusive in showing all factors that contribute to this sequence from experimentation to disease incidence, but it does include those who might be affected by menthol cigarettes.

The model implies various potential indicators of the consequences of menthol cigarettes: (1) rates of experimentation and initiation; (2) the prevalence of nicotine addiction; (3) rates of quit attempts and successful cessation; (4) population smoking prevalence, the summative consequence of initiation and cessation; and (5) incidence and mortality rates of smoking-caused diseases. These same indicators are of interest within particular subpopulations, reflecting TPSAC's charge in the Act. It is important to note that disease is not the primary or sole outcome that determines the public health impact of menthol cigarettes. The availability of menthol cigarettes could have no significant effect on risk for disease outcomes, yet have a significant effect on increasing initiation or reducing the success of cessation. The resultant increase in the prevalence of smoking would represent a negative public health impact.

**QUESTIONS TO BE ADDRESSED WITH REGARD TO MENTHOL CIGARETTES**

The framework (Figure 1) highlights issues for which focused reviews need to be carried out to address critical questions related to the charge to TPSAC. The following questions are addressed in the reviews included in this report and answered according to a standardized terminology for strength of evidence. Each is relevant to the assessment of public health impact and the recommendations to be made by TPSAC to FDA.

<u>Related to Individual Smokers</u>

1. Does availability of menthol cigarettes increase the likelihood of experimentation?
2. Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?
3. Does inclusion of menthol in cigarettes increase the likelihood of the smoker becoming addicted?

4. Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?
5. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?
6. Do biomarker studies indicate that smokers of menthol cigarettes receive greater doses of harmful agents per cigarette smoked compared with smokers of non-menthol cigarettes?
7. Do smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes?

Smoking at the Population Level

1. Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?
2. Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

**ORGANIZATION OF THE TPSAC REPORT**

This report contains seven additional chapters. They cover TPSAC's approach to identifying and weighing the scientific evidence; physiological responses to menthol and to menthol and nicotine; the prevalence and patterns of smoking among the population as a whole and in subpopulations such as by race/ethnicity and gender; marketing of menthol cigarettes; the effects of menthol cigarettes versus non-menthol cigarettes on initiation, dependence and cessation; and biomarkers of exposure and risks for health outcomes. The last chapter integrates the information from the preceding chapters. It offers TPSAC's answers to the questions above based on the weight of evidence. It also provides results of modeling that are informative as to public health impact. The report concludes with TPSAC's recommendations to FDA.

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## Chapter 2: TPSAC'S APPROACH TO ITS CHARGE

### INTRODUCTION

This report was developed by the Menthol Subcommittee of the TPSAC.The Menthol Subcommittee developed the chapter outline and general approach during open meetings. The initial draft chapters were written by subgroups of the subcommittee and then reviewed by all of its members. The completed report was then considered by the full TPSAC. The remainder of this chapter describes how TPSAC approached its charge.

### PRINCIPLES UNDERLYING TPSAC'S APPROACH

TPSAC is charged with reviewing and evaluating evidence, reaching conclusions based on the evidence and making recommendations to the FDA on the public health impact of menthol in cigarettes. In assuming this task, TPSAC adopted core principles to guide its approach and report, including being transparent and evidence-based, and reflecting consensus among TPSAC members.

First among these principles is that the fact finding, evidence gathering and synthesis, and deliberations about the evidence are conducted in a transparent manner. By transparency, TPSAC refers to using open and replicable processes that make the basis of its findings and recommendations completely accessible. In following the FDA's processes and meeting the requirements of the Federal Advisory Committee Act, TPSAC carried out its work in open meetings, unless a closed meeting was needed because of commercial, confidential information. Evidence evaluation and TPSAC deliberations were conducted in a transparent manner.

Second, the recommendations of the TPSAC are evidenced-based, meaning that TPSAC identified and relied on scientific and other information relevant to the topic of menthol cigarettes to develop its recommendations. The range of information considered by TPSAC was extremely broad, including survey data, the findings of laboratory studies of pharmacological activity and toxicity, epidemiological evidence, results of marketing research, and reviews of industry documents. Evidence gaps were anticipated and are identified in this report as specifically as possible. Where evidence was lacking or insufficient, TPSAC made its recommendations with acknowledgement of the gap. In cases where there was not enough evidence to make a recommendation, TPSAC identified the research to be done to address the gap. This strategy has been key to maintaining transparency.

While TPSAC made an effort to identify all relevant evidence on menthol in cigarettes, this was impracticable, given the timeframe for this report and the extent of the materials available. TPSAC has provided a clear statement and listing of what materials it did consider. Because there were too many tobacco industry documents to be systematically reviewed, these non-peer reviewed information sources were selectively reviewed and treated as evidence when appropriate. Reviews of these documents were carried out by FDA consultants and there are plans for publication of the summaries in the peer-reviewed literature. The internal documents were a source for understanding the menthol marketing practices of the tobacco industry targeting children, adolescents and ethnic minorities.

Third, the TPSAC used a consensus-based approach to develop this report. The draft report was developed by the Menthol Subcommittee of TPSAC for consideration and approval by the members of TPSAC. While individual TPSAC members and other Special Government Employees have authored various portions of the report, it is a product of the committee and its findings represent a consensus of TPSAC members. In complex and uncertain matters, such as the subject of this report, experts may not share precisely the same views of the scope and quality of the evidence and of its implications. This report captures a range of views, as appropriate, to characterize uncertainty in the evidence considered. After the evidence was collected and reviewed, TPSAC employed a consensus-based approach to develop the recommendations for this report.

**PROCESSES FOR EVIDENCE-BASED DECISION MAKING**
**Overview**

Processes for decision making in public health are grounded in an understanding of what is known and not known about the problem of concern. In making evidence-based decisions with regard to public health, there is a long history of using comprehensive reviews as the foundation for evaluating the state of evidence and for selecting among policy options. The reviews are generally systematic and often carried out by multidisciplinary expert panels, following protocols. Findings present the strength of evidence for a particular factor with regard to the outcome of interest, e.g., the strength of evidence for causation or for a beneficial effect of an intervention. The findings are followed by a decision-making process that might result in promulgation of a guideline, policy, or regulation.

The landmark 1964 Report of the US Surgeon General on tobacco and disease and the consequences of its findings are exemplary (US DHEW 1964). That report, which reached the momentous conclusion that smoking causes lung cancer in men, stands as one of the first comprehensive evidence-based reviews. It used a transparent methodology, involving a critical survey of all relevant literature by an expert panel whose members did not have committed viewpoints at the outset, and applied an explicit framework for assessing the strength of evidence for causation. The causal criteria applied, now often referred to as the "Surgeon General's criteria," are still in use today, and include: temporality, consistency, coherence, specificity, and strength (US DHHS 2004). The causal conclusions of the 1964 report triggered a wide range of individual and governmental actions, including the Federal Cigarette Labeling and Advertising Act of 1965 and a Congressional mandate that a health warning appear on all cigarette packages. In 1967, the Federal Communications Commission (FCC) ruled that the Fairness Doctrine in advertising applied to cigarette ads on television and radio and required broadcasters who aired cigarette commercials to provide air time for information about the health hazards of smoking. Policy actions have similarly followed findings of subsequent reports, e.g., the 1986 report on involuntary smoking (US DHHS 1986).

These same evidence-based approaches have become fundamental in many other areas in clinical medicine and public health. The current paradigm of "evidence-based medicine" involves the systematic review of evidence as the basis for formulating guidelines for clinical and public health practice. Standardized approaches have been developed for carrying out such reviews and the international Cochrane Collaboration engages thousands of researchers and clinicians throughout the world to carry out reviews. In the United States, the Agency for Health Care Research and Policy supports 14 Evidence-based Practice Centers to carry out reviews related to health care. There are also numerous reports from committees of the National Research Council and the Institute of Medicine that exemplify the use of systematic reviews in evaluating evidence as a guide to policy formulation.

Examples include reviews carried out on Agent Orange and the Gulf War, vaccines, asbestos and cancer, arsenic in drinking water, and secondhand smoke and cardiovascular disease risk. A 2008 report of the Institute of Medicine on presumptive disability decision making for veterans proposed a comprehensive scheme for evaluating evidence on whether an exposure sustained in military service had contributed to disease causation (IOM 2008).

Risk assessment is widely used within the government (including FDA) and by other entities in the management of risks from environmental and other factors (National Research Council 1983; 2009). It is an evidence-based decision-making tool that has four elements: (a) hazard identification (is there a risk?);( b) exposure assessment (what is the distribution of exposure to the agent?); (c) dose-response (how does risk vary with dose or exposure?); (d) risk characterization (what is the burden of risk associated with the agent of concern and how is that risk distributed?). The conduct of a risk assessment results in a clear documentation of what is known about a particular agent, and correspondingly what is not known, i.e., the sources of uncertainty. In applying risk assessment to environmental agents, there is also interest in whether particular groups are at higher risk to be exposed (vulnerability) or at heighted risk for the adverse effect(s) (susceptibility). These well worked-out concepts of risk assessment—uncertainty, vulnerability, and susceptibility—are applicable to TPSAC's consideration of menthol cigarettes.

This brief and necessarily selective examination of approaches to evidence review and evaluation documents that models are available for consideration by TPSAC that have proved successful in practice. They have several common elements: transparent and explicitly documented methods; consistent and critical evaluation of all relevant literature; application of a standardized approach for grading the strength of evidence; and clear and consistent phrasing of conclusions.

**Systematic reviews**

Systematic reviews have become the foundation for evidence-based policy in public health. A systematic review involves the identification of all relevant literature to a particular topic via a transparent and replicable search strategy; the culling of the identified publications for those meeting predetermined criteria for inclusion; a comprehensive and standardized assessment of the selected studies for strengths and weaknesses; the assembly of the findings into tables and figures; and the summarization of the findings and the statement of a conclusion on the strength of evidence. Protocols for carrying out such reviews are available.

A systematic review may also involve a quantitative analysis of the evidence, often referred to as a meta-analysis. Such meta-analyses are based on the summary findings of studies, generally as gleaned from papers, but sometimes from authors. The data from individual studies may be combined to yield a single point estimate for an association; by combining the findings of multiple studies, a more precise estimate can be made and the heterogeneity (variation) in the findings of studies formally assessed. If there is variation, the data might be explored for explanations of the variation, using stratification or meta-regression. Conducting a meta-analysis is beyond the scope of this report, but could be conducted for future consideration.

**Causal inference and classification of strength of evidence**

After gathering evidence through a defined process, e.g., a systematic review, the next step is the determination of what the evidence shows. In public health, a critical determination is whether there is sufficient evidence to show a causal association, i.e., whether some factor is either harming or benefiting human health. This process of assessing evidence and determining whether there is a causal relationship is referred to as causal inference.

There is an extensive literature on causal inference, both on its philosophical underpinnings and on the methodology for evaluating the strength of evidence for causation. These approaches have in common a systematic identification of all relevant evidence, i.e., a systematic review, criteria for evaluating the strength of evidence, and language for describing the strength of evidence for causation. The topic of causal inference and its role in decision-making has been recently covered in the 2004 report of the Surgeon General (US DHHS 2004) and in the 2008 report of the Institute of Medicine's Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (IOM 2008).

The 2004 Report of the US Surgeon General on smoking and health (US DHHS 2004) provides an updated review of the methods used in that series of reports, which began with the 1964 report (US DHEW 1964). The review approach embodies the common elements described in the preceding paragraph and uses evidence evaluation criteria that originated with the 1964 report and the writings of Sir Austin Bradford Hill (the "Hill criteria") (Hill 1965) (Table 1). The use of these criteria has now been refined through decades of application. These criteria are not rigid and are not applied in a "check list" manner. In fact, only one—temporality—is required for inferring a causal relationship, since exposure to the causal agent must precede the associated effect. Consistency refers to replication of the finding of an association between cause and effect in multiple studies carried out in different populations by different study types and by different investigators. Consistency of findings weighs against non-causal explanations for an association. Coherence refers to the meshing of different lines of evidence, including experimental findings and understanding of biological mechanisms. For many human diseases, other than the infectious diseases, specificity is not useful, since the non-communicable diseases, such as cancer and coronary heart disease, have multiple causes. In general, stronger associations and the presence of a dose-response relationship provide evidence against non-causal explanations for association. Stronger associations are less likely to be due to bias or confounding as is the presence of a dose-response relationship. The magnitude of an effect reflects underlying biological processes and, depending on these processes, might be appropriately small or large. An effect may not necessarily increase progressively with dose, depending on the underlying process.

The "bottom line" from causal inference is a clear statement on the strength of evidence for causation. Such statements should follow a standardized classification to avoid ambiguity and to assure comparability across different agents and outcomes.

TPSAC reviewed the above approach, which involves the systematic evaluation of evidence to reach a conclusion with regard to disease causation. TPSAC’s charge for menthol cigarettes extends beyond disease causation, however, and TPSAC needs to reach conclusions on diverse issues, include, for example, the consequences of marketing. In reviewing evidence, TPSAC has adopted the general approach described in the causal inference literature. This involves the compilation and review of relevant information to reach a judgment as to the strength of the available evidence in a structured and transparent fashion.

**TPSAC'S APPROACH**

**Sources of evidence and identification of evidence to be reviewed**

In writing this report, TPSAC had multiple sources of evidence to consider, including:

- The peer-reviewed literature: In using this term, TPSAC refers to the studies published in journals or other formats that undergo a process of peer review and editorial evaluation prior to publication. Peer review provides a filter, albeit imperfect, to assure quality prior to publication. Such publications can generally be identified by searching major data bases, such as PubMed.

- Reports written and commissioned by the FDA: TPSAC was provided with multiple reviews of the literature and other reports that were developed by FDA staff or contractors to the FDA. These reports included overviews of the evidence on menthol that were presented at the March 30–31, 2010 meeting and compilations of industry documents from the Legacy data base that were presented at the October 7–8, 2010 meeting. These reports also included the secondary analysis of existing datasets which were made available to TPSAC members and public for the January 10-11, 2011 meeting. Some of these reports have been submitted to the peer-reviewed literature and will become available through that route as well. The reviews of the Legacy documents will be published in a supplement to the journal *Tobacco Control.* FDA also arranged for secondary analyses of various studies and data bases that provided relevant data.

- Tobacco company submissions: The tobacco companies made various submissions to TPSAC under Section 904, some classified as commercial/confidential. These submissions were made on multiple occasions during TPSAC meetings and were directed at the general topic of the meetings. During its initial meeting on March 30–31, TPSAC developed 17 questions for documents to be provided under Section 904 and asked the industry to develop responses, which were offered at the July 15–16, 2010 meeting.

- Public comments: TPSAC received comments from a wide range of public stakeholders. The scope of such presentations was broad.

In developing this report, TPSAC considered evidence from these diverse sources, recognizing the potential strengths and weaknesses of each type of information. The peer-reviewed literature can be systematically accessed through various search engines and TPSAC has attempted to identify all relevant literature, using searches carried out by FDA and its contractors, and also carrying out its own searches. TPSAC used the bibliography assembled by FDA as one resource to identify the most relevant literature. The members of the Menthol Subcommittee also reviewed submissions by the tobacco industry and the public generally to identify other, relevant articles. For other sources, TPSAC did not have resources or sufficient time to carry out its own searches of the Legacy data base nor did it independently review the industry documents that were submitted. Instead, it relied on the reviews of those documents by FDA contractors.

**Selection and evaluation of evidence**

The report approached diverse topics, each drawing on somewhat disparate lines of evidence. For example, in describing patterns of menthol cigarette use, TPSAC relied in part on updated analyses of recent survey data, even though it had not been reported in the peer-reviewed literature. For such analyses, the methods are well standardized and TPSAC could use the results with confidence based on its review of the approach. In contrast, the research on whether smokers of menthol cigarettes have risks for smoking-caused diseases different from those of smokers of non-menthol cigarettes is based on reports of epidemiological studies that have been published in the peer-reviewed literature. TPSAC did not consider abstracts or meeting presentations for which additional documentation was not available.

TPSAC evaluated all studies considered using evaluation criteria appropriate to the particular type of evidence. For example, assessments of survey findings considered response rate and representativeness, the potential for information bias, and sample size. In considering epidemiological studies, the chapter authors assessed population selection and the external validity of findings, bias and confounding, sample size, and appropriateness of data analysis methods. For surveys, response rates and the potential for misclassification were considered. In considering the literature on marketing, attention was directed at the rigor of study design, the limitations of the data collected, analytical methods, and generalizability (external validity) of findings. These reviews were conducted by the various chapter authors, with referral to the Menthol Subcommittee as needed. Particular attention was given to those studies with findings that were more critical in evidence classification. Given the constraint of time, TPSAC did not establish a formal review process with a review template and multiple reviewers per study.

**Classification of the strength of evidence**

In this report, TPSAC addresses nine questions, seven at the individual level and two at the population level. Its reviews are the basis for the answers to these questions, which cover a wide range of factors and outcomes (Figure 1). To assure consistency and transparency, TPSAC provides its summary statements on the strength of evidence in a uniform fashion, offering a classification intended to be useful for decision making.

TPSAC used the following hierarchical classification for the strength of evidence providing its summary judgments:

- The evidence is sufficient to conclude that a relationship is more likely than not.
- The evidence is sufficient to conclude that a relationship is at least as likely as not.
- The evidence is insufficient to conclude that a relationship is more likely than not.
- There is insufficient evidence to determine whether a relationship exists.

This classification was discussed extensively by TPSAC and its members were unanimous in accepting it for use in this report. This classification is based around the concept of "equipoise", i.e., the point of strength of evidence at which the "weight of evidence" is in balance, equally for or against the presence of a relationship. This point reflects an approximate matching of the strength of evidence for a relationship with the evidence against, constituting findings pointing away from or toward a relationship, taking uncertainty into account. In basing this classification around the point of equipoise, TPSAC plans to use an identifiable point, albeit via judgment, as the anchor for its four-level

classification. Additionally, strength of evidence above the point of equipoise might be interpreted as offering a basis for considering a policy action.

In classifying the weight of evidence, TPSAC relied on the judgment of its members as they evaluated the systematically assembled evidence. In this regard, TPSAC followed standard professional practice in public health and regulatory decision making. Strength of evidence was considered to increase with (1) the number of studies providing consistent findings, and (2) the general proportion of studies providing consistent findings. Greater emphasis was given to larger, better executed studies that had been published in the peer-reviewed literature. The coherence of the evidence was also given weight. Because of the variable nature of the evidence considered from chapter to chapter, TPSAC did not propose specific criteria that would be applied uniformly.

These assessments were carried out by the individual chapter authors and then further discussed by the writing subgroup for the chapter. Conclusions were then reviewed and discussed by the Menthol Subcommittee and subsequently by all members of the TPSAC. Consistent with the principles set out by TPSAC, the conclusions reflect a consensus of its members.

**USE OF MODELS TO ASSESS IMPACT**

The TPSAC has the overall charge of addressing the "...impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, and other racial and ethnic minorities." The framework for considering the consequences of menthol cigarettes (Figure 1) identifies a series of indicators of impact under this charge: rates of experimentation, initiation, and progression or regular use or addiction among youths and young adults; rate of successful cessation; and risk for cigarette-caused morbidity and premature mortality. In approaching the assessment of the impact of menthol cigarettes, TPSAC intends to rely, in part, on models that are mathematical representations of the conceptual framework embodied in Figure 1. A model is constructed to reflect understanding of the mechanistic pathways that determine outcome(s) and how causal factors act through these pathways to produce outcome(s) in the "real world." Models can be used to quantify the impact of menthol cigarettes on the various indicators, providing estimates of impact that reflect the potential consequences of menthol cigarettes at the various, linked points in the framework.

Models are an element of a "systems approach" to characterizing the factors that drive the tobacco epidemic and resultant disease burden, and to assessing the potential consequences of tobacco control measures. Systems approaches based in "systems science" are an emerging paradigm for addressing public health problems (Best et al. 2007; Hammond 2009; Mabry et al. 2010). Systems science approaches are valuable for tobacco control and other complex public health problems because they involve comprehensive consideration of the set of determining factors and of the relationships among these factors. This broad-based understanding leads to the development of models that represent the actions of these factors in the "real world." While necessarily simplifying, models can be useful for exploring how different factors drive public health problems, and for exploring the utility of various control strategies.

Models have long been used to assess the impact of smoking on disease occurrence. In 1953, shortly after the publication of the first major studies that showed the strong association of smoking with lung cancer, Levin published a paper setting out a still-used method for calculating the burden of lung cancer

attributable to smoking (Levin 1953). He proposed a parameter, now often referred to as the population attributable risk or population attributable fraction (PAF). This parameter is estimated as:

$$PAF = P_E(RR - 1)/(1 + P_E(RR - 1))$$

where $P_E$ is the prevalence of exposure and RR is the relative risk of mortality associated with the risk factor. This parameter is estimated in the widely used Smoking Attributable Mortality, Morbidity and Economic Costs (SAMMEC) program developed by the Office on Smoking and Health of the Centers for Disease Control. One key concept embedded in this parameter is the comparison scenario for $P_E$, assumed to be a value of zero. This comparison state, which does not exist, is referred to as "the counterfactual," i.e., a scenario that is counter to the actual facts. For the purposes of the present report, TPSAC is concerned with counterfactual scenarios in which menthol cigarettes never existed.

This simple formula for estimating the PAF also indicates the two broad ways that menthol cigarettes could adversely impact public health: by increasing $P_E$ or by increasing RR. An increase in either parameter results in an increase in PAF. Thus, if menthol cigarettes increased $P_E$ but not RR, PAF would increase; if menthol cigarettes increased RR but not $P_E$, PAF would increase.

The utility of general models for tobacco control has gained increasing traction over the last decade, as the broad range of factors determining initiation and persistence of smoking and of disease risks within a population has been recognized (Best et al. 2007; Mendez 2010). The determinants range from the individual level, where genetics and education have a role, to the global level, where the actions of a small number of multinational companies affect the health of populations. A variety of models have been developed for use in the United States and other countries; they have been used to project consequences of various tobacco control approaches on smoking onset and prevalence and on disease burden (Levy et al. 2002; Best et al. 2007; Mabry et al. 2010).

For assessing the public health impact of menthol in cigarettes, a systems approach is warranted, given the diverse factors driving the smoking of menthol cigarettes. TPSAC cannot satisfactorily address its charge without taking a holistic approach that acknowledges the multiplicity of relevant factors and the potential for them to interact in complex ways. The relevant factors range from the biological impacts of tobacco and smoking on human cells to the influence of marketing on the population. There are well-defined interactions related to race and marketing. Evaluating menthol in isolation of social (ethnic, cultural and community), biologic (nicotine metabolism and receptor affinity), engineered (menthol-nicotine-tobacco matrix) and economic (price and marketing) influences may not easily be achieved and may lead to distorted conclusions about the major influences of menthol cigarettes on the public health. Consequently, TPSAC used models wherever appropriate to address its charge related to public health impact. The basic models might be extended to further explore specific issues, such as negative consequences of removing menthol from cigarettes in which it is a characterizing flavor.

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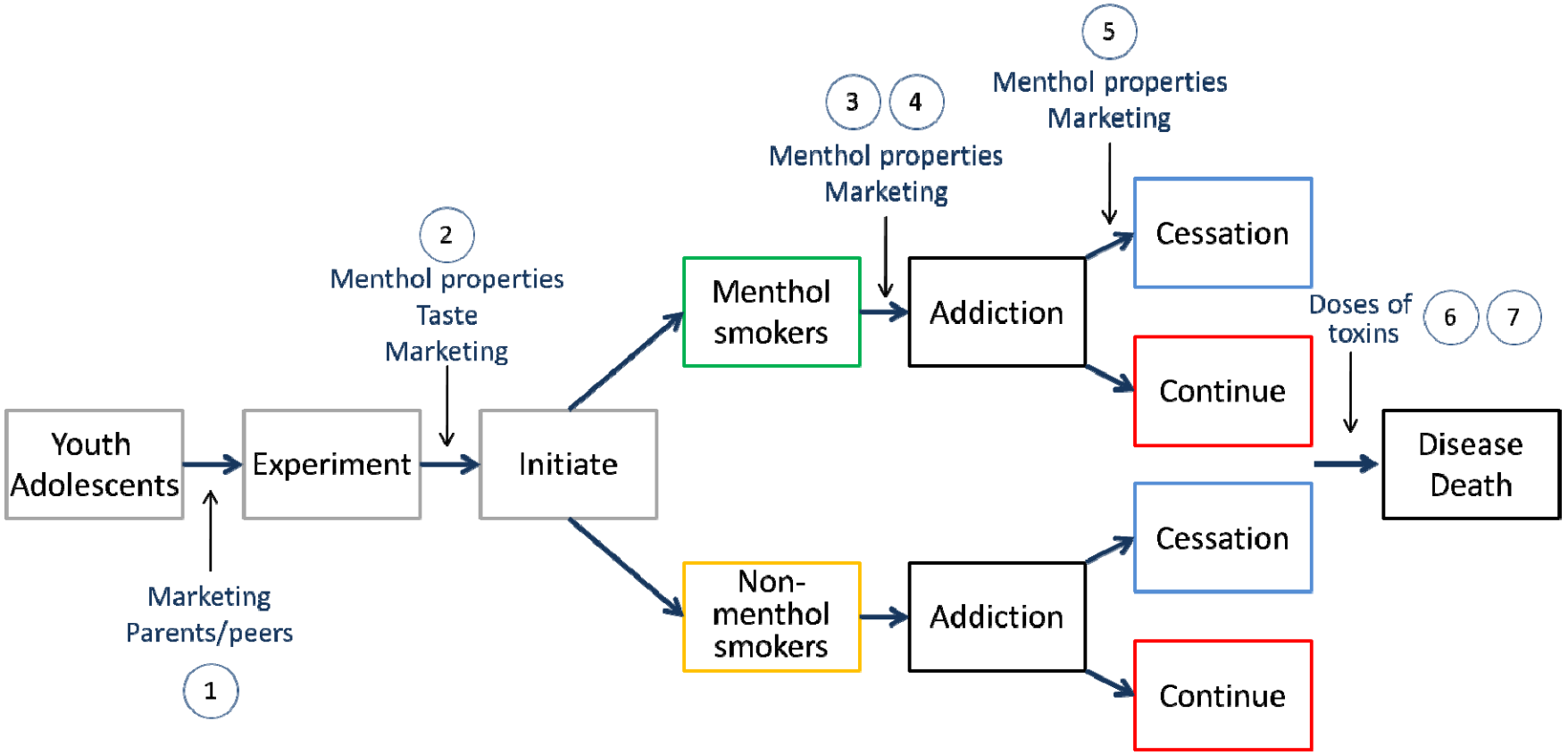
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Figure 1. Model of Smoking and Health: From Experimentation to Disease




Footnote: Numbers refer to TPSAC questions related to individuals. Marketing refers to marketing of menthol cigarettes.

## CHAPTER 3: THE PHYSIOLOGICAL EFFECTS OF MENTHOL CIGARETTES

### INTRODUCTION

Menthol is a flavor additive widely used in consumer and medicinal products. It can be natural or synthetic, has a minty taste and aroma, and may have cooling, analgesic or irritating properties. As noted in chapter 1, menthol is an active ingredient in certain medicinal products, such as cough drops, and when used in medicinal products, it is regulated as a drug. The use of menthol in tobacco products is not regulated. Menthol is present in varying concentrations in 90 percent of tobacco products, including cigarettes that are not marketed as menthol cigarettes.

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "the issue of the impact of the use of menthol in cigarettes on the public health including such use among children, African Americans, Hispanics, and other racial and ethnic minorities." Chapter 3 reviews the physiological effects of menthol in cigarettes. It reviews menthol's chemical structure, its mechanism of action, its interaction with key constituents of tobacco and tobacco smoke, and its affect on the sensory experience of smoking.

Specifically, chapter 3 will address the following questions:

- Does menthol have cooling and/or anesthetic properties that moderate the harshness of cigarette smoke?
- Does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers?
- Does menthol have an effect on nicotine or nicotine-derived nitrosamine metabolism?
- Is it biologically plausible that menthol increases the addictiveness of cigarette smoking?

The answers will assist TPSAC in addressing the nine overarching questions listed and discussed in chapter 1 that are the subject of this report. While the information in chapter 3 is relevant to all nine questions, it is of particular importance to those examining the impact of menthol cigarettes on individual smokers.

### METHODS

Chapter 2 provided the general framework for this report and the Tobacco Products Scientific Advisory Committee's approach to gathering, reviewing and weighing the evidence. Using this framework, chapter 3 draws on sources that provide information about the physiological effects of menthol or necessary background information. The sources of information includes papers published in peer-reviewed literature, documents supplied to the committee by tobacco companies, FDA white papers and unpublished tobacco company documents. Chapter 3 relies in part on animal and human studies that biochemically and/or behaviorally assess the physiological effects of exposure to menthol.

### WHAT IS MENTHOL?

Chemically, menthol is a monocyclic terpene alcohol. It is a naturally occurring chemical chiefly derived from the peppermint plant (*Mentha piperita*) or the corn mint (*Mentha arvensis*), but it can also be synthetically produced. The chemical structure of menthol is shown in Figure 1. Menthol can exist as one of eight stereoisomers—molecules with identical formulas but different three-dimensional shapes. These isomers include menthol, isomenthol, neomenthol and neoisomenthol, each of which can exist as l, also called (-), or d, also called (+). Each of the stereoisomers has distinct pharmacologic characteristics. The l, or (-), isomer of menthol is the natural isomer and conveys the typical taste and sensory characteristics of menthol. The d, or (+), isomer is active but less so than l-menthol (Eccles 1994).

Tobacco companies use both natural and synthetic menthol in cigarettes. The natural menthol found in cigarettes (l isomer) is typically crystallized from steam-distilled oil of the corn mint plant (R.J. Reynolds 2010, p.6). Synthetic menthol (dl - menthol) is racemic, meaning it contains both the d and l isomers and has different taste characteristics from natural menthol (Lorillard Tobacco Company 2010, p.11, Heck 2010). Some cigarette manufacturers use natural menthol only; others use a mixture of natural and synthetic menthol. Natural menthol has been reported to impart greater cooling and mintness and less sharpness, perhaps due to trace chemicals in the natural extract (Wayne and Connolly 2004). Peppermint and spearmint oils may also be added along with menthol to some cigarettes to modify the taste and other sensory characteristics of the smoke (Wayne and Connolly 2004).

Menthol is volatile and has a relatively low boiling point (212 degrees C) (Heck 2010). Consequently, menthol readily vaporizes during cigarette smoking and easily transfers from the cigarette smoke to the smoker, with little pyrolysis, or decomposition. (Jenkins et al. 1970). In mainstream smoke, the vast majority of menthol is in the particulate phase (Jenkins et al. 1970).

Menthol is added to cigarettes in numerous ways: (1) spraying the cut tobacco during blending; (2) application to the pack foil; (3) injection into the tobacco stream in the cigarette maker; (4) injection into the filter on the filter maker; (5) insertion of crushable capsule in the filter; (6) placement of a menthol thread in the filter; and (7) a combination of the above (R.J. Reynolds 2010, p.7, Altria Client Services 2010). Over time, menthol diffuses throughout the cigarette irrespective of where it was applied. Menthol cigarettes are typically blended using more flue-cured and less burley tobacco (Wayne and Connolly 2004). This is because some of the chemicals in burley tobaccos create an incompatible taste character with menthol.

Menthol in cigarettes can be measured either by weight or yield. When measured by weight, menthol content is expressed either as the ratio of the weight of menthol to the weight of the tobacco in the cigarette (mg menthol/gm tobacco), or the weight of menthol in the entire cigarette (mg menthol/ cigarette). Ratios also can be expressed as parts per million (ppm), where 1000 ppm is equivalent to 0.1 percent. Yield per cigarette measures menthol in cigarette smoke and is expressed in mg. Though the menthol-in-smoke measurement is more biologically relevant, it is important to note that menthol yield is generated using standard smoking machine test methods and may not reflect how individual smokers consume menthol cigarettes. Smokers on average take in larger amount of smoke that the machine predicts, particularly when smoking lower yield cigarettes. Thus smokers of menthol cigarettes are likely to be exposed to more than the machine determined menthol yield per cigarette.

Menthol produces a minty taste and aroma and elicits cooling sensations. At low concentrations menthol has a soothing effect, but at high concentrations menthol is irritating. Menthol is reportedly added to cigarettes both as a characterizing flavor (higher levels) and for other taste reasons (lower levels). These other taste reasons include brightening the flavor of tobacco blends and/or smoothing or

balancing the taste of the blend (R.J. Reynolds 2010, p.15). The lowest detectable concentration identified by smokers as menthol characterizing is about 0.12 percent (Lorillard Tobacco Company 2010, p.13). Most menthol cigarettes contain 0.30 percent or higher. Menthol concentrations in non-menthol cigarettes average about 0.01 to 0.03 percent (Wayne et al. 2004). (b) (4) . In addition to taste, menthol also contributes to smoke impact and to modulation of the irritation from nicotine.

In a recent survey of 48 U.S. menthol cigarette brands and sub-brands, the average menthol content in cigarettes by weight was 2.64 mg/ cigarette, with a range from 1.61 to 4.38 mg (Celebucki et al. 2005). The average menthol content in tobacco by weight was 3.89 mg/ gm tobacco, with a range from 2.35 to 7.76. Menthol concentrations tended to be highest in cigarettes with the lowest machined-measured tar deliveries, for reasons discussed below. Thus ultralight cigarettes typically had the most menthol, followed by light cigarettes and full flavor cigarettes. Altria presented data on menthol concentration in tobacco and in smoke for U.S. menthol cigarettes marketed in 2008 and 2009 (Altria Client Services 2010, p.25). The median menthol in tobacco was about 0.6 percent (6 mg/gm tobacco) and the median menthol in smoke was about 0.6 mg/cigarette. The lowest menthol in smoke was 0.35 mg/cigarette and the highest 1.29 mg/cigarette. The latter was in Camel LT KS Men HP cigarettes in which a menthol capsule is crushed prior to machine smoking. Menthol is also present in many non-menthol cigarettes at lower concentrations.

Examples of the menthol contained in the cigarettes and delivered in the smoke (as tested by standard condition machine smoking) for common full flavor menthol cigarette sub-brands are as follows (units are mg): Marlboro FF DS Men HP – 4.1, 0.71; Camel Crush KS HP, breaking capsule – 5.3, 0.87; Camel FF KS Men HP – 3.6, 0.71; Kool FF 100 HP/SP – 4.4, 0.74; Salem FF KS HP Green Label – 3.3, 0.61; Newport FF LS Men HP – 2.3, 0.46 (Altria Client Services 2010).

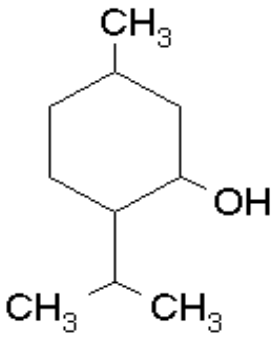
Low yield cigarettes – light and ultralight brands – are low yield primarily due to increased ventilation or air dilution. Compared to full flavor menthol cigarettes, light and ultralight menthol cigarettes have lower transfer efficiency—the percentage of menthol in the smoke compared to the menthol in the cigarette. The increased filtration and ventilation of lower tar delivery products decreases transfer efficiency. In full flavor menthol cigarettes, the transfer efficiency of menthol averages 10–20 percent, while the transfer efficiency in ultralight menthol cigarettes can be as low as 5 percent (Altria Client Services 2010, p.22–24; Cook et al. 1999). To cite a specific example, menthol transfer from the Newport cigarette is 20 percent, while transfer from Newport Light is 12 percent (Lorillard Tobacco Company 2010, p.6). The higher menthol content in light and ultralight cigarettes compensates for the lower transfer efficiency. The transfer efficiency can change with storage of cigarettes as menthol moves from the tobacco to the filter, from which it may be less available for elution (Altria Client Services 2010).

Tobacco companies have explored adding chemicals with menthol-like cooling effects to cigarettes. A number of cooling agents were developed by Wilkinson Sword Ltd in the 1970s and are identified as WS compounds (Leffingwell & Associates 2010). Several of these chemicals including WS-3, WS-5, WS-12, WS-14 and WS-23, act on the same receptors as menthol and have similar cooling effects, but lack menthol's minty taste and aroma (Ma et al. 2008). Other cooling chemicals have been developed by other companies. (b) (4) but to TPSAC's knowledge, they were never added to mass marketed cigarettes. (b) (4)

(b) (4)

. In any case, when considering regulation of menthol in cigarette, the presence of menthol analogs or alternative should also be considered.

Figure 1




**MENTHOL'S MECHANISMS OF ACTION**

Menthol acts on receptors expressed primarily on sensory nerves, including in the trigeminal nerves that innervate the nose, mouth and airways (Abe et al. 2005). Specifically, menthol acts on Transient Receptor Potential (TRP) channels that contribute to the detection of physical stimuli, including temperature and chemical irritation (Levine et al. 2007; Macpherson et al. 2006). Menthol has been reported to act on three of these receptors: the TRPM8 (transient receptor potential melastatin 8), TRPA1 (transient receptor potential ankyrin1) and TRPV3 (transient receptor potential, vanilloid family, member 3). (b) (4) The TRPM8 receptor, which is responsive to cold, and the TRPA1 receptor, which is a chemosensory receptor, are expressed in the sensory neurons of the trigeminal and dorsal root ganglia. The TRPV3 and TRPV1 receptors are responsive to heat and capsaicin. The TRPV3 receptors are expressed in skin cells, and TRPV1 in trigeminal nerve and dorsal root ganglia cells. All of these receptors have roles in mediating sensations of pain or irritation (Eid et al. 2009).

The TRPM8 receptor is activated by both cold and by menthol (Voets et al. 2004; Maccpherson et al. 2006; Bautista et al. 2007), explaining why menthol elicits sensations of cooling. Menthol decreases cold pain thresholds and enhances pain responses to noxious cold stimuli (Hatem et al. 2006; Wasner et al. 2004). TRPM8 receptors are located on sensory, or afferent, nerves. At low doses menthol produces cooling and analgesia and at high doses menthol can cause irritation and pain via effects on these receptors. With prolonged stimulation menthol desensitizes TRPM8 receptors (Kuhn et al. 2009).

The TRPA1 receptor chiefly mediates the pain response to irritant chemicals, including the unsaturated aldehydes in cigarettes smoke (Andre et al. 2008; Bessac and Jordt 2008). This receptor also transmits responses to noxious cold (Karashima et al. 2009), and inflammatory pain (Bautista et al. 2006). Chemicals interact with TRPA1 to produce cough and airway inflammation (Geppetti et al. 2010). Menthol activates and inhibits the TRPA1 receptor, through which menthol can produce or reduce the irritation from tobacco smoke (Bressac and Jordt 2008; Talavera et al. 2009; Xiao et al. 2008; Karashima

et al. 2007). Nicotine, a known irritant, also activates TRPA1 receptors (Karashima et al. 2007; Xiao et al. 2008). Menthol activates TRPV3 receptors to induce cooling in skin (Macpherson et al. 2006).

TRPV1 receptors, found in airway sensory fibers as well as the nasal mucosa, respond to chemical stimuli including capsaicin and many other irritant chemicals (Bessac and Jordt 2008). Nicotine induces irritation by effects both on nicotinic cholinergic receptors and on TRPA1 and TRPV1 receptors (Talavera et al. 2009; Dussor at el. 2003; Simons et al. 2003; Lee et al. 2009).

Menthol acts on olfactory nerves to produce a minty aroma and pungency, effects that decrease as people age (Murphy 1983). When applied to skin, menthol has cooling and antipruritic effects (Bromm et al. 1995). These anti-itching effects have been attributed to menthol's interaction with cold receptors and possibly with kappa opioid receptors (Galeotti et al. 2002).

In addition to its ability to relieve itching, menthol is a topical analgesic. Menthol desensitizes nociceptive C receptors, which are responsible for sending pain signals to the brain; this activity may contribute to analgesia (Cliff and Green 1994). Given in high doses orally (10 mg/kg) or in smaller doses into the brain (10 mcg intracerebroventricularly) menthol has potent analgesic effects in rodents, effects that depend on activation of the endogeneous opioid system, acting on kappa opioid receptors (Galeotti et al. 2002). Thus in high concentrations, menthol acts on the brain. However, the concentration threshold for effects on the brain is not known. Menthol increases skin blood flow at the site of application, which may also contribute to local analgesia (Harris et al. 2006). Menthol's other attributes include antibacterial and antifungal properties and the ability to enhance of penetration of topical drugs and chemicals (Iscan et al. 2002).

**MENTHOL DESENSITIZATION AND INTERACTION WITH NICOTINE**

With repeated or prolonged administration, menthol is known to cause desensitization to its own cooling and irritant effects. Menthol is also reported to reduce sensitivity to noxious chemicals, including nicotine. The irritating effects of nicotine on the airway are mediated by activation of nicotinic cholinergic receptors and TRPA1. In cellular electrophysiology studies and in a rodent model of nicotine-induced airway constriction reflex response, menthol inhibits effects of nicotine (Talavera et al. 2009). Other in vitro studies have reported that menthol results in desensitization of nicotine-induced neuronal activation (Hans et al. 2006; Reeh et al. 2006). (b) (4)



In an experimental study, people whose tongues were repetitively dosed with menthol in solution became less sensitive to menthol's irritating and cooling effects (Dessirier et al. 2001). Menthol also

reduced irritation from nicotine when applied to the tongues of people (Dessirier et al. 2001). (b) (4) . Menthol did however reduce burning pain both in baseline and nicotine conditions. Higher levels of nicotine reduced the subjects' ability to discriminate dose-related odor and cooling effects of menthol compared to lower nicotine levels. While both menthol and nicotine have the potential to desensitize responses with repeated exposure, a study comparing olfactory thresholds for menthol and nicotine in smokers and non-smokers found the smokers had a much higher olfactory threshold for nicotine but no difference in threshold for menthol (Rosenblatt et al. 1998). The same was seen in both menthol and non-menthol smokers. Thus the effects of menthol are persistent in smokers.

**MENTHOL KINETICS, METABOLISM AND METABOLIC INTERACTIONS WITH NICOTINE AND TOBACCO-SPECIFIC NITROSAMINES**

Menthol moves from cigarette smoke into the lungs and then into the bloodstream. Smokers systemically absorb an average of 5–20 percent of the menthol in a menthol cigarette, depending on the extent of ventilation (Altria Client Services 2010, Benowitz et al. 2004). For a cigarette containing 3 mg of menthol (0.3 percent), a smoker of 20 cigarettes per day is exposed to an average systemic dose of 12.5 mg menthol per day.

Once it enters the general circulation, menthol is rapidly metabolized, making it difficult to measure free menthol in the blood or urine. Menthol is metabolized primarily through glucuronidation, a process that takes place in the liver to detoxify substances, and through oxidation, which also takes place in the liver. Glururonidation primarily is driven by the liver enzyme UDP-glucuronosyl transferase 1A4 (Green and Tephly 1998). The result of this process is a compound called menthol glucuronide. Oxidation of menthol to hydroxylated metabolites has been observed in studies in rats (Yamaguchi et al. 1994; Madyastha and Srivatsan 1988). In humans, approximately 50 percent of an oral dose of menthol is excreted in the urine as menthol glucuronide (Gelal et al. 1999). The half-life of menthol glucuronide after oral menthol dosing is about 50 minutes in plasma and 74 minutes in urine, although there appears to be a longer terminal half-life, most likely due to the slow release of the highly lipid-soluble menthol from body tissues and/or due to enterohepatic recirculation (Gelal et al. 1999). It is difficult to do pharmacokinetic studies with inhaled menthol because the dose absorbed cannot be known with certainty. Urine menthol glucuronide concentrations have been measured in a cross-sectional study of smokers of menthol and non-menthol cigarettes (Benowitz et al. 2010). On average, menthol levels are higher in menthol smokers, but many non-menthol smokers also have high menthol levels due to consumption of menthol-containing foods.

While free menthol concentrations are quite low in blood, they are high in tobacco smoke. As a result, menthol concentrations will be high in the mouth, throat and lungs. Estimating concentrations in smoke is important to assess the plausibility that menthol has effects on sensory nerves and possible drug metabolism in the upper and lower airways in relation to concentrations that have effects in animals or cell preparations. Assuming that a menthol cigarette delivers 0.8 mg of menthol in smoke and that a smoker takes 8 puffs on a cigarette, the menthol per puff is 0.1 mg. Assuming that all of the menthol in a puff is absorbed and that the inhalation volume associated with one puff (puff volume plus air) is 800 ml, the concentration of menthol would be 1250 mcg/L, which would be 8.0 uM/L. There is uncertainty about the partition of menthol between smoke and lung tissue, but this gives some rough approximation about what levels might act in the lungs, where there are drug metabolizing enzymes. Concentrations could be considerably higher in the mouth and throat, before the inhaled smoke is fully diluted with the fresh air inhaled with the smoke. These high concentrations are in contrast with the

low concentrations of free menthol in the blood stream and presumably in the liver, as discussed in more detail below.

**Interactions with nicotine**

Menthol may alter the metabolism of constituents of tobacco smoke, including nicotine. Menthol inhibits the metabolism of nicotine in liver microsomal test systems (MacDougall et al. 2003). (b) (4) . The IC 50 (concentration that inhibits metabolism by 50%) was 70.5 uM for l menthol and 37.8 uM for d menthol in the MacDougall study. This concentration is higher than the concentrations typically detected in the blood of smokers, raising the question of whether circulating menthol levels in smokers would be adequate to inhibit liver metabolism of nicotine. However, nicotine is also metabolized in the lungs (Turner et al. 1975), where, as described previously, menthol levels in smoke are likely to be high enough to inhibit nicotine metabolism. In an experimental study of smokers, Benowitz et al. (2004) found that smoking menthol cigarettes inhibits nicotine metabolism in smokers. This was a two-week crossover study in which 14 smokers smoked menthol or non-menthol cigarettes on alternating weeks. After smoking a particular type of cigarette for several days, each subject was given an intravenous infusion of deuterium-labeled nicotine and cotinine to determine the effects of menthol cigarette smoking on the disposition kinetics of nicotine and cotinine. Nicotine clearance was on average 10 percent slower while smoking menthol cigarettes. Menthol inhibited both oxidative metabolism of nicotine to cotinine, and glucuronidation of nicotine. Menthol had no effect on cotinine metabolism. Potential limitations of this study include its small sample size, that its subjects were all heavy smokers and that its subjects were predominantly men.

Studies that used a different measure of nicotine oxidative metabolism found that menthol had no statistically significant effect on the breakdown of nicotine. These studies measured the ratio of the nicotine metabolites trans-3' hydroxycotinine to cotinine (Dempsey et al. 2004), which result from the activity of the enzyme CYP2A6, the major enzyme involved in the oxidation of nicotine. The ratio of trans-3' hydroxycotinine to cotinine, which can be measured in blood, saliva or urine, is highly correlated with the clearance of nicotine. Using this ratio, three studies found no difference in nicotine metabolism between menthol and non-menthol smokers. One was a cross-sectional multi-site study of 1044 menthol and 2297 non-menthol smokers conducted by Altria (Total Exposure Study, Wang et al. 2010). Another was a study of 755 African American smokers participating in a clinical trial of smoking cessation (Ho et al. 2009). The third was a study of 89 smokers with schizophrenia and 53 controls (Williams et al. 2007). The lack of a menthol effect is consistent with either no effect or a small effect of menthol on oxidative metabolism. The ratio would not be sensitive to an effect of menthol on nicotine conjugation. The Altria Total Exposure Study did look at urine ratios of nicotine glucuronide to nicotine, and found no effect of menthol cigarette smoking, arguing against an effect of menthol on nicotine conjugation (Altria Client Services 2010).

**Interaction with tobacco-specific nitrosamines**

Menthol may also inhibit the detoxification of the tobacco-specific carcinogen 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL). NNAL is formed as a major metabolite of the potent tobacco-specific nitrosamine and carcinogen 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone NNK (Hecht). NNK is present in cigarette tobacco, and is formed primarily by nitrosation of nicotine in the curing process. A major pathway of detoxification of NNAL is by glucuronidation, considered to be

mediated by the isoenzymes UGT2B7 (Ren et al. 2000) UGT2B10 (Chen et al. 2007) and UGT2B17 (Lazarus et al. 2005). A substance that inhibits the detoxification of NNAL could potentially increase the risk of cancer. Richie et al. (1997) found in a study of 34 African American smokers and 27 Caucasian smokers that the ratio of NNAL glucuronide / NNAL in urine was significantly lower in African Americans. This finding suggested slower glucuronidation detoxification of NNAL in African American smokers. Since African Americans predominantly smoke menthol and Caucasians predominantly non-menthol cigarettes, Ritchie et al. hypothesized that menthol inhibits NNAL glucuronidation. Muscat (2009) specifically compared 67 menthol smokers to 80 non-menthol smokers, and found that the glucuronidation ratio was significantly lower in white menthol smokers and menthol smokers overall, with a non-significant trend in the same direction for African American smokers. Muscat et al. also found that menthol inhibited NNAL glucuronidation in vitro using human liver microsomes. In the latter study, the IC 50 values for inhibition of N-glucuronidation and O-glucuronidation of NNAL were 0.26 and 0.41 mM, respectively. These levels are higher than those found in the blood and presumably liver of menthol cigarette smokers. Whether such glucuronidation can occur in the lung is not clear. The Altria-sponsored Total Exposure Study, which included 1044 menthol and 2297 non-menthol cigarette smokers, mentioned previously, found no effect of menthol cigarette smoking within racial groups on the ratio (Altria Client Services 2010).

## MENTHOL AND SENSORY RESPONSE TO CIGARETTE SMOKING

### Effects on smoke smoothness and impact

Sensory attributes of tobacco smoke can be considered as a combination of taste, smell and chemesthesis (the latter referring to the feel, such as cooling, biting and burning) (Carpenter et al. 2007). These occur in the context of stimulation of physiological responses in olfactory and trigeminal nerves. These responses have been described by Philip Morris as tobacco smoke flavor, which includes attributes derived from aromatic volatile substances, tastes and feeling qualities such as dryness and cooling (Philip Morris 1999). Sensory attributes overall include resistance to draw, throat response (such as smooth, stinging, peppery, cool), mouth response, mouth fullness, dryness and harshness, tobacco taste, aftertaste strength and cooling effect.

As noted above, menthol produces a variety of sensory effects, including a minty taste and aroma, cooling/ soothing effects, anesthetic effects and irritant effects. Menthol contributes to many of the sensory effects of cigarette smoke, including strength, taste, harshness, smoothness, mildness, coolness taste, and aftertaste. (R.J. Reynolds 1984). The effects of menthol are related to concentration. Lower menthol concentrations produce cooling and anesthetic effects, while higher menthol concentrations produce burning and irritation.

At the very low menthol concentrations used in non-menthol cigarettes, menthol is likely to make smoke smoother and less harsh even though the distinctive minty tasted and aroma is not detectable (Wayne and Connolly 2004). At the concentrations found in menthol cigarettes, smokers report that menthol reduces irritation and that menthol cigarettes are less harsh and smoother than non-menthol cigarettes. Smokers of high menthol cigarettes appear to particularly like the taste and aroma of menthol.

Menthol also has irritant effects, as noted above. Throat irritation is an important contributor to smoke impact, which is a key component of the perceived strength and satisfaction of the cigarette. Both nicotine and menthol stimulate the trigeminal nerve in the mouth and throat to jointly produce the sensory effect of “bite,” or “throat grab.” Reviews of tobacco company documents and a submission

from Altria describe the interaction between menthol, nicotine and tar in producing impact and other sensory effects (Wayne et al. 2004; Kreslake et al. 2008; Altria Client Services 2010; RJ Reynolds 1985). In cigarettes with low levels of tar and nicotine, the addition of menthol can enhance the "bite" or "throat grab" of the smoke, making such cigarettes more acceptable to consumers. Conversely, the addition of menthol to cigarettes high in tar and nicotine can reduce the irritating effect of nicotine, perhaps by cross desensitization, making these cigarettes more palatable. Among menthol cigarette smokers, perception of strength and impact correlate better with menthol delivery than with nicotine delivery (Perfetti 1982).

Thus menthol is not simply a flavoring agent but has drug-like characteristics that modulate the effects of nicotine on the smoker. The consequences of these effects for menthol cigarette smokers are twofold: the sensory stimulation from the "throat grab" of menthol could provide greater reinforcement of smoking behavior, and the reduced irritation provided by lower levels of menthol could lessen aversion to initial self-administration of nicotine among novice smokers, thereby facilitating continued smoking that leads to addiction. Additionally RJR documents (Carpenter et al. 2007) found a relationship between sensory preferences and smoking topography. Smokers who desired a strong cigarette took larger puffs compared to individuals who desired less strength. Since menthol is a determinant of perceived strength, this could be another reason for a relationship between menthol and greater intake of cigarette smoke.

(b) (4)

**Genetic interactions**

Individual differences in taste perception, such as the ability to taste bitter chemicals, are well known. These differences are at least in part genetically determined. There has been much research on genetic differences in response to the bitter chemicals phenylthiocarbamate (PTC) and 6-n-propylthiouracil (PROP). Some people can taste bitter taste ("tasters") and some cannot ("non-tasters"). Tasters are less likely to become a smoker, suggesting that bitter taste makes smoking more aversive (Enoch et al. 2001; Cannon et al. 2005; Snedecor et al. 2006). The family of bitter receptors, TAS2R (taste receptor type 2) contribute substantially to the ability to taste bitter. One of the genes, TAS2R38, accounts for 85% of individual variability in response to bitter (Wooding 2004). The two most common genetic variants (haplotypes) of TAS2R38 are PAV and AVI. PAV homozygotes are most sensitive and AVI homozygotes are least sensitive to PTC/PROP. Among people of European descent, smokers with the AVI genotype rate higher taste/sensory and cue exposure-related motivations for smoking compared to smokers with the PAV genotype (Cannon et al. 2005). Thus the ability to perceive bitter taste seems to decrease taste-related motivations for smoking. This study found however that an intermediate taste sensitivity genotype, AAV, was protective against smoking, which seems inconsistent with earlier studies based on the taste sensitivity phenotype. Among African Americans the taster PAV genotype was inversely associated with smoking quantity, whereas the non taster AVI genotype was positively associated with smoking quantity (Mangold et al. 2008). Furthermore, in women, the non-taster genotype was associated with the level of nicotine dependence. Neither the Cannon nor the Mangold study examined interactions between genotype and menthol cigarette smoking. However, since menthol reduces bitterness for some cigarettes, and since reduced bitterness is associated with smoking

more, the genetic data support the idea that menthol may affect smoking behavior and associated dependence. These studies also raise the possibility that menthol might interact with genetically determined taste sensitivity to facilitate smoking. That is, menthol could mask bitterness to allow smokers who are genetically more sensitive to bitterness to better tolerate tobacco smoke and therefore to become a smoker.

**Respiratory effects**

Menthol is used medicinally in decongestant products. Menthol produces a sensation of increased nasal patency, although nasal congestion is unaffected (Eccles 1990; Nishino et al. 1997; Kenia et al. 2008). Menthol inhibits ventilation (Harris 2006) and increases breath-hold time in humans (Sloan 1993). Menthol also acts as a cough suppressant (Laude et al. 1994; Morice et al. 1994). The respiratory effects of menthol—a sensation of cooling, increased breath-hold time and cough suppression—could promote deeper inhalation and/or longer retention of smoke in the lungs while smoking menthol cigarettes. In animal studies, menthol promotes bronchodilation (Wright et al. 1997) and the clearance of mucous from the lungs (Nishino 1997).

**Other effects**

Orally dosed menthol can cause vasodilation and relaxation of intestinal smooth muscle (Hawthorne et al. 1988). These effects, which are believed to be related to inhibition of calcium currents in smooth muscle (Hawthorne et al. 1988; Taylor et al. 1984), may explain the medical utility of menthol as a treatment for gastrointestinal disturbances. The relevance to the pharmacology of inhaled menthol is unclear. Oral menthol also has been found to increase heart rate, possibly a reflex response to menthol-induced vasodilation (Gelal et al. 1999). However, studies comparing menthol and non-menthol cigarettes have not found any cardiovascular effects of menthol (Pritchard et al. 1999; Pickworth et al. 2002). Studies of electroencephalographic responses to smoking found that response correlated with perceived impact and liking, which may be determined in part by menthol (Gullotta et al. 1989a, 1990, cited in Wayne, 2004). However menthol added to cigarettes had no direct effect on the electroencephalogram (Pritchard et al. 1999).

**EVIDENCE SYNTHESIS**

Chapter 3 set out to answer four questions relating to the physiological effects of menthol pursuant to TPSAC's charge. The responses to those questions are given below. TPSAC considered this information, along with other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

**Does menthol have cooling or anesthetic properties that moderate the harshness of cigarette smoke?**

The evidence is sufficient to conclude that menthol has cooling and anesthetic effects that reduce the harshness of cigarette smoke. Research indicates that menthol acts on both thermal and nociceptive receptors. This dual action results in both cooling and counter-irritant effects. Menthol desensitizes receptors by which nicotine produces irritant effects, thereby, reducing the irritation from nicotine in tobacco smoke.

The implications of these findings are that by reducing the harshness of tobacco smoke menthol could facilitate initiation or early persistence of smoking by youth. Also, by reducing the harshness of smoke, menthol could facilitate deeper and more prolonged inhalation of tobacco smoke, resulting in greater smoke intake per cigarette.

**Does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers?**

The evidence is sufficient to conclude that menthol makes low-tar, low-nicotine cigarettes more acceptable to smokers. Like nicotine, menthol has irritant effects that contribute to the impact or "throat grab," of tobacco smoke. In light or ultralight cigarettes with lower nicotine delivery, menthol can be used to provide impact.

The implications of these findings are that menthol is likely to make low-yield cigarettes more satisfying, and smokers who switch to low-yield cigarettes for health concerns may be more likely to continue to smoke rather than quit.

**Does menthol have an effect on the metabolism of nicotine or tobacco-specific nitrosamines?**

The evidence is sufficient to conclude that it is at least as likely as not that menthol inhibits the metabolism of nicotine in smokers. The evidence in not sufficient to conclude that it is at least as likely as not that menthol inhibits the glucuronidation of NNAL in smokers. Studies using liver micosomes demonstrate that menthol can inhibit the metabolism of nicotine. One experimental within-subject human study, using a state-of-art method of measuring the rate of nicotine metabolism, indicates that menthol cigarette smoking inhibits the metabolism of nicotine by about 10 percent. Menthol could be affecting nicotine metabolism in the lungs, where some nicotine metabolism is known to occur and where menthol concentrations are likely quite high in menthol cigarette smokers. Several cross-sectional studies show menthol has no effect on the nicotine metabolite ratio, a biomarker of the rate of nicotine oxidation. However cross-sectional studies may not have adequate power to detect a 10 percent difference in the metabolite ratio. Given the small magnitude of the menthol effect on nicotine metabolism in the positive human experimental study, it is unlikely that such a metabolic difference would have much, if any, effect on smoking behavior.

Menthol in high concentrations has been shown to inhibit the metabolism of the tobacco-specific nitrosamine, NNAL, in isolated liver preparations. One cross-sectional study found lower ratios of NNAL glucuronide to NNAL in menthol cigarette smokers, but another larger study did not find such an effect. On balance the evidence to date is not sufficient to demonstrate a significant effect. However if menthol does inhibit NNAL metabolism, this could be a basis for higher cancer risk in menthol cigarette smokers.

Menthol is known to enhance the dermal penetration of a variety of drugs, and might in theory enhance the pulmonary absorption of nicotine and/or tobacco carcinogens. The data on menthol and exposure to tobacco toxins is reviewed in chapter 6.

**Is it biologically plausible that menthol enhances the addictiveness of cigarette smoking?**

The evidence is sufficient to conclude that it is biologically plausible that menthol makes cigarette smoking more addictive. The evidence reviewed suggests several mechanisms by which menthol could contribute to the initiation and persistence of cigarette smoking.

- Nicotine is required for the acquisition and maintenance of addiction to cigarette smoking. But as described previously, menthol can modulate nicotine effects and may act directly on nicotinic cholinergic receptors to alter nicotine response.

- While nicotine is required for nicotine addiction, the addictiveness of cigarettes is also influenced by sensory factors (Rose 2006; Henningfield et al. 2011 in press). Menthol provides an unmistakable

- Sensory experiences can contribute to conditioned aspects of smoking behavior. Once drug self-administration has been established, taste and other sensory factors can function as stimuli that can substantially enhance the strength and persistence of drug self-administration (Carroll and Meisch 2011; Panlilio et al. 2005).
- Stimuli associated with drug intake and/or withdrawal can come to evoke craving that promotes resumption of self-administration of the drug after a period of abstinence. Thus, menthol from food or toothpaste could serve as a sensory cue to prompt relapse to smoking. These mechanisms have been demonstrated in a variety of animal and human studies with a variety of addictive drugs (Wilson et al. 2004; Sayette and Griffin 2010).
- Another potentially relevant issue is the relationship between menthol and genetic differences in perception of taste. As noted above, various studies raise the possibility that menthol might interact with genetically determined taste sensitivity to facilitate smoking. Thus, there may be a genetically susceptible population for whom menthol cigarettes facilitate smoking.

## CHAPTER 4: PATTERNS OF MENTHOL CIGARETTE SMOKING

### INTRODUCTION

Chapter 4 summarizes recent national survey findings on patterns and trends of menthol cigarette use, providing a background for subsequent chapters on marketing (chapter 5) and initiation, dependence and cessation (chapter 6). In keeping with TPSAC's charge, this chapter gives particular attention to menthol cigarette use in special populations including adolescents, African Americans, Hispanics and other racial or ethnic minorities. This chapter also addresses the prevalence of menthol cigarette use in the generally population of smokers and provides some historical context to help understand the current demographics of menthol cigarette use. The trajectories of brands and use patterns over time are relevant to understanding current consumption patterns.

In order for the TPSAC to reach conclusions about the public health impact of menthol cigarettes and to make evidence-based recommendations to the FDA, TPSAC carefully considered the patterns and trends of menthol cigarette smoking. The first chapter of this report presented nine questions relevant to the TPSAC discussion of the public health impact of menthol cigarettes; seven questions are related to individual smokers and two are related to the population effects of smoking. The information and analysis presented in this chapter are particularly relevant to the following population-level questions:

- Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

### EARLY MENTHOL CIGARETTE USE

The invention of menthol cigarettes is generally credited to Lloyd "Spud" Hughes. In the 1920s, the Ohio smoker stored his tobacco in a tin with the menthol crystals he used to treat a persistent cold. He discovered that the tobacco absorbed the menthol flavor, which made the cigarettes easier to smoke. He started a menthol cigarette company, and his product spurred imitators. In the decades since, menthol cigarettes have grown to become an important product in the U.S. cigarette market. Today, approximately 25 percent of cigarette smokers use menthol cigarettes.

The development and use of menthol cigarettes in the U.S. is well-documented in scholarly articles and books, such as "Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris" (Alfred A. Knopf 1997) by Richard Kluger and "The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America" (Basic Books 2007) by Allan M. Brandt. In preparing this chapter, TPSAC relied on "The Growth of Menthols 1933–1977," a 1978 report produced for Brown & Williamson by Market Science Associates (MSA), and "Menthol Review and Product Implications" (bates # 2044123054), which covers the period 1985–89. These two tobacco industry documents provide

information on menthol cigarette use before 2000, a period not covered by the data sets and surveys discussed in the methods section of this chapter.

The “Growth of Menthols” report describes the salient trends in menthol cigarette development and use during four distinct time periods from 1933–1977. A summary of each period follows, based on this report.

The first period, from 1933–1955, begins with Hughes’ accidental invention of menthol cigarettes. The company he founded started selling Spud brand cigarettes. By 1932, Spud, which no longer exists, was the fifth best-selling cigarette brand in the country, behind non-menthol brands Lucky Strike, Camels, Chesterfield and Old Gold. In 1933, Brown & Williamson introduced Kool, and by 1935, the brand captured 2.2 percent of the U.S. cigarette market. From the beginning, Kool had a therapeutic image. The brand was promoted as an alternative to the heavy, harsh-tasting experience of some non-menthol cigarettes, or for use during the winter months when lower indoor humidity was thought to contribute to dry throats. Kool marketing campaigns included, “For occasional use—Kool for a change,” “In between the others, rest your throat with Kools,” and “Switch to Kools from Hots.”

In 1942, the Federal Trade Commission filed a suit and won a judgment against Brown & Williamson for false advertising related to the purported “health benefits” of Kool. By 1943, the brand’s market share had fallen to 1.55 percent. To address this decline, Brown & Williamson brought out Willie the Penguin in 1947 as a “spokesanimal” for the ice-cool nature of the brand and by 1949 Kool’s market share had climbed to 2.2 percent. In June, 1950, the landmark Reader’s Digest article, “How Harmful Are Cigarettes?” reported on the potential health hazards of cigarettes. Nonetheless, Kool’s market share rose to 2.6 percent. By 1952, Kool claimed approximately a 3 percent market share. With introduction of a king-size version in 1954, Kool’s share edged up to 3.4 percent. The MSA report summarized Kool’s early history as follows:

> “This quasi-medical appeal, and the increased advertising, while effective in increasing its market share, also retained and reinforced the Kools' image as a specialty product appealing to that special segment that wished to avoid "throat dryness" or wished to "rest their throat "from "hot" cigarettes.” (MSA).

The second period, from 1956–1962, is described as “The Rise of Salem.” R.J. Reynolds Tobacco Co. introduced Salem, the first menthol cigarette with a filter, in 1956. Salem had less menthol taste but more tobacco taste and tar delivery than Kool. According to the MSA report, reaction was phenomenal and within the year, Salem’s share of market had caught up to Kool’s. Salem’s advertising positioned the brand as “a new idea in smoking,” with a rich tobacco taste and menthol-fresh comfort. Salem had more burley tobacco but was only slightly flavored with menthol so the tobacco taste would not be masked. Its advertising was keyed to light, refreshing springtime smoking— “*refreshing as all outdoors*” was the slogan. Newport cigarettes also were introduced during this period but did not garner a noticeable market share. A 1956 product comparison found that Newport was a “very light” product. It lacked tobacco taste and had much less tar and nicotine compared to Salem and Kool.

In four years, annual sales of Salem rose to $35 billion in 1960 from $4 billion in 1956, giving the brand 7.5 percent of the cigarette market, far exceeding the market share of Kool. Thanks

largely to Salem, menthol cigarette sales grew to account for 11 percent of the total U.S. cigarette market. With the success of Salem, menthol cigarettes evolved from a specialty product into a large, successful category.

During third period covered by the MSA report, from 1963–1974, Kool overtook Salem to re-establish itself as the menthol market leader, in part by capitalizing on its existing popularity with young adults and African Americans. In 1963, Kool already was the preferred cigarette of young smokers. Brown & Williamson saw the increasing number of marijuana users aged 12–17 (who seemed to prefer menthol cigarettes) as a potential market, according to the report. At the same time, Kool, already popular with African Americans, rapidly became the most popular cigarette within that racial group, in part due to advertising and promotions aimed at them. Data on African American smokers age 16 and over in 10 metropolitan areas showed that menthol cigarette use went from 14 percent in 1968 to 38 percent in 1975 before dropping slightly to 33 percent in 1977. Kool accounted for 60 percent of the menthol cigarette market among African Americans under age 35. The report estimates that 70 percent of the Kool's total 4-point share gain between 1968 and 1974 came from the gains among African Americans. Other surveys cited in the report indicated that Kool was making inroads with younger smokers. Kool's share of 16–25 year old smokers advanced from 3 percent in 1966 to about 16 percent in 1974. The report stated:

> "Kool is facing new risks at both ends of the age spectrum. It is attempting to stem the outflow to low tars (among older users) by offering lower tar line extensions. Simultaneously, programs capable of strengthening Kool's image among the new generation of starters, particularly blacks, are critical to maintaining Kool's overall market position."

Between 1964 and 1971, the number of menthol brands and sub-brands more than doubled from nine to 23. Newport's growth trend got underway in 1973, driven by its "Alive With Pleasure" campaign, which continued into the 1980s. The final period covered in the MSA report marks the growth of low-tar menthol cigarettes from 1975-1977.

By 1976 and through 1988, menthol cigarettes accounted for 28–29 percent of the overall cigarette market, according to Federal Trade Commission reports. Newport emerged as the best-selling menthol cigarette brand in 1993. Although Marlboro Menthols were introduced in 1965, they did not become popular until the mid-1990s. In 2003, Marlboro Menthols were the second-leading menthol brand behind Newport, with 5.4 percent of the total cigarette market.

"Menthol Review and New Product Implications," a Feb. 6, 1990 report produced for Philip Morris by the Leo Burnett Company (bates # 2044123055), examined menthol cigarette use patterns from 1985 to 1989. The report documents that menthol smoking among certain populations was well-established. It provided this description of menthol cigarette smokers in 1989: "Compared to non-menthol smokers, menthol smokers are likely to be female, black, younger and city dwellers." Reviewing the five-year trend from 1985 to 1989, the report noted that menthol cigarette smokers had become more African American, Spanish-speaking, older, wealthier, and more rural. The following chart summarized menthol smoking among different populations using the industry method of "indexing" menthol use to a standard of 100. A number under 90 indicates less menthol use among the identified group while a number over 120 means signals more menthol cigarette use among the identified group.

**Table 1: Index of Menthol Smokers 1988-89**

| Demographic | Index Menthol Vs. Non-Menthol<br>12 Months Ending 6/89 |
|---|---|
| Male | 77 |
| Female | 126 |
| White | 82 |
| Black | 633 |
| Spanish - speaking | 150 |
| 18-34 | 115 |
| 35+ | 90 |
| Under $30 | 102 |
| $30+ | 100 |
| No College | 95 |
| Any College | 88 |

**Source: Menthol Review and New Product Implications, 1990**

In 1989, the three top menthols have strikingly different profiles. Salem smokers were more female, older, educated and rural; Kool smokers were more male, and Newport smokers were black, young, urban, and less affluent and less educated than smokers of competing brands

**METHODS**

TPSAC searched PubMed for studies that quantitatively assessed patterns of menthol cigarette use within and among U.S. demographic groups. The search terms were "menthol cigarettes" [MeSH Terms] OR "cigarettes"[All Fields] OR "menthol" [All Fields] and "patterns "[All Fields]. The search yielded 11 potentially relevant references. TPSAC reviewed key information from each report, including the year of data collection, study methods, population sampled, the geographic region studied, smoking behavior, demographic variables and a summary of the methods. Reports were selected for inclusion if they directly compared patterns of menthol cigarette smoking among U.S. demographic groups. Manuscripts were excluded if they did not include patterns of menthol cigarettes in the U.S. population. Articles were also excluded if they were opinion pieces, policy statements, or review articles. Only articles from peer-reviewed journals were considered.

**Evidence evaluation**

***Primary sources***

TPSAC selected reports based on one or more of three primary data sources: the National Survey on Drug Use and Health (NSDUH), the Tobacco Use Supplements to the Current Population Survey (TUS-CPS), and the National Youth Tobacco Survey (NYTS). These three primary sources are described below.

NSDUH is a household survey which collects information on the U.S. civilian, non-institutionalized population aged 12 years and older. NSDUH had more than 68,000

respondents in 2008. NSDUH includes two questions that are relevant to cigarette use. The two questions read: *On the one day you smoked cigarettes during the past 30 days, how many cigarettes did you smoke? Were the cigarettes you smoked during the past 30 days menthol*? Prior to 2004, this question was worded differently. Thus TPSAC reviewed NSDUH data from 2004 to 2008 only. The NSDUH survey also asked about the specific brand that respondents smoked in the past 30 days. However, the responses to that question cannot be used to accurately track menthol cigarette use; many brands have menthol and non-menthol sub-brands but details about sub-brands are not collected in the survey. A description of menthol definitions for NSDUH and other surveys are described in table 2 below.

TUS CPS is cross-sectional data from 2003 and 2006/07. The data includes adult smokers (at least 18 years old) (*n* = 69,193). The CPS, administered by the U.S .Census Bureau, uses a multistage probability design to collect data from about 50,000 families monthly. This data, obtained in person or through computer-assisted telephone interviews, are used to produce reliable national and state estimates on labor force characteristics among the civilian, non-institutionalized U.S. population. The TUS is a supplement conducted with the CPS every two to three years to collect data on tobacco use, quitting behaviors, nicotine addiction and related attitudes and practices. The 2003 and 2006/2007 TUS CPS included one question that is relevant to cigarette use. The question reads*, Is your usual cigarette brand menthol or non-menthol?*

NYTS is an anonymous school-based survey that used a three-stage cluster sample design that oversampled African-American, Hispanic, and Asian students. NYTS was administered to 27,038 students Grades 6–12 in spring 2006. This survey was conducted among youth who had smoked in the past 30 days, had a usual cigarette brand, and could identify their usual brand as menthol or non-menthol. TPSAC's analysis was conducted among likely menthol smokers—those who said they smoked menthol cigarettes and identified a menthol brand (e.g., Kool) as their usual product.

**Table 2: Measurement of menthol cigarette smoking**

| Study | Survey | Definition of menthol cigarette smoking | Related survey question(s) |
|---|---|---|---|
| Lawrence et al. 2010 | TUS CPS | Respondents reported the status of their usual cigarette smoked as menthol or nonmenthol | Is your usual cigarette brand menthol or non-menthol? |
| Rock et al. 2010 | NSDUH | Respondents reported smoking part or all of a menthol cigarette in the past 30 days | Were the cigarettes you smoked during the past 30 days menthol? |
| FDA presentation (Ralph S. Caraballo) | NSDUH | Cigarettes smoked in the past 30 days were menthol | Were the cigarettes you smoked during the past 30 days menthol? |

| | | | |
|---|---|---|---|
| Hersey et al. 2010 | NYTS | Based on consistency between smokers' report of the brand and the menthol status of the cigarettes they usually smoked. | Is the brand of cigarettes that you usually smoked during the past 30 days, menthol or non-menthol? |

***Selected reports***

Based on the above criteria, TPSAC selected four data sets and the associated reports for inclusion in this chapter. They are NSDUH itself; Hersey et al. 2010; Lawrence et al. 2010; and Giovino et al. 2004; 2009. TPSAC also drew from a presentation given by Ralph S. Caraballo (Office of Smoking and Health, CDC) at the FDA Tobacco Products Scientific Advisory Committee meeting on March 30, 2010. This presentation included an in-depth analysis of NSDUH. All journal articles and the presentation selected for review included nationally representative data**.** These publications provide a national picture of demographic patterns of menthol cigarette use Table 4 provides more detail on the selected reports.

**Limitations of the data**

One methodological concern is the possibility that both youth and adult smokers may misreport menthol cigarette use. This issue has been discussed in the scientific literature; the Giovino et al. (2004), for example, found that 7.9 percent of smokers age 12 and older who said they mostly smoked Kool, Newport or another menthol brand also reported they did not smoke menthol cigarettes. Conversely, Giovino et al. found that 4.2 percent of those who smoked brands that are only available in non-menthol form (e.g., Winston) said they smoked menthol cigarettes. According to Giovino et al., discrepancies in self-reported menthol cigarette use were higher for adolescent smokers aged 12 to 17 years than for adult smokers, although the 2004 paper does not provide specific data on this issue. TPSAC concludes that these discrepancies, over the time span considered, do not affect its trend analysis.

A second limitation is that TPSAC's primary sources—NSDUH, TUS CPS and NYTS—are cross-sectional annual surveys, i.e., data are collected at only a single point in time from the respondents. We have limited longitudinal data that track how smoking changes in specific individuals over time. Thus, our analyses of trends are at the population level.

Curtin et al. (submission to the FDA, June 2010) from R.J. Reynolds criticized the NSDUH data. They said the NSDUH question— *Were the cigarettes you smoked during the past 30 days menthol*?—was not specific enough to identify smokers whose usual cigarette was menthol (i.e., the question could capture non-menthol cigarette smokers who smoked one menthol cigarette). To address this, Curtain et al. reanalyzed data from a number of different surveys: National Health and Nutrition Surveys (NHANES; 2005/06, 2007/08), National Health Interview Survey (NHIS; 2005); NSDUH (2007); National Youth Tobacco Survey (NYTS, 2006). These surveys defined current smokers as those who had smoked on 10 or more of the last 30 days. Menthol use among current smokers was defined as usual cigarettes, usual brand, or usual brand smoked during the last 30 days for NHANES, NHIS, NYTS respectively. Based on these definitions, no differences were found in the rate of menthol cigarette use across the different age spectrum for the NHANES and NHIS surveys. The NYTS and NSDUH surveys showed a trend toward decreasing menthol cigarette use with increasing age.

Giovino (unpublished FDA submission 2010) presented data as a public comment that provided clarification on the NSDUH question regarding whether menthol cigarettes were smoked during the past 30 days. He noted that the question that eventually assessed menthol vs. non-menthol cigarette use status was preceded by a question regarding the brand of cigarettes that was smoked most often in the last 30 days. Once this inquiry was made, then subjects were asked if the brand of cigarettes smoked during the past 30 days was menthol. Using cross-sectional NSDUH data from 2004 to 2008 and based on the definition of use of menthol in the past 30 days, and making corrections for misclassifications (e.g., reporting Newport cigarettes as non-menthol cigarettes), he observed a statistically significant age gradient across smokers 12–17 years old (49.3 percent), 18–25 years old (37.5 percent) and 26–34 years old (29.9 percent), replicating the main findings from Rock et al. (2010). (See tables 2 and 4; also chapter 6).

**PREVALENCE OF MENTHOL CIGARETTE SMOKING**

There are approximately 19.2 million menthol cigarette smokers in the U.S. (Caraballo 2010). Of this group, 18.1 million are adults ages 18 years or older. The remaining 1.3 million menthol smokers—nearly 6 percent of the total—are adolescents ages 12 to 17 (see Figures 1 & 2).

As a group, menthol smokers account for between 28 percent and 34 percent of all U.S. cigarette smokers, depending on the data used (Lawrence et al. 2010; NSDUH 2009). Detailed demographic information about menthol cigarette smokers is presented below. In keeping with TPSAC's charge, this information focuses on children, adolescents, African Americans, Hispanics and other racial and/or ethnic minorities.

**Adolescents**

Adolescents 12 to 17 years of age smoke menthol cigarettes at a higher rate than any other age group (NSDUH 2009). Among adolescent smokers, 49.9 percent of those in middle school and 44.9 percent of those in high school report that they usually smoke a menthol cigarette brand (Caraballo and Asman, white paper).

Rates of menthol cigarette smoking are higher among established middle school smokers—those who have smoked cigarettes for at least one year—than among novice middle school smokers. According to Hersey et al., where they analyzed the NYTS 54.7 percent of established middle school smokers and 42.2 percent of novice middle school smokers usually smoke menthol cigarettes.

With regard to high school smokers, experienced and novice smokers use menthol cigarettes in roughly the same proportion; 43.1 percent of established high school smokers and 42.8 percent of new high school smokers say they usually smoke menthol cigarettes (Hersey et al. 2010).

Data from the TUS CPS, which does not survey people under 18, show that menthol smoking prevalence is highest among 18–24 year olds—an additional indication that menthol cigarettes are particularly popular among younger smokers (Lawrence et al. 2010).

**Race and ethnicity**

The prevalence of menthol cigarette smoking is highest among African Americans across all socio-demographic and smoking-related categories, whether stratified by income, age, gender,

marital status, region, education, age of initiation, and length of time smoking (NSDUH 2009; Lawrence et al. 2010).

Menthol cigarette use is particularly high among minority youth ages 12 to 17, according to an analysis of NYTS data by Hersey et al. The NYTS classifies smokers as "likely menthol cigarette smokers" based on their answers to questions that ask them to identify their brand and to state whether they usually smoke menthol.

**Figure 1: Percent of menthol cigarette use among past month cigarette smokers: 2004-2008, NSDUH**

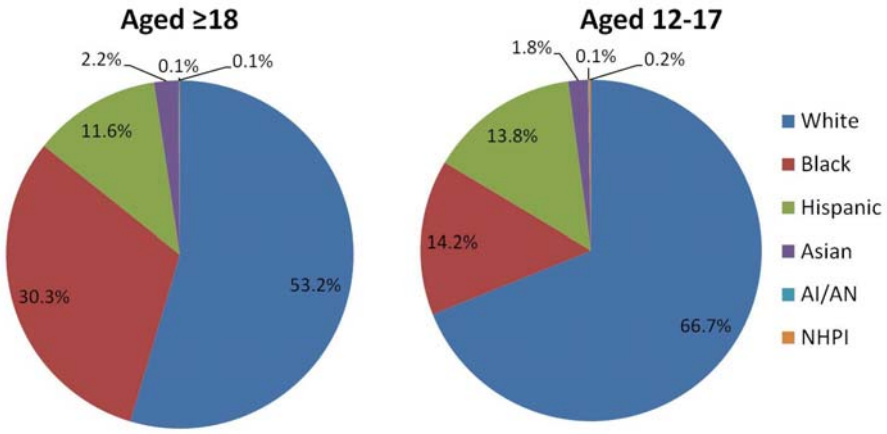
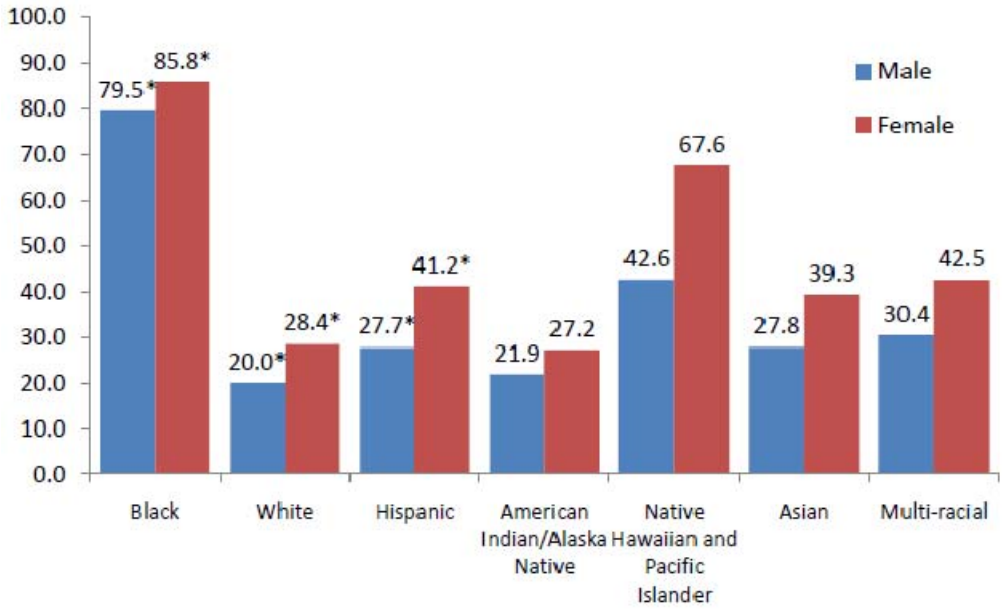



**Figure 2: Percent menthol cigarette use among past month cigarette smokers aged 12 and older by race/ethnicity: 2004-2008, NSDUH**




The respondents in this survey are identified as menthol smokers if they report that they smoke menthol cigarettes and they also report using a specific menthol brand (e.g., Newport). The

answers to these two questions must be consistent in order for respondents to be classified correctly with certainty.

According to this definition, 80.6 percent of African American middle school smokers and 84.8 percent of African American high school smokers regularly smoke menthol cigarettes. Among Hispanics, 57.9 percent of middle school smokers and 56.4 percent of high school smokers reported smoking menthol cigarettes. In Asian Americans a menthol brand is used by 57.4 percent of middle school smokers and 43.6 percent of high school smokers (Hersey et al. 2010; see table 3). Menthol cigarettes were used less among non-Hispanic white youths; in this demographic, 43.1 percent of middle school smokers and 37.6 percent of high school smokers said they regularly smoked menthol cigarettes (Hersey et al. 2010).

The prevalence of menthol cigarette smoking varied for each racial/ethnic group by region (Lawrence et al. 2010). Rates of menthol cigarette use among white, Hispanic and American Indian/Alaska Native smokers are highest in the Northeast. For African American smokers, the rate of menthol smoking is highest in the Midwest. For Asian and Pacific Islander smokers, the prevalence of menthol cigarette smoking is highest in the West. Menthol cigarette smoking is significantly higher in metropolitan areas for all racial and ethnic groups except American Indians/Alaska Natives and Asian and Pacific Islanders.

**Table 3. Percentage of Youth Smokers Who Used a Menthol Brand of Cigarettes in Middle School and High School**

| **Subgroup** | **All current smokers** | |
|---|---|---|
| | **Middle school (*n* = 771)** | **High school (*n* = 2,510)** |
| All youth smokers | 51.7 (45.8–57.5) | 43.1 (37.0–49.1) |
| Male | 55.1 (43.9–54.7) | 39.4 (33.6–45.2) |
| Female | 48.1 (28.1–51.6) | 46.9 (38.9–54.9) |
| Less than 1 year | 42.2 (29.8–54.7) | 42.8 (34.5–51.2) |
| 1 year or more | 54.7 (48.2–61.3) | 43.1 (36.6–49.6) |
| African-American | 80.6 (72.0–89.3) | 84.8 (77.3–92.3) |
| Asian American | 57.4 (27.7–87.1) | 43.6 (24.3–63.0) |
| Hispanic | 57.9 (48.8–67.0) | 56.4 (48.7–64.2) |
| White (non-Hispanic) | 43.1 (36.2–50.0) | 37.6 (31.0–44.3) |
| Youth who are current smokers with either a menthol or a non-menthol brands | 6.3 (5.1–7.5) | 19.7 (18.1–21.4) |

**Source: NYTS 2006**

### Gender

Women are more likely to smoke menthol cigarettes than men (NSDUH 2009). This pattern is seen across all racial/ethnic groups except among American Indians/Alaskan Natives; in that group, men are more likely to smoke menthol cigarettes (NSDUH 2009; Lawrence et al. 2010).

### People with mental illness

While smoking prevalence is high among people with mental illness (Lasser et al. 2000), there are no peer-reviewed journal articles on menthol cigarette in this vulnerable group.

## TRENDS IN MENTHOL CIGARETTE USE

### Trends by age

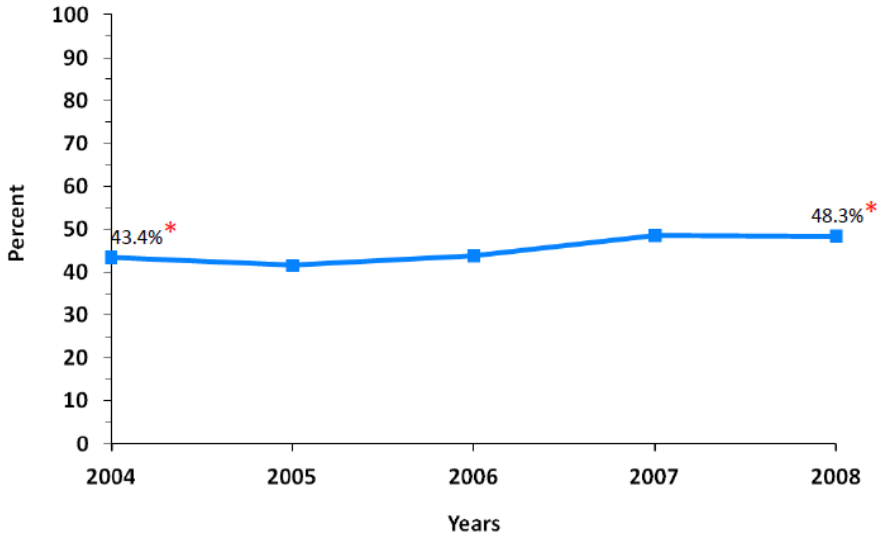
#### *Adolescent smokers*

According to the NSDUH data, among all past month smokers 12 to 17 years of age, the proportion of menthol cigarette smokers rose to 48.3 percent in 2008 from 43.4 percent in 2004—a statistically significant 11 percent increase over four years (see Figure. 3). Driving this increase was a jump in menthol cigarette use among white adolescent smokers, the only racial/ethnic group to show a statistically significant increase over this period.

#### *Adult smokers*

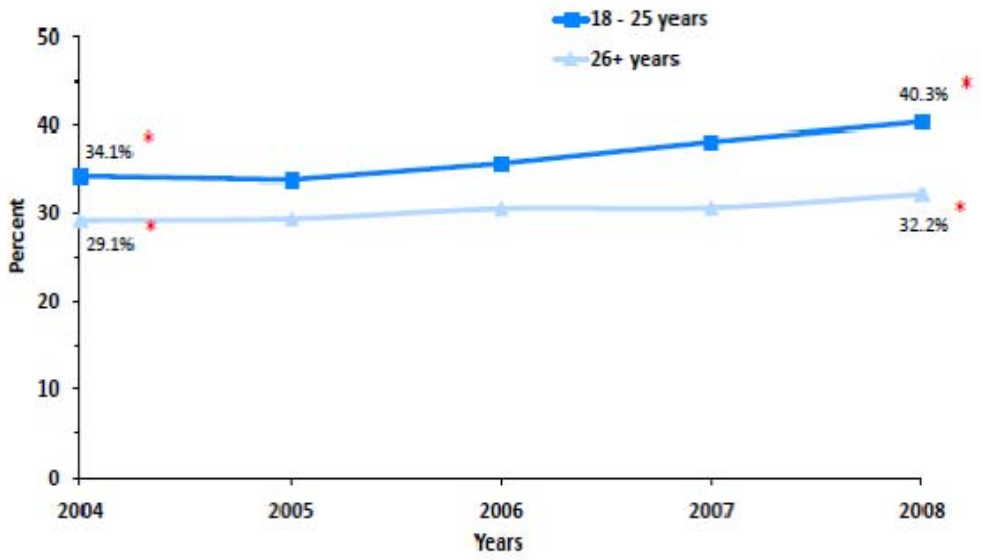
Among all past month adult smokers, the proportion of menthol cigarette smokers rose to 33.8 percent in 2008 from 30.2 percent in 2004—a 13 percent increase over four years (NSDUH 2009; see Figure 4). The increase was particularly sharp among young adults. The proportion of smokers aged 18 to 25 years who smoked menthol cigarettes rose to 40.3 percent in 2008 from 34.1 percent in 2004—a statistically significant 17 percent jump. Among smokers aged 26 years and older, the proportion who smoked menthol cigarettes rose to 32.2 percent in 2008 from 29.1 percent in 2004—an increase of 10 percent.

**Figure 3: Trends in menthol cigarette use among past month smokers aged 12-17 years: 2004-2008**




Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

**Figure 4: Trends in menthol cigarette use among past month adult smokers, by age group: 2004-2008**



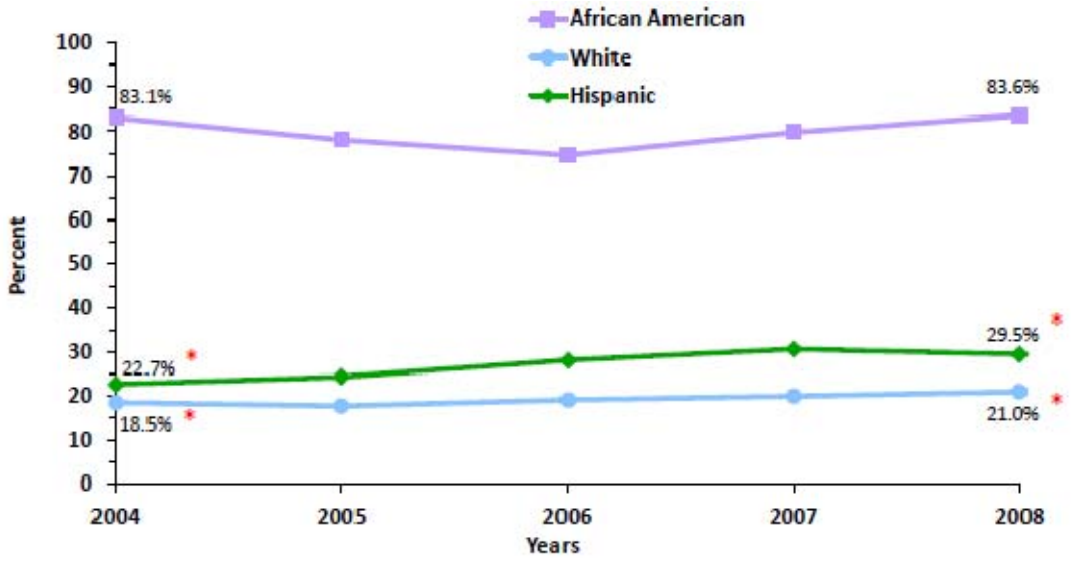

Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

**Trends by gender**

***Men***

The proportion of male cigarette smokers aged 12 years or older who smoked menthol cigarettes increased to 30.8 percent in 2008 from 26.9 percent in 2004, a statistically significant gain (NSDUH 2009). Statistically significant increases in past-month menthol cigarette use were observed among white and Hispanic male smokers aged 18 and older, according to NSDUH data. The proportion of white adult male past-month cigarette smokers who smoked menthol cigarettes increased to 21 percent in 2008 from 18.5 percent in 2004. The proportion of Hispanic adult male past-month cigarette smokers who smoked menthol cigarettes increased to 29.5 percent in 2008 from 22.7 percent in 2004.The proportion of African American adult male past-month cigarette smokers who smoked menthol cigarettes did not change, standing at 83 percent in both 2004 and 2008 (see Figure 5).

**Figure 5: Trends in menthol cigarette use among African American, White, and Hispanic men aged ≥ 18 years: 2004-2008**

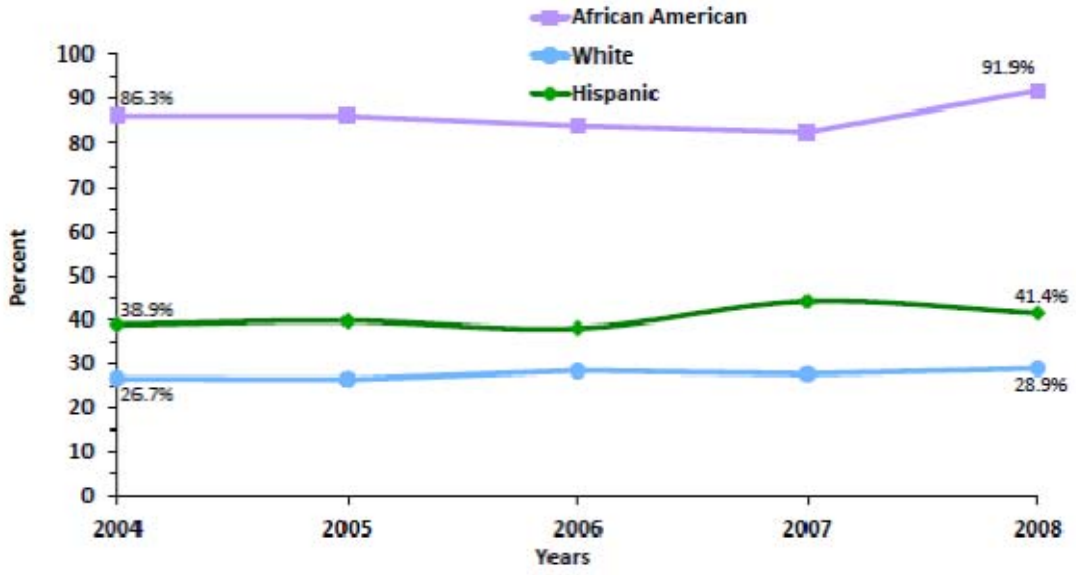



Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

***Women***

Although the proportion of adolescent and adult female smokers who smoked menthol cigarettes increased between 2004 and 2008, the changes were not statistically significant in any age or racial/ethnic category examined (NSDUH 2009; Caraballo 2010). The proportion of female cigarette smokers age 12 and older who smoked menthol cigarettes rose to 37.5 percent in 2008 from 35.9 percent in 2004. Among adult female African American smokers, the proportion of menthol smokers rose to 91.9 percent in 2008 from 86.3 percent in 2004. Among adult female white and Hispanic smokers, the proportion who smoked menthol cigarettes rose to 28.9 percent from 26.7 percent and to 41.4 percent from 38.9 percent, respectively, over the same period (Figure 6).

**Figure 6: Trends in menthol cigarette use among African American, White, and Hispanic women aged ≥ 18 years: 2004-2008**

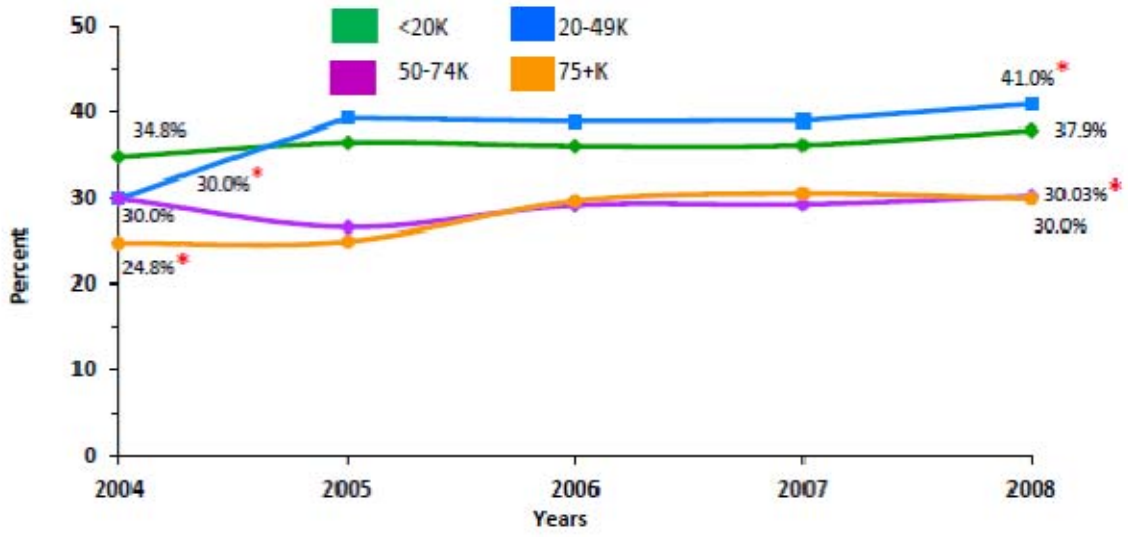



Source: National Surveys on Drug Use & Health, 2004-2008

**Trends by income**

Between 2004 and 2008, there were increases in the proportion of adult smokers who smoked menthol cigarettes among families with smokers and incomes between $20,000 and $49,999 and of $75,000 or more (see Figure 7).

**Figure 7: Trends in menthol cigarette use among past month smokers aged ≥ 18 years, by family income: 2004-2008**




Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

**SUMMARY**

Based primarily on three national data sets on smoking, the review in this chapter demonstrates that menthol cigarette use is high among women and the special populations relevant to TPSAC's charge—ethnic/racial minorities, including African-Americans and Hispanics, and adolescents. Specifically, TPSAC finds:

- Menthol cigarette use is very high among minority youth. More than 80 percent of adolescent African American smokers and more than half of adolescent Hispanic smokers use menthol cigarettes. Menthol cigarettes are used by more than half of Asian American middle-school smokers.

- Use of menthol cigarettes is rising among adolescents, driven by a significant increase in the number of white youth ages 12–17 who are smoking menthol cigarettes. Trend data also shows a significant increase in menthol cigarette use among young adult smokers and white and Hispanic men.

- The review of these national data sets also shows that menthol use is prevalent among the unemployed, people with an annual family income of less than $10,000 and people who never married.

| Table 4: Studies of Patterns of Menthol Cigarette Smoking | | | | |
|---|---|---|---|---|
| | **Study Periods** | **Population** | **Key Results** | **Limitations** |
| Lawrence et al. 2010 | 2003 and 2006/07 TUS CPS | Adult current smokers (*n* = 63,193) | African-American smokers were 10–11 times more likely to smoke mentholated cigarettes than white smokers men: odds ratio (OR): 11.59, 99% confidence interval (CI): 9.79–13.72; women: OR: 10.12, 99% CI: 8.45–12.11).<br><br>With the exception of American Indian / Aleut/ Eskimo smokers, non-white smokers were significantly more likely to smoke mentholated cigarettes than were white smokers.<br><br>Additional significant factors associated with mentholated cigarette smoking included being unmarried (never married: OR: 1.21, 99% CI: 1.09–1.34; divorced/separated: OR: 1.13, 99% CI: 1.03–1.23), being born in a US territory (OR: 2.01, 99% CI: 1.35–3.01), living in a non-metropolitan area (OR: 0.87, 99% CI: 0.80–0.96), being unemployed (OR: 1.24, 99% CI: 1.06–1.44) and lower levels of education.<br><br>Race/ethnicity-stratified analyses showed that women were more likely than men to smoke mentholated cigarettes.<br>Among African-American smokers, young adults (aged 18–24 years) were four times more likely to smoke mentholated cigarettes compared with individuals aged 65+ | Cross-sectional study<br>Small sample sizes for the AI/AN and API |
| National Survey on Drug Use and Health | 2004 to 2008 | Persons aged 12 or older (n =68,736) | Among past month smokers, the rate of smoking menthol cigarettes increased from 31.0 percent in 2004 to 33.9 percent in 2008; increases were most pronounced for adolescents aged 12 to 17 (43.5 percent in 2004 vs. 47.7 percent in 2008), young adults aged 18 to 25 (34.1 vs. 40.8 percent), and males (26.9 vs. 30.8 percent).<br><br>Past month smoking of menthol cigarettes was more likely among those who were recent smoking initiates (i.e., began smoking in the past year) than among those who were longer term smokers (i.e., initiated use more than a year ago) (44.6 vs. 1.8 percent, respectively); this pattern was consistent for persons aged 12 to 17 and those aged 18 to 25, for both genders, and for whites and Hispanics.<br>For African-Americans, past month use of menthol cigarettes was less likely among past month smokers who were recent smoking initiates than among their counterparts who were longer term smokers (73.9 vs. 82.8 percent). | Cross-sectional study |

| Table 4: Studies of Patterns of Menthol Cigarette Smoking | | | | |
|---|---|---|---|---|
| **Study** | **Study Periods** | **Population** | **Key Results** | **Limitations** |
| Giovino et al. 2003 | 1999 National Household Survey (NHS)<br><br>1998,99, 2000 Monitoring the Future (MtF)<br><br>2000 National Youth Tobacco Survey (NYTS)<br><br>2002 International Tobacco Control Policy Evaluation Survey (ITCPES) | 12 and older<br><br>(n= 71,764)<br><br>8th, 10th, and 12th graders<br><br>(n= 136,000)<br><br>middle and high school students (n= 35,838)<br><br>18 and older ever smokers (n=2500) | NHS and NYTS both confirm that Newport is the far leading brand among African-American adolescents.<br><br>Among African-American smokers more than three-fourths of the adolescents ages (12-17 yrs) and young adults (18-25 yrs old) used Newport<br><br>Baseline data from the ITCPES indicated that among adult smokers, females were more likely than males to use mentholated brands in the US (31.8% vs 22.1%) | Misclassification of self reported menthol status<br><br>Cross-sectional study |
| FDA Presentation (Ralph S. Caraballo) | 2004-2008 NSDUH Survey | 12 years old and older (n=68,000) | Total of 19.2 million menthol cigarette smokers<br><br>Among smokers aged 12-17 years, 1.1 million menthol smokers<br><br>Among smokers aged 18 and older. 18.1 million menthol smokers<br><br>African-American smokers are far more likely to smoke menthol cigarettes than smokers of other US racial and ethnic groups<br><br>7 of 10 African-American adolescent smokers reported smoking menthol cigarettes followed by about half of multirace and Asian smokers.<br><br>8 of 10 African-American adult smokers reported smoking menthol cigarettes followed by about half Native Hawaiian and other Pacific Islander adult smokers.<br>Female smokers more likely to smoke menthol cigarettes than male smokers. | Cross-sectional study<br>Accuracy for self-reporting smoking methanol cigarettes |
| Hersey et al. 2010 | 2006 National Youth Tobacco Survey | Grades 6th- 12th<br>N= 27,038 | 51.7% (95% *CI*: 45.8–57.5) of middle school smokers and 43.1% (95% C.I.: 37.0, 49.1) of high school smokers reported that they usually smoked a menthol brand of cigarettes, | Misclassification of self reported menthol status<br>Cross-sectional study |

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## CHAPTER 5: MARKETING AND CONSUMER PERCEPTION

### INTRODUCTION

This chapter is concerned with addressing the question as to whether tobacco company marketing of menthol cigarettes increases the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available, and if this is the case in subgroups within the population. Accordingly, chapter 5 reviews menthol cigarette marketing strategies, against the background of broader tobacco marketing strategies and with reference to general marketing principles. In addition, this chapter examines consumer beliefs relevant to menthol cigarettes.

Specifically, Chapter 5 will address the following questions:

- How is menthol marketing different from and similar to non-menthol marketing, in terms of product, place, price, promotion and packaging?
- What health reassurance messages were/are used in menthol marketing messages?
- What other messages were/are conveyed to potential consumers by menthol marketing messages?
- Who are the target populations for menthol marketing? Is there evidence to show that youth, women, and specific racial/ethnic groups were targeted?
- Does menthol marketing influence the perceived taste and/or sensory experience of menthol cigarettes?
- Do consumers perceive menthol cigarettes as safer or less harmful than non-menthol cigarettes?

Chapter 4 contains additional information on the history of menthol cigarette marketing.

### METHODS

Chapter 2 provided the general framework for the report and the Tobacco Products Scientific Advisory Committee's (TPSAC) approach to gathering, reviewing and weighing evidence. Using this approach, chapter 5 drew on peer-reviewed papers and government reports; white papers and analyses either written or commissioned by the FDA; tobacco company presentations and written submissions; and public presentations and comments to TPSAC that provided data relevant to the topic at hand.

**HOW IS MENTHOL MARKETING DIFFERENT FROM AND SIMILAR TO NON-MENTHOL MARKETING, IN TERMS OF PRODUCT, PLACE, PRICE, PROMOTION AND PACKAGING?**

This section addresses similarities and differences between menthol and non-menthol marketing. The studies and reports were organized according to the elements that make up the tobacco marketing mix. Like the marketing of other products, cigarette marketing strategy typically involves specifying a target audience and establishing an appropriate marketing mix known as the "4P's," involving product, place, price, and promotion (NCI 2008). *Product* refers to brand name and variety, as well as more tangible physical aspects of functionality. *Place* refers to where tobacco products are sold and their availability to consumers. *Price* includes wholesale and retail pricing, and other discount strategies. *Promotion* includes advertising in traditional and non-traditional media, as well as sponsorship, sampling, direct marketing and other strategies. A fifth "P" – packaging – is sometimes added in more recent formulations of the 4P's model, although packaging can also be included either as part of Product or Promotion.

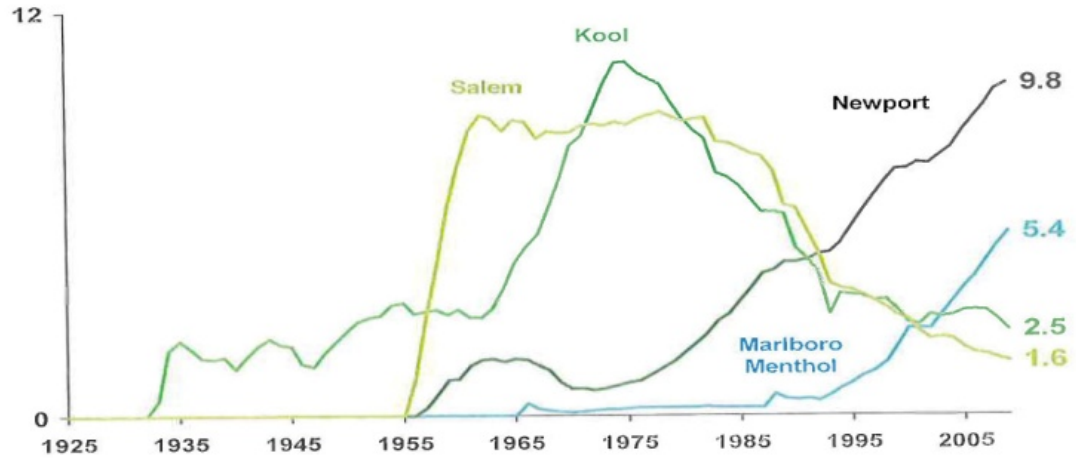
**Product**

Menthol cigarettes accounted for 27 percent of all cigarettes sold in the U.S. in 2009 (Altria Client Services, July, 2010; Graves/R.J. Reynolds Tobacco Co. , July, 2010). According to the Federal Trade Commission's Cigarette Report for 2006 (the most recent available), menthol market share increased from 16 percent in 1963 to 27 percent in 2005 of all cigarette sales, then decreased to 20 percent in 2006 (Federal Trade Commission 2009). However, this drop in market share was not reflected in the data that tobacco companies provided to FDA. Menthol market share has been increasing since 2005, and the current share is as high as it has been since the 1980s. These patterns were reported in submissions from the three major tobacco companies, Altria (manufacturer of Marlboro), R.J. Reynolds Tobacco Company (manufacturer of Kool, Salem, and Camel), and Lorillard (manufacturer of Newport). The prevalence surveys reviewed in chapter 4 also reflect increasing preference for menthol cigarettes among smokers.

Loomis (Oct 2010) described sales trends using AC Nielsen scanner data that were collected between August 2008 and July 2010 from convenience stores and a combination of food retailers, drug stores, and mass merchandisers. Consistent with the industry's reports, the percent of total sales for menthol cigarettes increased slightly, to 27.0 percent from 25.1 percent in convenience stores and to 25.7 percent from 24.5 percent in the combined channel. Approximately 80 percent of 195 different brand families featured at least one menthol variety. Menthol varieties accounted for 36.5 percent of the 1,401 varieties of cigarettes sold.

There are more than 350 different varieties of menthol cigarettes (R.J. Reynolds Tobacco Company, July, 2010), but five brand families accounted for 20.6 percent of total market share in 2009 (Altria Client Services, July 2010, Figure 2.2). As shown in Altria's figure, market share was 9.8 percent for Newport, 5.4 percent for Marlboro Menthol, 2.5 percent for Kool, and 1.6 percent for Salem. In addition, a 1.3 percent market share for Camel Menthol was reported separately by Altria. The pattern for market share is reflected in the brand preferences of adult smokers aged 20 or older: 11.6 percent smoked Newport; 5.9 percent, Marlboro Menthol; 2.7 percent, Kool; 1.2 percent, Salem; and 8.9 percent smoked other menthol brands (NHANES 2007-08, see Caraballo & Asman 2010). Additional comparisons of brand preference by race/ethnicity, gender, and age group are summarized in chapter 6.

Figure 2.2. Key menthol brand share history




SOURCE: Maxwell Reports 1925-1973; Management Science Associates, Inc. Shipment History 1974-2008; 72 Month Shipment Database 2009

Newport has been the most popular menthol brand since 1993 (Lorillard July, 2010). It is the most popular cigarette brand among African American smokers, preferred by 49.5 percent of African American smokers aged 12 or older (NSDUH 2005, see NSDUH Report 2007). Newport is distinctly more popular with younger smokers: 23.2 percent of adolescent smokers (ages 12–17) and 17.8 percent of young adult smokers (ages 18–25) smoked Newport, but only 8.7 percent of older smokers preferred the brand (NSDUH 2005, see NSDUH Report 2007). The brand's popularity with younger smokers is evident in all three racial/ethnic subgroups that were examined in the analysis of the NSDUH 2000 data by Giovino et al. (2004). Among African Americans, Newport was the most frequently used brand. Of African Americans who smoked in the past 30 days, 79.2 percent of 12–17 year olds, 76.7 percent of 18–25 year olds, and 31.5 percent of adults aged 26 or older smoked Newport. Among Hispanic smokers, Newport was the second most popular cigarette brand, preferred by 31.4 percent of 12–17 year olds, 16.7 percent of 18–25 year olds, and 7.1 percent of adults aged 26 or older. Newport was less popular among non-Hispanic white smokers, but preferred by 18.0 percent of 12–17 year olds, 9.3 percent of 18–25 year olds, and 2.9 percent of adults aged 26 or older. From its introduction in 1957, Newport was an exclusively menthol brand, but non-menthol varieties were test marketed in the 1980s (Stein 1982) and Newport Red, a non-menthol variety, was introduced in 2010.

Kool and Salem (both manufactured by R.J. Reynolds Tobacco Company) have been exclusively menthol brands since their introduction and gained the largest market share in the 1960s. Kool is the second most popular cigarette brand among African American smokers, preferred by 11.4 percent of African American smokers aged 12 or older (NSDUH 2005, see NSDUH Report 2007). The brand is more popular with older smokers: Among African Americans, Kool was the cigarette brand used most often by 14.1 percent of adults aged 26 or older, 4.6 percent of 18-25 year olds, and 2.1 percent of 12-17 year olds who smoked during the past 30 days (NSDUH 2000, see Giovino et al. 2004). Salem is also preferred by older smokers and is the fourth most popular cigarette brand among African American smokers: 6.9 percent of adults aged 26 or older, and 1.9 percent of 18–25 year olds and of 12–17 year olds used Salem most often (NSDUH 2000, see Giovino et al. 2004). Among Hispanic smokers aged 26 or older, 3.6 percent smoked Kool and 3.4 percent smoked Salem. Salem was slightly more popular than Kool among non-Hispanic white smokers aged 26 or older (3.0 percent vs. 1.8 percent). Among Hispanics and non-Hispanic whites, less than 1 percent of younger smokers reported smoking these brands. Salem is also favored primarily by female smokers (Giovino et al. 2004).

Introduced in 1965, Marlboro Menthol (manufactured by Altria/Philip Morris USA) is now the second leading brand of menthol cigarettes in the U.S.; it surpassed Kool and Salem in popularity after the introduction of Marlboro Milds in 2000 (Altria July, 2010). Its increase in market share is reflected in the Caraballo (2010) analysis of the NSDUH data: The proportion of smokers aged 20 or older for whom Marlboro Menthol was the brand used most often increased from 3.9 percent in 2003–2004, to 4.2 percent in 2005–2006, and to 5.9 percent in 2007–2008 (table 5 in Caraballo & Asman 2010).

Tobacco companies manipulate the concentration of menthol to achieve a desired taste, aroma, and cooling sensation based on anticipated consumer preference and demand. As discussed in chapter 3, many cigarettes contain menthol in quantities insufficient to be considered a characterizing flavor. Lorillard described this use of menthol as analogous "to the use of a few grains of salt in a sweet dish" (Lorillard, July, 2010, p. 19). Lower concentrations of menthol are known to appeal to younger smokers and women (Kreslake et al. 2008 NTR; Lee & Glantz, in press). A survey of products purchased and tested in 2003 observed lower concentrations of menthol in cigarettes labeled "light" and "ultralight" (Celebucki, Wayne, Connolly, et al. 2005). In the full flavor, 100 mm varieties, menthol concentration (measured in milligrams per gram of tobacco weight) was 2.44 mg/g for Newport, 2.64 mg/g for Marlboro Menthol, 2.78 mg/g for Salem, and 3.56 mg/g for Kool (Celebucki et al. 2005). A different rank order of brands was observed in Altria's summary of products that were tested in 2008–2009: 2.9 mg/g for Newport, 3.3 mg/g for Salem, 4.4 mg/g for Kool, and 4.5 mg/g for Marlboro Menthol (also full-flavor,100mm varieties) (July, 2010, Table 1.3). Kreslake et al. (2008, AJPH) compared menthol concentration for eight products tested in 2007 with values reported in tobacco industry documents for the same brands. The authors observed that the concentration of menthol had decreased in Newport, Kool, and Salem brands between 2000 and 2007, and increased by 25 percent in Marlboro Menthol. They concluded that increasing menthol content was intended to reposition Marlboro Menthol for older smokers and to distinguish it from Marlboro Milds, a variety with a lower menthol content that appealed to younger smokers. Lorillard presented data indicating that the menthol concentration of its Newport brand did not decrease during this time period (July 2010, Fig 1). Additional research about consumer perceptions of menthol content is addressed later in this chapter and in chapter 6.

**Place**

Menthol and non-menthol cigarettes are distributed in identical channels. The primary venues are retail outlets: convenience stores, small grocery or "corner" stores, gas stations, liquor stores, supermarkets, mass merchants, pharmacies, and tobacco stores. The total number of U.S. stores that sell cigarettes is unknown. The 2007 Economic Census identified at least 100 different types of businesses that sell tobacco and estimated sales for approximately 235,000 retailers in the U.S. (http://www.census.gov/econ/census07/). However, that figure likely underestimates the total number of retailers because the survey is limited to payroll establishments. A larger estimate of 543,000 retailers was obtained by extrapolating from the subset of states that maintained licensing records (DiFranza, Peck et al. 2001).

The retail channel is ideally positioned to target the lower income and racial/ethnic minority populations who smoke menthol cigarettes. Indeed, inequities in the concentration of tobacco retailers by neighborhood demographics are well documented. For example, the tobacco retailer density (outlets per roadway kilometer) was almost four times greater in Erie County census tracts with the lowest income residents than in tracts with the highest income residents; tobacco retailer density was two times greater in tracts with the highest proportions of African American residents than in tracts with the lowest proportions (Hyland, Travers, et al. 2003). Similar disparities in tobacco outlet density by income, race/ethnicity or both were observed in census tracts in New Jersey (Yu, Peterson, Sheffer et al. 2010), Iowa (Schneider, Reid, Peterson, et al. 2005), and Chicago (Novak,

Reardon et al. 2006). In addition, more tobacco retailers were located near California high schools with larger proportions of low-income and Hispanic students (Henriksen, Feighery et al. 2008). Such disparities in tobacco retailer density contribute to the greater availability of cigarettes, both menthol and non-menthol, in areas of social and economic disadvantage.

**Price**

Price is a critical feature of tobacco marketing and influences myriad aspects of smoking behavior. Higher prices discourage initiation, reduce consumption, promote quitting, prevent relapse, and may lead smokers to substitute cheaper brands (Chaloupka et al. 2010). According to the Federal Trade Commission's Cigarette Report, the tobacco industry spends the largest share of its annual marketing budget—74 percent of $12.5 billion in 2006—on price discounts (Federal Trade Commission 2009). This section uses the term "price promotions" to refer to discounts and other strategies that reduce the price of cigarettes at the point of sale, such as retailer promotional allowances, multi-pack offers and gifts with purchase. Additional data about expenditures for sales promotions in relation to other marketing activities is provided in the section on Promotion.

Information about price and price promotions was obtained from multiple sources, including submissions to FDA by tobacco companies and other presentations to TPSAC, as well as peer-reviewed articles that analyzed data from retail scanners, or receipts from single-pack purchases, or audits of advertised prices at point of sale, or purchase prices reported by smokers themselves. Most studies examined reported data from nationally representative samples of stores or smokers. The studies below are grouped by data source.

***Industry submissions***

In its submission to FDA, R.J. Reynolds Tobacco Co. reported that the average price paid per carton of cigarettes was slightly higher for menthol than for non-menthol cigarettes for each year from 2000 to 2009, with more discrepant prices observed in more recent years (e.g., an average $49 for menthol and $46 for non-menthol in 2009) (presentation by Graves/RJ Reynolds, July, 2010). Data on the average price paid per pack (which constitutes the way that the majority of smokers buy their cigarettes) was not provided, but in response to a question, Monica Graves from R.J. Reynolds indicated the same trends held for pack prices. These data were presented in an aggregated form for the entire industry, and no data were presented by company or by individual brand, precluding determination of the use of different pricing approaches for individual brands. In addition, the data did not address whether there was a differential price paid for menthol and non-menthol cigarettes in geographic areas with different proportional representations of race/ethnicity, or during focal time periods (e.g., when tobacco taxes were increased).

From 2000 to 2009, the proportion of sales volume with a price promotion nearly doubled for non-menthol cigarettes (to 71 percent from 36 percent) and it more than doubled for menthol cigarettes (to 67 percent from 26 percent). However, these data were similarly aggregated over brands and companies, and by geographic location, and were not provided for more fine-grained time periods in relation to tobacco tax increases. In addition, these particular data only indicate whether or not some kind of price promotion was applied to menthol and non-menthol, and not the relative value of the price promotion. R.J. Reynolds drew attention to the menthol share of shipments being flat from 2000 to 2004 during a period when the percentage of volume promoted for menthol increased, and also that the menthol share of shipments grew from 2005 to 2009 when menthol promotional levels were relatively stable. This interpretation overlooks the alternative that the percentage of volume promoted may have reached a critical threshold by 2005, which acted to increase the share of menthol shipments thereafter.

***Retail scanner data***

Cigarette pack prices and sales volume derived from ACNielsen scanner data are designed to represent national markets for different types of retail outlets (Loomis Oct 2010). Loomis (2010) compared price and promotions for menthol and non-menthol sales in two retail channels: convenience stores and food retailers (supermarkets, drug stores and mass merchants combined) from 2008 to 2010. The average pack price was higher for menthol than non-menthol cigarettes in both retail channels, and 13 cents more (3 percent higher) in convenience stores, which is the retail channel that sells the largest volume of cigarettes. Over time, the use of multi-pack discounts was replaced by the use of "cents off" discounts for both menthol and non-menthol sales. In both retail channels, promoted sales accounted for a greater proportion of total sales for menthol than for non-menthol cigarettes. In convenience stores, 8.31 percent of menthol sales involved a promotion, compared with 5.11 percent of non-menthol sales. These figures cannot be compared with those reported by R.J. Reynolds because the two describe different types of promotions (retail vs. what appears to be wholesale) and different denominators (total pack sales in convenience stores vs. volume of shipments).

Using ACNielsen scanner data from supermarkets for the period 1994–2004, Farrelly et al. (2007) compared estimated change in pack price as well as tar and nicotine per cigarette for menthol and non-menthol brands (Farrelly, Loomis, & Mann 2007). Slightly higher average prices were observed for menthol than for non-menthol packs, and the discrepancy increased after the 1998 Master Settlement Agreement (MSA), in which tobacco companies agreed to restrict certain advertising practices. Over time, price increases were associated with increases in sales of cigarettes that contained more tar and nicotine, but this trend was more pronounced for menthol than for non-menthol cigarette sales. The authors concluded that menthol smokers are more likely than non-menthol smokers to compensate for price increases by smoking cigarettes with higher levels of tar and nicotine.

One limitation of studying retail scanner data is the potential for under-reporting of promoted sales due to missing information for some transactions. In addition, the scanner data are derived from a proprietary method of projecting to the population and are not a representative sample of stores. This proprietary sampling method also precludes researchers from determining whether promoted sales were higher in regions or neighborhoods with different race and ethnic group distributions.

***Store audits***

Store audits typically used trained coders to record advertised prices and sales promotions for particular cigarette brands or flavor categories in a random sample of tobacco retailers. For example, Ruel et al. (2004) conducted annual observations (1999–2002) in a geographically stratified sample of 11,703 stores in the U.S. (Ruel, Mani, Sandoval et al. 2004). They recorded the lowest advertised pack price for the leading menthol (Newport) and leading non-menthol (Marlboro) brand. Over the three years, the average price for Newport increased 78 cents (25 percent change) compared to 85 cents (29 percent change) for Marlboro. Increases in Newport prices were observed for all regions (West, Midwest, South, Northeast) and locales (urban, suburban, town, rural). The proportion of stores that advertised a price promotion for Newport increased by 19 percentage points, but the proportion of stores with a promotion for Marlboro increased by only 7 percentage points. In urban areas, a linear increase was observed for Newport promotions but not for Marlboro promotions. One shortcoming of these comparisons is that the two brands represent different corporate marketing strategies. According to Lorillard, Newport maintains the highest average price of major U.S. cigarette brands (Lorillard July 2010).

Toomey et al. (2009) observed the same pattern of differential pricing for menthol and non-menthol

varieties of the same brand family. In a random sample of 214 Minneapolis convenience stores, the average difference between the single-pack price for the menthol and non-menthol varieties of the same (unidentified) brand was 37 cents (11 percent more for menthol). Menthol price was not correlated with the proportion of non-white residents or youth in the census tracts where the stores were located; non-menthol price was positively correlated with the proportion of non-white residents and negatively correlated with the proportion of youth. However, the study did not examine the availability of discounts or other price promotions.

***Population surveys***

Three surveys illustrated differences between menthol and non-menthol smokers in response to pricing. A 2002 survey of 4,618 California smokers found relatively more of those who smoked menthol brands reported taking advantage of price promotions than those who smoked non-menthol brands: percentages were 57.1 percent for those who smoked menthol-only brands (Newport or Kool), compared to 49.1 percent for Camel and 34.8 percent for Marlboro (given menthol variants were a small percentage of the market for both these brands) (White et al., 2006). This finding is consistent with the results of the scanner data showing that a larger proportion of menthol compared to non-menthol cigarette sales involved price promotions (Loomis, 2010). Among African American smokers in the California survey, 65.4percent of menthol smokers compared to 28.7percent of non-menthol smokers reported using promotional offers. Young adults, women, and daily smokers were also more likely to use promotional offers, but the difference between menthol and non-menthol smokers in these subgroups was not reported.

Fernander et al. (2010) undertook an analysis of the data from the 2003 and 2006-2007 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) in order to compare the demographic traits and purchase behaviors of menthol and non-menthol smokers (Fernander et al. 2010). A larger proportion of menthol smokers (68.8 percent) than non-menthol smokers (59.2 percent) reported buying cigarettes by the pack. Adjusting for other factors, such as gender, race/ethnicity, age group, education level, income, smoking frequency and age of initiation, the odds of being a menthol smoker were significantly lower for smokers who reported buying cigarettes by the carton exclusively. The authors concluded that the finding is consistent with other studies suggesting that menthol smokers smoke fewer cigarettes.

In a separate analysis of the TUS-CPS, Tauras et al. (2010) examined questions about the type of cigarette smoked and the price that smokers last paid for either a pack or carton. Using data aggregated over multiple survey waves (2003 and 2006-2007), Tauras et al. (2010) estimated state-specific prices for menthol and non-menthol packs. Adjusted to 2010 dollars, the average menthol price was $3.88, which was 9 cents more than the average non-menthol price.

Tauras et al. (2010) also estimated the probability of being a menthol smoker, based on different state-specific prices for menthol and non-menthol cigarettes and adjusting for other characteristics of smokers. Holding these variables constant, a 10 percent increase in the price of menthol cigarettes was associated with a 2.3 percent decrease in the probability of being a menthol smoker. A 10 percent increase in the price of non-menthol cigarettes was associated with a 4.7 percent increase in the probability of being a menthol smoker. These different price elasticities suggest that menthol and non-menthol cigarettes are not close substitutes for each other. The authors concluded that, holding other factors constant, menthol smokers would be much less likely to switch to non-menthol cigarettes than non-menthol smokers would be likely to switch to menthol cigarettes. The pattern of results did not differ by gender or income. However, younger smokers (aged 18–24) and African American smokers were even less likely to substitute non-menthol cigarettes for menthol cigarettes, indicating stronger preference to menthol cigarettes among the population subgroups with a higher prevalence of smoking menthol. A limitation of this cross-sectional study is that it could not model change in smoker behavior (switching or quitting) over time. In addition, the analysis

excluded smokers who indicated no preference for menthol or non-menthol cigarettes. However, this comprised only 2.3 percent of the sample, indicating that the vast majority of adult smokers had a definite preference.

*Summary*. Prices for both menthol and non-menthol cigarettes are increasing and the average price for menthol cigarettes is slightly higher than for non-menthol cigarettes. These patterns emerged regardless of the different data sources used to study price. There was limited information available on menthol pricing and price promotion by neighborhood race/ethnicity characteristics, in relation to tobacco tax increases, and in relation to brand. The retail scanner data indicates that a larger proportion of menthol than non-menthol sales is promoted. More menthol smokers take advantage of price promotions than non-menthol smokers, and this is particularly true for African Americans. Menthol smokers have stronger loyalty to their cigarette preference and are less sensitive to price fluctuations than non-menthol smokers.

**Promotion**

The main goals of the *Promotion* part of the marketing mix are to inform, persuade and remind (NCI 2008). Informing is generally considered important for newly developed products in order to tell consumers something about the product. Promotions aimed at reminding are typically aimed at consumers who already have positive attitudes towards the brand. Promotions that persuade tend to focus on the advantages of one brand over another. Branding is the use of a name, term, symbol or design to identify a product and the creation of a 'brand image,' is key to a successful promotional strategy. As explained further in a later section on menthol marketing messages, cigarette advertising is short on factual information and rich in imagery designed to establish and reinforce branding.

The aim of branding is to create a set of associations or perceptions about a brand in the mind of consumers, so that they will want to buy try the product and keep buying it (NCI 2008). Branding is a key aspect of marketing, whereby marketers create an image for the brand they promote, a brand image that promises the target market something they value. Persuasion-based promotions often link products with desirable images (such as lifestyle or healthful imagery) and identities (such as slogans or brand symbols), in order that consumers associate the brand with positive emotions or reduced negative emotions (NCI 2008). In a comprehensive review of the evidence, the NCI review concluded that "*tobacco advertising has been dominated by three broad themes: providing satisfaction (taste, freshness, mildness etc.), assuaging anxieties about the dangers of smoking, and creating associations between smoking and desirable outcomes (independence, social success, sexual attraction, thinness etc.)*" (NCI 2008, p170).

Later sections about messaging and targeting describe the message themes that distinguish menthol from non-menthol marketing. This section describes similar types of marketing activities used to promote both menthol and non-menthol cigarettes, noting some differences in practice. Price promotions that were discussed in the price section are included here because these are reflected in various marketing activities, such as retail advertising and direct mail, and are essential to understand the context of tobacco marketing practices.

As reported to the Federal Trade Commission, current promotional activities for cigarettes include advertising (print media and point-of-sale), direct marketing (direct mail, coupons, distribution of free cigarettes and specialty items, company website, other internet and telephone), sponsorship, public entertainment, promotional allowances for wholesalers and retailers, and retail price promotions (as described in the section on price). After the MSA eliminated billboard and transit advertising and curtailed sponsored events by tobacco companies, their annual spending on retail marketing more than doubled to $10.7 billion in 2006 from $4.7 billion in 1998 (Federal Trade

Commission 2009). Over the same period, retail marketing expenditures increased to 86 percent from 70 percent of the industry's total annual marketing dollars. These figures include retail advertising, promotional allowances, and price promotions (discounts, bonus cigarettes, and gifts with purchase). While total marketing expenditures decreased every year since 2003, proportional expenditures on point-of-sale advertising nearly doubled to 1.9 percent in 2006 from 1.1 percent in 2003. Proportional expenditures on price promotions increased to 80.4 percent in 2006 from 76.0 percent in 2003.

Tobacco companies exercise strict control over the retail outlet, using contractual obligations with store merchants to maximize the visibility of products and advertising for selected brands (Pollay 2007; Feighery, Ribisl, Clark et al. 2003; John, Cheney, & Azad 2009). The shift toward retail marketing is apparent to consumers; the average number of cigarette marketing materials per store and the proportion of stores with price promotions have increased since the MSA (Celebucki & Diskin 2002; Feighery, Schleicher, Cruz & Unger 2008; Wakefield et al. 2000). As described in the previous section about price, a larger increase was observed in the proportion of stores that promoted Newport than in the proportion of stores that promoted Marlboro (Ruel et al. 2004).

Lorillard (July, 2010) described its marketing plan in terms of four components: retail price promotions, retail advertising, print advertising, and direct marketing. The latter category includes a direct mail list for distributing coupons and its "P.S. Pleasure Scene" magazine that was started in 2003. The company reported that coupons represented the largest proportion of its direct mailing expenditures, but did not disclose the amounts. In 2008, Lorillard spent $19.7 million on magazine advertising, a category that represented less than 1 percent of its annual marketing budget in 2009. Retail price promotions comprise more than 90 percent of the company's annual marketing expenditures. In 2006, magazine advertising represented 0.4 percent of annual tobacco industry marketing expenditures and price promotions (discounts and retail value-added) represented 80.4 percent of total expenditures (Federal Trade Commission 2009).

R.J. Reynolds Tobacco Co. (July, 2010) reported using price promotion, direct mail, email, website promotion, event promotion, and direct sales in bars and clubs to promote both menthol and non-menthol brands, but did not disclose expenditures or compare them by brand type. The company proposed that a recent shift in preferences toward menthol could not be attributed to marketing activities because these were substantially constrained and because "menthol advertising has changed little in message and medium during this time frame" (Graves/RJ Reynolds, July 2010). In spite of a restricted environment, the industry's total expenditures for cigarette marketing increased every year after the MSA until 2003 (Federal Trade Commission 2009). In addition, even if message and medium remained constant for menthol brands, proportional expenditures to advertise and promote menthol brands could have increased.

The FTC does not publish expenditures separately by manufacturer, brand, or variety of cigarette (menthol vs. non-menthol). However, expenditure data for some marketing channels can be purchased from commercial sources. Using such data for cigarette advertising in magazines, one study found that spending for non-menthol brands decreased to $39.8 million in 2005 from $309.3 million in 1998, but spending for menthol brands increased to $43.8 million from $36.5 million in the same time period (Kreslake, Wayne, Alpert, et al. 2008). The proportion of expenditures for menthol brands increased to 52.4 percent from 10.6 percent of the total expenditures over this time period, and the spending for menthol exceeded spending for non-menthol brands in 2005. This pattern suggests greater effort to advertise menthol than non-menthol brands in magazines during a period of increased advertising restrictions.

(b) (4)

(b) (4)

*Summary*. In a restricted environment, retail has become the dominant channel for tobacco marketing. Tobacco companies use similar marketing activities to promote menthol and non-menthol brands, but expenditure data suggest some differences in practice. In recent years, the tobacco industry spent as much or more on magazine advertising for menthol as for non-menthol brands, even though menthol brands represent a much smaller share of the market (b) (4)
(b) (4)
. Further evidence that speaks to differences in promotional practices for menthol—that the mix of marketing strategies used to promote these brands are determined by neighborhood demographics—is addressed in a later section on targeting.

**Packaging**

Cigarette packaging plays a key role in the creation and reinforcement of brand imagery (NCI 2008) and tobacco companies conduct considerable consumer research on all elements of packaging (Wakefield et al. 2002; DiFranza et al. 2002). Unlike many other products where the packaging is discarded after opening, smokers generally keep their cigarette pack with them until all the cigarettes in it are smoked. This means that the pack is frequently being taken out and put on display. This high degree of social visibility leads cigarettes to be described by marketers as "badge products." The use of a badge product associates the user with the brand image, giving the smoker some of the identity of the brand image. As one cigarette package designer, John Digianni, stated: "*A cigarette package is unique because the consumer carries it around with him all day . . .it's a part of a smoker's clothing, and when he saunters into a bar and plunks it down, he makes a statement about himself*." (Koten, cited in Wakefield et al. 2002).

Cigarette packaging becomes more important for overall marketing strategy, as traditional avenues for cigarette advertising are restricted. In a restricted advertising environment, aside from its key role in communicating brand image, cigarette packaging is used to create greater salience for brand families at the retail display (NCI 2008). Reviews of internal tobacco industry documents on cigarette packaging show that that variants within one brand family are designed to be sufficiently similar to

indicate membership of the overall parent brand, and different enough for consumers to be able to distinguish between the variants. In this way, the arrangement of packs from the same brand family achieve greater "stand out" from the clutter of competing brands at the point of sale (Wakefield et al. 2002; DiFranza et al. 2002).

For both menthol and non-menthol cigarettes, different shades of the same color and the proportion of white space are commonly used to distinguish between variants of the same brand family. Lighter colors on packs are used to signify 'lower tar' cigarettes (Wakefield et al, 2002; DiFranza et al. 2002) and consumers interpret lighter shades on cigarette packaging to infer that the cigarettes are less harmful (Hammond & Parkinson 2009). In the presence of a ban on terms such as 'light', 'low tar' and 'mild' which connote reduced harm, tobacco companies use alternative brand descriptors such as 'smooth,' color descriptors such as 'silver,' and 'tar' numbers that are incorporated into brand names, and that consumers also interpret to mean reduced harm (Hammond & Parkinson 2009). The relationship between branding and consumer perceptions of harm and related sensory experience is discussed further in a later section.

Given the central role of packaging in cigarette branding and marketing (NCI 2008), it is somewhat surprising that no study has attempted to quantify and describe changes in cigarette packing over time or differences between packaging for menthol and non-menthol brands. However, historical examples of cigarette packs are available on the internet *http://www.cigarettespedia.com/index.php/Main_Page* (click on brand name) and more recently *http://www.tobaccolabels.ca/cigarettepackagepictures/unitedstates*. In a submission to FDA, R.J. Reynolds (June 30, 2010) reported using cool and fresh imagery for menthol products and blue and green colors in package labeling. According to consumer perception studies conducted by Lorillard, smokers generally associate and prefer green packaging with menthol cigarettes (Lorillard July, 2010). However, these studies were not described in the company's report. Color theories suggest that green is commonly associated with "health" and "healing," in addition to "nature," "renewal," "new beginnings," and "harmony" (Frazer & Banks, 2004 in NCI, 2008). Green also connotes positive affective states, such as "calming," "gentle," and "peaceful" (cite in Anderson, Ling, & Glantz 2007). The following section describes the use of imagery and other messages in menthol marketing in more detail in connoting health reassurance.

**WHAT HEALTH REASSURANCE MESSAGES WERE/ARE USED IN MENTHOL MARKETING MESSAGES?**

In this section, we distinguish between two main types of messages that may provide health reassurance to consumers. First, messages may be explicit in nature, in that they make an obvious and direct connection between use of the product and a consequent expected health benefit or reduction of health risk. An example of an explicit health claim might be "*a cigarette to soothe a sore throat."* This claim overtly promises that the product confers a medicinal benefit in relieving the symptoms of a specific health condition. Second, messages may be implicit, in that they connote some kind of benefit related to health or well-being, without expressly saying so. These implicit messages tend to be more indirect and make use of imagery, associations and/or descriptive language. An example of an implicit health claim might be "*a cigarette as fresh as a mountain stream.*" By associating its product with a fresh mountain stream, this phrase invokes imagery of nature and cleanliness and thereby infers healthiness. Implicit messages can be highly effective as communication tools, in covertly shaping consumers expectations about a product. In addition, their ambiguity makes them difficult for consumers to discount.

During the 1950s, growing concern among consumers about the health harms of cigarettes created considerable dissonance within smokers, who were anxious about the fact that they were incurring a health risk, but found themselves unable to quit. This cognitive dissonance made smokers open to

messages that might reassure their health concerns (Pollay & Dewhirst 2002). From a marketing point of view, since the health harms of tobacco became widely known, explicit claims that one cigarette brand was healthier, safer or less harmful than another risked being rejected by consumers as not being believable. Furthermore, explicit claims had the undesirable consequence for the tobacco industry of reminding smokers that they were engaging in a behavior that was inherently harmful to their health. Instead, the tobacco industry turned to implicit marketing messages through the use of brand descriptors, slogans, and rich advertising imagery, to offer health reassurance (Pollay & Dewhirst 2002). These implicit messages promoted attributes such as taste, flavor, sensory experience, satisfaction and enjoyment.

In a review of tobacco industry documents and advertising, Sutton and Robinson (2004) identified extensive use of four types of messages in menthol marketing: healthy/medicinal claims, taste sensation (e.g., fresh, refreshing, cool, clean, crisp), youthfulness, and ethnic awareness. The first two categories are the focus of one section because these themes are inextricably linked in marketing messages and in the minds of consumers (see later sections on consumer perceptions).

**Healthy/medicinal claims and taste sensation**

Until the mid 1950's, marketing messages positioned menthol cigarettes for occasional use as a remedy for myriad ailments (Gardiner, 2004; Sutton & Robinson, 2004). For example, Samji and Jackler (2008) archived and reviewed several thousands of cigarette ads that were sampled from popular magazines and scholarly journals between 1920 and 1954. Only ads that depicted the throat or a throat doctor were selected for further description and their analysis was not specific to menthol advertising. Brand slogans for Spud, the first menthol cigarette (Ashton-Fisher Tobacco Co.), and for Kool, promoted these products as remedies for nose and throat irritation and for congestion. A 1937 ad featured a prescription from Dr. Kool, a cartoon penguin: "*Tell him to switch to Kools and he'll be all right. Doctors…agree that Kools are soothing to your throat*." The researchers remarked that the introduction of menthol played a central role in positioning tobacco products as a treatment rather than an irritant.

In their overview of research reviews of qualitative tobacco industry documents that were prepared for FDA, Lee and Glantz (in press) also noted that explicit health claims characterized menthol cigarettes as a healthier, less harsh alternative for smokers who required temporary relief from symptoms. To illustrate the extent to which health claims were widely accepted, the authors cited an example of a 1951 case report from the Journal of American Medical Association that referred to menthol cigarettes as "medicated cigarettes" with an "anesthetic and cooling effect" (Highstein & Zeligman 1951, cited in Lee & Glantz in press).

A brief history of tobacco marketing from the Institute of Medicine (2003) noted that explicit health claims persisted in spite of a 1942 agreement between the Federal Trade Commission and Brown & Williamson to end such advertising. The IOM report cited two slogans from 1946 and 1949: "*HEAD STOPPED UP? GOT THE SNEEZES? SWITCH TO KOOLS. . . THE FLAVOR PLEASES!*" and "*Got a COLD? Smoke KOOLS as your steady smoke for that clean, KOOL taste"* (table 3-1 in IOM, 2003). These and other examples serve to illustrate that early marketing messages linked claims about the perceived health benefits of menthol with its taste sensation. After the Federal Trade Commission codified the cigarette advertising guidelines in 1955, marketing messages about taste, flavor, aroma, and enjoyment replaced explicit health claims. The IOM report highlighted the industry's use of taste and sensory descriptors such as "mild," "light" and "smooth" to suggest the concept of product safety.

In a review of tobacco industry documents about marketing for "light" and "low-tar" cigarettes, Pollay and Dewhirst (2002) described how the industry repositioned menthol cigarettes from a health remedy for occasional use to a positive smoking experience for regular use. In response to

growing public concern about the health impacts of smoking, motivation researchers and trade analysts advised the industry to adopt subtler tactics, using visual imagery and ad copy that implied healthfulness (Pollay 1989, cited in Pollay & Dewhirst 2000). A Brown & Williamson document highlighted the important role of menthol in assuaging smokers' concerns about health: "*Menthol in the filter form in the Salem advertising was a 'refreshing' taste experience. It can be very 'reassuring' in a personal concern climate. Undoubtedly, the medicinal menthol connotation carried forward in a therapeutic fashion as positive taste benefit*." (Cunningham & Walsh, 1980, cited in Pollay & Dewhirst 2002). The authors concluded the use of menthol was a critical element of the tobacco industry's efforts to convince consumers that particular cigarette brands are relatively healthy. As described by Pollay & Dewhirst, "*cigarette advertising is notoriously uninformative, with characteristic forms using veiled health implications and pictures of health along with vague promises of taste and satisfaction*" (2002, p.i28).

Sutton and Robinson (2004) observed that general market magazine and newspaper advertising of the 1950s and 1960s promoted menthol brands with outdoor scenes, such as woodlands, rain forests, rock gardens, and country streams. These images were paired with sensory descriptors, such as "cool," "clean," "fresh"—terms that connote health benefits. For example, advertising for Salem mentioned "perpetual springtime" and "a wonderful world of freshness" (MSA Inc. 1978, cited in Gardiner 2004) and Newport's introduction in 1957 featured the slogan: "*Rich taste – with a touch of refreshing mint*" (Anderson, in press).

Anderson (in press) examined 953 tobacco industry internal documents gleaned from a string of search terms about menthol marketing and consumer perception. Consistent with other accounts, she reported that menthol cigarettes were first popularized as a remedy to the burn, dryness and throat irritation that accompany smoking. The industry documents included examples of early advertising slogans for menthol cigarettes that promised healthful outcomes, such as "*Breathe easy, smoke clean*," (Brown & Williamson 1978 cited in Anderson, in press) and "*The beneficial head-clearing qualities of menthol*" (Brown & Williamson undated, cited in Anderson in press). When overtly health-oriented messages were forbidden, marketing messages exploited consumer perception of the characterizing flavor as both a taste and a sensation. In addition, the messages capitalized on the perception of a cooling sensation as healthful: "*What a wonderful difference when you switch to snow fresh Kools. Your mouth feels clean and cool, your throat feels soothed and fresh. Enjoy the most refreshing experience smoking*" (Brown & Williamson,1968, cited in Anderson, in press). Indeed, tobacco companies sought to preserve the connotations of menthol with health. For example, a 1978 Brown & Williamson document described its objective to "*provide product safety reassurance while enhanc[ing] the satisfaction and refreshment perception of the appropriate Kool styles…*" (Brown & Williamson,1978, cited in Anderson 2010). Anderson concluded that marketing messages served to reassure smokers that menthol cigarettes were healthier than non-menthol cigarettes and that this reassurance continues in contemporary marketing messages that feature more oblique references to health.

A study by Paek et al. (2010) highlighted the contributions of product labeling and visual imagery to communicate implicit health-related claims. Their content analysis examined the prevalence of implicit health-promotion messages for cigarettes in 1,300 magazine ads from 1954 to 2003. Equal numbers of ads for 10 brands were sampled from five time periods. The sample included ads for 10 brands, including Newport and Kool, but the analysis did not compare menthol and non-menthol advertising. The presence of an implicit health claim was coded whenever verbal cues used either factual terms (e.g., low tar, no additives, filter) or impressionistic terms (e.g., mild, natural, gentle calm, soft, smooth) to characterize cigarettes. The presence of an implicit health claim was coded whenever visual cues associated cigarettes with healthful places or objects, such as mountains, fields, an ocean, or a glass of water. Verbal health claims appeared in advertising copy for 49 percent of the ads from the post-MSA era (1999-2003) compared to 45 percent of the ads overall. Visual

health claims were found in 50 percent of the post-MSA era ads, compared to 42 percent overall. The researchers concluded that implicit claims about health are as prevalent in contemporary cigarette advertising as they have been previously.

Throughout TPSAC meetings, tobacco industry representatives consistently pointed to taste as being the main driver of preference for menthol cigarettes among menthol cigarette smokers, with cooling sensation being considered to be part of the overall consumer taste experience (July 2010). Lorillard indicated in its submission that terms such as 'smooth,' 'fresh,' 'refreshing' and 'mild' are only intended to communicate taste, flavor and satisfaction (Lorillard, July 2010), and not to implicitly communicate that menthol cigarettes are less hazardous than non-menthol cigarettes.

*Summary*. Analyses of tobacco industry internal documents and the marketing messages the industry produced provide corroborating evidence of explicit and unwarranted claims that smoking menthol cigarettes would improve smokers' health. Over time, marketing messages increasingly relied on sensory descriptors and imagery to imply that menthol cigarettes are safer than non-menthol cigarettes.

**WHAT OTHER MESSAGES WERE/ARE CONVEYED TO POTENTIAL CONSUMERS BY MENTHOL MARKETING MESSAGES?**

Marketing messages about health claims and sensory appeals derive from direct references to menthol, but other marketing messages convey the product's appeal without reference to its characterizing flavor. In a 1982 marketing report, R.J. Reynolds characterized menthol smokers (the "Coolness Segment") as the youngest, the most economically disadvantaged, and the most likely to be in minority and ethnic groups, who "*tend, more than average, to desire their brand of cigarettes to symbolize personal qualities such as youth; modern womanhood; romance; career orientation; and success*" (cited in Anderson, in press). Previous research describes two dominant themes used to appeal to these target audiences and their aspirations. One theme is the exuberance of youth, which Sutton and Robinson (2005) labeled as "youthful, silliness, fun" and Anderson (in press) characterized as "fun-loving, sociable, and youthful." Menthol advertising also associates product use with images of an idealized self and social identity—a theme that Sutton and Robinson (2005) labeled as "ethnic awareness," and Anderson (in press) characterized more broadly as "identity or in-group belonging." These themes are not mutually exclusive; the same advertisement may serve to communicate both types of messages (see for example, Figure 3 in Anderson in press).

**Youthfulness and sociability**

Newport introduced its "Alive with Pleasure!" campaign in 1972 with advertising that portrayed young people having fun, but engaged in activities that seemed childish or juvenile (Sutton and Robinson, 2005). According to Klausner's (in press) review of tobacco industry documents, the Newport campaign was based on the assumption that peer influence is critical to smoking uptake and the advertising imagery sought to recreate and reinforce that influence. After the first four years, Newport was still lagging behind Kool and Salem, but its market share increased among youth. "*Newport's SOM [share of market] among smokers 14–17 years old is significantly higher than brand's Total SOM, reflecting strong appeal to young/new smokers*" (Esty 1976, cited in Klausner, in press). Newport's "Pleasure" campaign (the "Alive with…" part of the slogan was later dropped) continues to this day. Newport has been the leading menthol cigarette brand and the second leading cigarette brand among youth since the early 1990s.

Anderson (in press) acknowledged that images of youthfulness and sociability were not unique to marketing messages for menthol. Indeed, a 1981 R.J. Reynolds report observed, *"…The benefit of smoking which has most frequently and most successfully been exploited by brand families appears to*

*be Social Interaction*." After this approach proved effective for Lorillard's Newport brand, R.J. Reynolds launched a similar campaign for Salem. "*Advertising must convince younger adult smokers that Salem is smoked by natural, unpretentious but interesting people who are social leaders/catalysts (make things happen) whose sense of humor and wit makes them fun and exciting to be with*" (RJ Reynolds 1981, cited in Anderson in press). Anderson concluded that it was menthol's younger profile relative to other cigarettes that made the themes of youthfulness and sociability particularly appealing and persuasive.

Two empirical studies addressed consumer perceptions of youthfulness in cigarette marketing messages. In one study, 561 adults viewed and rated the perceived age and level of attractiveness of models in magazine ads for menthol and regular cigarettes (Mazis et al. 1992). Advertisements for menthol brands were judged to have significantly younger models (average 25.7 years) than advertisements for regular cigarette brands (average 31.9 years). Irrespective of their own age group, people rated younger models in the advertisements as being more attractive than older models.

Barbeau et al. (1998) asked 913 sixth- to eighth-grade students from Massachusetts to rate magazine ads for four cigarette brands (Newport, Camel, Marlboro and Virginia Slims) and four non-cigarette products. All the ads were from 1994 and featured human figures or anthropomorphic characters. The majority of students judged each of the four cigarette ads to say that smoking will make people look cool (72 percent to 84 percent), attractive (53 percent to 81 percent), popular (50 percent to 80 percent) and healthy (51 percent to 71 percent). Students' responses indicated that the advertisements communicate ideas that were in violation of the Tobacco Institute Voluntary Advertising and Promotion Code. Like the adults in the previous study (Mazis et al. 1992), the students rated Newport models as looking younger than the models appearing in ads for other cigarette brands. Weaknesses of both studies are that they surveyed convenience samples and could not control for objective differences between models that appeared in ads. Nonetheless, the results suggest that the message that Newport is a brand for younger consumers was apparent to both adults and adolescents.

**Identity/In-group belonging**

Establishing a sense of belonging is a central task of identity development in adolescence, particularly for racial/ethnic minorities (Castro 2004). Images of the self as a smoker or non-smoker contribute to this identity. As concluded in chapter 7 of NCI's Monograph 19 (2008), much tobacco advertising creates the perception that smoking will satisfy adolescent psychological needs relating to popularity, peer acceptance and positive self-image. Furthermore, adolescents who believe that smoking can satisfy their psychological needs or whose desired image of themselves is similar to their image of smokers are more likely to experiment with cigarettes (NCI 2008, p280).

Several histories of menthol marketing commented on appeals to racial identity, which coincided with increased market share among African Americans in the 1960s and 1970s (Gardiner 2004; Sutton & Robinson 2005). For example, commenting on Kool brand advertising of this period, Sutton and Robinson (2005) observed a departure from the standard fare of waterfalls, country streams and romantic couples found in white-oriented media to darker-skinned models, slang terms, and more masculine imagery in African American-oriented media. Increasingly, marketing messages for menthol cigarettes appropriated images of athletes, entertainers, hairstyles, clothing, music and other elements of African American popular culture (Gardiner 2004; Giovino et al. 2004; Hafez & Ling 2005; Sutton & Robinson 2004). Several researchers observed that the word "cool," and its significance to the African American community, played a central role in the appeal of the Kool brand as well as the product category (Gardiner 2004; Castro 2004).

Balbach et al. (2003) examined ads for R.J. Reynolds' brands from three magazines aimed at an African American audience. Nearly all of the ads were for menthol brands. Between 1989 and 1990, every ad depicted an escapist or fantasy theme when a setting was visible, most of the ads (74 percent) featured expensive objects when objects were visible, and approximately half of the ads (58 percent) portrayed nightlife whenever social life was shown. All three themes remained evident in ads that were sampled from the same magazines a decade later, although fewer of the ads featured expensive objects. In combination with evidence gleaned from their review of R.J. Reynolds' internal documents (discussed in the section on targeting), the authors concluded that marketing messages associated menthol cigarettes with luxury objects, a glamorous nightlife, and a fantasy world in order to appeal to the aspirations of young adult African Americans.

Nightlife settings were observed in menthol marketing aimed at a broader audience of young adults. Belstock et al. (2008) examined all cigarette and alcohol advertising that appeared in Maxim, FHM, Cosmopolitan and Ebony in 2003 and 2004. These magazines were selected because of their popularity with young adult readers (ages 18–24). Although none of the 317 alcohol ads referred to cigarettes, 32 of the 114 cigarette ads (28 percent) included text or imagery related to alcohol. Cigarette and alcohol advertisements were equally likely to portray a bar or club setting that implied a nighttime or after-hours social gathering. Newport and Kool were two of the four cigarette brands that featured alcohol-related content in their advertising. However, the proportion of total ads for menthol and the proportion of menthol ads with alcohol content were not reported.

Anderson's review of industry documents (in press) noted that menthol marketing appeals to multiple group identities, especially, but not exclusively, to African Americans. She observed that menthol marketing conveys varied images of menthol smokers because the three largest, exclusively menthol brands developed such different identities. Several examples from industry documents characterized Kool as having a more masculine image than other brands, Salem a more feminine image, and Newport as the brand with the youngest demographics in the industry. Anderson concluded that no single unified image of a menthol smoker emerges from marketing messages about the product.

Two empirical studies examined consumer perceptions of menthol smokers, and commented on the degree to which perceptions fit the messages conveyed in menthol marketing. Allen and Unger (2007) examined selected socio-cultural factors associated with menthol smoking in a convenience sample of African Americans from Los Angeles. They interviewed 432 smokers of at least five cigarettes per day (296 menthol and 136 non-menthol) recruited from a campus medical center, shopping malls and other community sites. Differences between groups of smokers were presented as odds ratios (adjusted for age and employment status) and without response frequencies. The results suggested that for both males and females, a significant correlate of menthol use was the belief that most African Americans smoke menthols. Among females (but not males), an additional correlate was a lack of belief that menthol smoking "*is a Black thing*."

Segerstrom et al. (1994) randomly assigned 100 white and 94 African American community college and university students with a short written description of a target smoker that varied by race (African American or white) and cigarette type (menthol or regular). Students then rated the smoker on 15 attributes using semantic differential scales (e.g., rich/poor, unpopular/popular, weak/strong). Overall, the pattern of ratings according to the subject's own race and smoking status was inconsistent and no single unified image of a menthol smoker emerged. Although the small sample size limits conclusions about differences in perceptions between groups, the study finding is consistent with the conclusion of Anderson's document review (in press). However, the study did not examine perceptions of those who smoked different brands of menthol cigarettes, which would likely differ.

*Summary*. Menthol marketing features youthful imagery and consumers perceive differences between menthol and non-menthol marketing in terms of the relative age of the models. Menthol marketing also uses socially and culturally relevant messages about in-group identity to appeal to different market segments. Different group identities are emphasized in marketing for different brand families, which may explain why consumers do not share a singular impression of a menthol smoker.

The next section considers the role of youthful imagery and other messages about in-group identity in cultivating target markets for menthol brands.

## WHO ARE THE TARGET POPULATIONS FOR MENTHOL MARKETING? IS THERE EVIDENCE TO SHOW THAT YOUTH, WOMEN, AND SPECIFIC RACIAL/ETHNIC GROUPS WERE TARGETED?

Few products are promoted to the entire population in an undifferentiated manner. The planning of promotional strategy requires the definition of a clear target market, whereby the population is segmented into defined subgroups. This target market can include people who are potential buyers, current users, those who make the buying decision, or those who influence it. Extensive qualitative and quantitative research is undertaken to identify the salient beliefs, values and preferences of the planned target market, which might be defined on the basis of age, gender, ethnicity, income, and lifestyle, among other attributes (NCI 2008). Promotional strategies are then designed for and directed to this well-defined consumer group (or segment). Typically, many consumer tests are undertaken to pre-test and refine branding elements. The message in a segmented campaign may have broad appeal, but will be most salient to and resonate with the specific targeted segment. The NCI review concluded that "*the tobacco industry has become increasingly sophisticated in applying market research to population segments in order to design products, messages, communication channels and promotions more aligned with the needs and susceptibilities of particular market segments. This research results in more efficiency, greater reach, and increased effectiveness for marketing activities aimed at targeted populations*." (NCI 2008, p171).

This section draws on three types of evidence about target marketing: (1) analyses of tobacco industry documents that described the development, intent, and consequences of marketing menthol brands, (2) analyses of the advertising environment that compared the quantity of menthol advertising either by neighborhood characteristics or by audience demographics, and (3) observational studies that compared advertising recall and recognition by audience demographics.

### Targeting: Youth and young adults

In relation to tobacco use, brand image is especially important for adolescents because this is the age during which the vast majority of people take up smoking and brand choices are made. A recent review of tobacco marketing and its effects on tobacco use published by the National Cancer Institute (2008) concluded that "*much tobacco advertising targets the psychological needs of adolescents, such as popularity, peer acceptance and positive self-image. Advertising creates the perception that smoking will satisfy these needs.*"(NCI 2008, p280).

Tobacco companies frame their marketing efforts as being solely aimed at influencing brand switching in current users, and deny their advertising and promotional strategies promote youth smoking uptake. However, there is an abundance of empirical studies to show that the tobacco industry does target its marketing efforts towards youth and young adults and that youth are strategically important for the customer base. As concluded by Pollay et al. (1996), "*the battle of the brands for market share is waged largely among the young, for it is a brand's success among the*

*young that leads to greater brand sales and profit in the long term*"(p.13). Despite restrictions on more traditional forms of tobacco marketing, youth notice and are influenced by tobacco marketing efforts in ways that increase their likelihood of taking up smoking (NCI 2008). The recent NCI review examined research studies linking tobacco advertising and promotion with smoking attitudes and behaviour, including qualitative, cross-sectional, experimental, cohort and time series studies. The review concluded that "*the total weight of evidence from multiple types of studies, conducted by investigators from different disciplines, using data from many countries, demonstrates a causal relationship between tobacco advertising and promotion and increased tobacco use, as manifested by increased smoking initiation and increased per capita tobacco consumption in the population*" (NCI 2008, p281).

***Industry documents research***

Ling & Glantz (2002), in a review of tobacco industry documents from Philip Morris, RJ. Reynolds and Lorillard, explored tobacco industry strategies for marketing to young adults aged 18 to 24 years. They concluded that tobacco advertising encourages regular smoking and increased consumption by integrating smoking into social activities and places that reflect life changes experienced by young adults, with menthol brands such as Newport being featured in example documents. Kreslake et al. AJPH (2008), in a review of tobacco industry documents, found evidence that younger smokers preferred milder brands with lower menthol levels, with R.J. Reynolds observing that "*the want for less menthol does indeed skew younger adult*"(Etzel 1993, cited in Kreslake 2008). The success of Newport among younger consumers—Newport has lower menthol levels than Kool and Salem brands—was attributed to this feature, and the authors noted that from the 1980s, all other major menthol brands actively pursued a low-level menthol formulation to attract this market (Kreslake et al. AJPH 2008). In Kreslake NTR (2008), industry documents indicated a clear acknowledgment of this low-menthol formulation being more attractive for those initiating smoking. For example, one Brown & Williamson document outlined that "*a successful starter cigarette would need to provide a low tobacco taste, low impact and irritation, low tobacco aftertaste, and low menthol content*"(Cantrell, 1987 cited in Kreslake NTR 2008). Kreslake et al. (NTR 2008) refer to several Lorillard documents that detailed studies finding lower satisfaction ratings among younger people in their twenties when given cigarettes with higher menthol levels. By comparison, smokers aged 45 and older had higher satisfaction ratings of cigarettes with higher menthol levels.

Klausner (in press), in her industry document review, concluded that youth were a target of menthol marketing. She notes Philip Morris was concerned in the late 1970s that it lacked a competitive menthol product at a time when menthol cigarette use was increasing among the young, women and African Americans. "*We knew that Blacks, females, and younger smokers were more likely to smoke menthol cigarettes than whites, males and older smokers. …These differences could have a profound effect on the future growth of the menthol share of the market. We know, for example, that males, whites and older smokers are more likely to quit smoking than females, Blacks and younger smokers*" (cited in Klausner, in press). Anderson's tobacco industry document review (in press) also noted the importance of young people as a primary target group for menthol cigarette marketing. For example, she found documents that indicated that the marketing strategy for Newport through much of the 1990s was to "*continue to improve Newport's appeal as the 'peer' brand among young adult smokers*"(cited in Anderson, in press). She concluded that menthol is targeted to young people in the U.S. and that although different menthol brands are associated with different "brand identities," menthol in general is perceived to be for females, younger smokers and lighter smokers. She concludes that marketing that emphasizes "*coolness, refreshing sensations, mildness, soothing taste and youth fun-loving imagery*" contributes to these perceptions (Anderson in press). As detailed further in a later section on targeting to African Americans, Hafez & Ling (2005) document how the company used music to appeal initially to African Americans with its Kool Jazz concerts and related music efforts, but initially failed in its aim to "*find an idea or symbol that was truly pan racial*

*(universal racial*)." With its 2004 Kool Mixx campaign, which promoted elements of hip-hop culture through colorful cigarette packaging and related giveaways, such as radios, and music compact disks, the brand finally succeeded in reaching beyond its core target group of African Americans to young adults in general.

***Empirical studies***

Two empirical studies addressed the content and/or appeal of menthol marketing to adolescents or young adults. Unger et al. (1995) had 386 eighth-grade students in southern California rate each of 20 cigarette and alcohol ads that appeared in magazines or on television during early 1993. Brand name information was concealed on each ad. For Newport ads, 63.3 percent of students correctly identified the ad/s as being for cigarettes and 31.4 percent correctly identified the brand. For Kool ads, 10.5 percent correctly identified the ad/s as being for cigarettes and 11.6 percent identified the brand. This compared with correct identification of cigarette ad/s for Marlboro ads (87.8 percent) and correct identification of the brand (71.7 percent). Stage of smoking uptake (non-susceptible nonsmoker; susceptible non-smoker; user) was significantly associated with correct brand name recognition for all seven cigarette brands analyzed together and for Newport specifically, with users recognizing the ads significantly more than non-susceptible nonsmokers. Smoking susceptibility was positively associated with ad liking for the menthol brands Kool and Newport, and non-menthol brands Marlboro, Camel and Capri. These results were noted by the authors as consistent with the notion that cigarette advertising is attractive to susceptible nonsmokers as well and may influence them to experiment with the product.

Arnett & Terhanian (1998) showed 534 sixth- to twelfth-graders one print advertisement for each of five cigarettes brands—Marlboro, Camel, Kool, Benson & Hedges or Lucky Strike—and after each viewing they completed questions about the ad. Overall, 56 percent had seen the Kool ad more than six times, 38 percent liked it, 30 percent said it made smoking look appealing and 9 percent said it made them want to smoke that brand. Responses to these questions were higher for Marlboro and Camel and lower for Benson & Hedges and Lucky Strike. As for other brands, smokers more frequently indicated than non-smokers that they liked the Kool ad, and that the Kool ad made them want to smoke the brand.

Two studies provide ecological evidence that menthol marketing expenditures are related to adolescent cigarette brand preference. In a survey reported by Barker et al. (1994) the three most commonly purchased brands among adolescent smokers in 1993 (Marlboro, Camel and Newport) were the three most heavily advertised brands in 1993. This is despite the fact that Camel and Newport ranked seventh and fifth, respectively, in overall market share. Similarly, the increase from 1989–1993 in adolescents' brand preference for Camel cigarettes and the decrease in preference for Marlboro cigarettes during that period were not explained by changes in overall market share for these brands. Rather, these changes mirrored the direction of changes in brand-specific advertising expenditures: from 1989–1993, Marlboro advertising decreased to $75 million from $102 million, while Camel advertising increased to $43 million from $27 million. In contrast, the increased preference for Newport menthol cigarettes did not reflect the decrease in Newport menthol advertising expenditures to $35 million from $49 million during the same period. The authors suggest that regional differences in brand preference of adolescents and changes in those preferences during 1989–1993 might be explained by further analysis of the relation between regional advertising expenditures and brand preferences.

Pollay et al. (1996) modeled the relationship between advertising expenditures for nine brands including Newport, Kool and Salem and youth and adult cigarette brand preference between 1974 and 1993. Brand preference data was sourced from population surveys of youth and from Maxwell Report market share data for adults. Using standard techniques to analyze market share involving

Koyck-type models, they found that brand choices among teenagers were related to the extent of brand-specific cigarette advertising. Furthermore, the relationship between brand choice and brand advertising was significantly stronger among teenagers than among adults, by a factor of almost three (Pollay et al. 1996). These findings were robust to different assumptions, including the removal from the model of the most popular brand, Marlboro. These findings suggest that advertising for cigarette brands, including menthol cigarette advertising, has a greater impact on the brand preferences of teenagers than on adults.

*Summary*. Taken together, the section on youthful imagery in menthol marketing and the studies of industry documents described in this section confirm that the industry developed menthol marketing to appeal to youth. This is particularly true of the Newport brand, but that strategy was also adopted by other tobacco companies. Marketing messages positioned menthol cigarettes as an attractive starter product for new smokers who are unaccustomed to intense tobacco taste and/or high levels of menthol. Empirical studies provide further evidence of targeting: youth pay attention to and are attracted to menthol cigarette advertising. Cigarette advertising, including menthol advertising, has a greater impact on the brand choice of adolescents than it does for adult smokers. Studies of the role of menthol cigarettes in smoking initiation are discussed in chapter 6.

**Targeting: Women**

The white paper by Rising & Alexander (2010) points out that neither of two reviews of tobacco use among women included information that was menthol-specific. However, four tobacco industry document reviews included information about menthol marketing to women and one empirical study was focused on menthol marketing to women.

Carpenter et al. (2005) reviewed tobacco industry documents to show that extensive research was conducted by the industry on female smoking patterns, needs and product preferences, including menthol brands. The industry took account of women's social and cosmetic concerns for cleanliness and freshness through menthol cigarette product design and marketing. Lorillard, for example, experimented with a lemon-flavored menthol brand to address female sensitivity to unpleasant odor and aftertaste while capitalizing on their greater willingness to experiment with flavored cigarettes (Carpenter et al. 2005).

In their review of menthol cigarette marketing which includes tobacco industry documents, Sutton & Robinson (2004) point out that female smokers were the first targeted population for menthol cigarettes, when a 1930's advertisement for Spud menthol cigarettes proclaimed that "*to read the advertisements these days, a fellow'd think the pretty girls do all the smoking*" (USDHHS, cited in Sutton & Robinson 2004). These authors also noted that advertisements for menthol cigarettes from the 1950s onward had a distinctly feminine aura, featuring images of romance, flowering fields and springtime.

Klausner's document review (in press), mentioned above, described examples of marketing efforts directed at young females. For example in 1976, R.J. Reynolds described Lorillard's marketing effort as follows: "*Newport is placing increased emphasis on both young female and young male publications reducing older female publications [magazines]. Trend is toward younger readers and more men although overall female skew continues*"(document cited in Klausner, in press). Anderson's document review (in press) found that the three largest stand-alone menthol brands had different brand identities in the mind of both manufacturers and consumers. R.J. Reynolds documents portrayed Salem as a brand for smokers who are "*passive, feminine,*" describing its Salem Slim Lights variant to be positioned for consumers "*who desire a refreshing, low tar cigarette with (a) stylish, unpretentious feminine image*" (cited in Anderson, in press). Although the menthol segment "*skews female*" (documents cited in Anderson, in press), the Kool brand has a more masculine image,

described by Lorillard as "*a strong tasting, 'tough guy' cigarette*" (documents cited in Anderson, in press).

Fernandez et al (2005) conducted a descriptive analysis of menthol advertising in women's magazines compared to one men's magazine from 1988 to 2002. They found that the proportion of menthol ads out of all cigarette ads in each issue of magazines for white women did not differ from those for white men. However, as discussed more fully in the next section on ethnicity, there was a higher prevalence in magazines for Hispanic women.

*Summary*. Some menthol brands appear to be more targeted to women than men, while others have more masculine branding. However, there is more evidence that menthol marketing efforts are directed to youth and young adults in general, and to racial/ethnic subgroups of women (see also next section).

**Targeting: African Americans**

A large body of research has documented a disproportionate volume of cigarette advertising aimed at African Americans (cf. Primack et al. 2007). Only the subset of studies that categorized or quantified advertising for menthol cigarettes were examined for this section.

***Industry documents research***

The tobacco industry's internal documents illustrate sustained efforts to target African Americans through the development and advertising of menthol products and through corporate involvement in community-based organizations.

Balbach et al. (2003) reviewed 21,000 industry documents from a search string of terms related to R.J. Reynolds' launch of Uptown, a full flavor cigarette with lower levels of menthol than Salem, that was designed to appeal to young African American men. In a 1988 speech, a senior marketing official noted that the company had been using targeted marketing programs for decades: "*Reynolds tobacco has made a special effort to reach Black Smokers since the early 1960s…almost 70 percent of Black smokers choose a menthol brand. That's why special advertising and promotions for Salem cigarettes make a lot of sense in Black media and Black communities*" (Winebrenner 1988, cited in Balbach et al. 2003). The objective of R.J.Reynolds' Black Initiative Program was to regain its share of the African American market with a plan that featured "targeted Black print media (Jet, Essence, Ebony, key newspapers)" and a heavy "outdoor presence" (R.J. Reynolds 1990, cited in Balbach et al. 2003). Special packaging for Uptown reflected the company's beliefs that African American smokers opened cigarettes from the bottom and that a pack containing only 10 cigarettes would address the price sensitivity of the target audience. As a result of intense public pressure that followed R.J.Reynolds' press release, the company canceled the test marketing in Philadelphia and it abandoned the Uptown brand. A 1990 Philip Morris memorandum attributed this failure to its competitor's miscalculation: *"…marketing cigarettes to minorities was not new, saying so was."* (Philip Morris 1990, cited in Balbach et al., 2003) R.J. Reynolds' continued efforts to build brand share in the African American market were informed by the idea that "a highly visible commitment to social responsibility is fundamental to successful ethnic marketing" (R.J. Reynolds 1994, cited in Balbach et al. 2003). The authors noted that the company's strategy represented a combination of marketing existing menthol brands and building community relationships through support of local events and programs.

Hafez and Ling (2005) examined 210 industry documents related to music sponsorship and the Kool brand. Using music as the unifying element of an integrated marketing campaign aimed at young African American smokers was a proven formula for Brown & Williamson. Beginning with the first Kool Jazz concert in 1975, music promotions were used to maintain and augment market share in the

African American community. For example, a 1981 marketing document suggested that Kool's music campaign was originally developed "*on a strategy of more effectively reaching a major segment of our target audience, providing some kind of reward for this same group in the form of shows at bargain prices, and using the events to offset Black media availability deficiencies*." (Broecker 1981, cited in Hafez & Ling 2005). Vans equipped with loudspeakers, such as the "Kool Mobile Music Tour," were used to distribute free Kool cigarette samples in inner-city neighborhoods. Similar promotional techniques were the foundation of a 1981 Kool Market Development Program, which also encouraged the involvement of Brown & Williamson's sales representatives and managers in "*retail and community organizations that will assist in fostering positive relations in the Black community*." (Brown & Williamson,1982, cited in Hafez & Ling,2005).

Yerger et al. (2007) examined documents from the four companies (Brown & Williamson, Lorillard, Philip Morris, and R.J. Reynolds) whose menthol brands were the most heavily marketed in African American neighborhoods, using search terms related to African American, inner city, and urban. The analysis highlighted four strategies that were common to the industry's marketing programs in the inner cities from 1980 to the late 1990s: collecting psychographic and other data about African American consumers, using mobile vans to maximize the distribution of free cigarettes, developing specialized promotions for inner-city retailers, and engaging with local organizations to improve corporate image in the African American community. For example, Philip Morris sought to resolve problems with product availability and visibility in its "Black accounts," which were smaller liquor, grocery, and convenience stores in inner cities (Philip Morris 1984, cited in Yerger et al. 2007). The company redesigned product displays and paid retailers incentives to expand inventories and maintain visually prominent displays. First tested in Detroit, the program was later expanded nationwide to promote only menthol extensions of the company's most popular brands. Similarly, Brown & Williamson's "Kool Inner City Family Program" targeted the top 20 African American markets with free gifts for retailers and distributors, in-store advertising with African American models, and a variety of consumer offers (Lagreca 1987, cited in Yerger et al. 2007). R.J. Reynolds conducted interviews in inner-city zip codes with at least 50 percent African American residents and yearly household incomes under $20,000 in order to determine the boundaries of target neighborhoods for a "BYAS" (Black Young Adult Smoker) Initiative to increase market share for its Salem brand (Hawkins et al. 1989, cited in Yerger et al. 2007). Additionally, the value of the target audience for increasing brand share was described in the company's marketing report: "*The daring, flamboyant aspect of YA [young adult] Black smokers' personalities are evident in the many trends they start. And the fact that these trends often spread to the general population speaks to the unrecognized power and influence this subgroup yields on society…*" [emphases in original]. (Leferman Associates 1989, cited in Yerger et al. 2007). The authors concluded that geographically specific, aggressive, and intentionally disproportionate levels of marketing contributed to the tobacco-related health disparities that are evident among African Americans.
In their review of 144 industry documents, Johnson et al. (2008) identified similar targeting strategies, including industry-sponsored studies of African American culture, geographic targeting of urban areas, and investments in community, ethnic, and cultural events to enhance the industry's image in the African American community. For example, a 1976 marketing plan for Brown & Williamson reported: "*Kool is to develop programs which ingratiate themselves with the Black community. These programs are to show the makers of Kool as a community citizen, be backfire-proof and pave the way for supporting the brand*." (Brown & Williamson 1976, cited in Johnson et al. 2008).

Cruz et al. (2010) combined data from interviews with a former Brown & Williamson executive with analyses of tobacco industry documents to examine how a mix of marketing strategies was used to promote growth in menthol brand share among new and existing African American smokers in urban areas. According to the executive, Brown & Williamson used the term "focus" to refer to communities or stores in predominately low-income, African American areas that were identified as

being critical to increasing market share. For example, a 2002 business plan stated: "*Kool is delivering a premium message to its anticipated audience and concentrating in 22 trend-setting urban cities where the majority of this audience lives. These cities house the 102 focus assignments that Kool has identified to be key to the growth of the brand*" (Kool USA 2002, cited in Cruz et al. 2010). The company placed a greater quantity of interior and exterior signs in focus stores, and installed pack displays that featured more shelf space for menthol than for non-menthol brands. In addition, a 2002 marketing report documented that a multi-pack discount offered in 1,600 stores resulted in a larger market share for menthol than was observed in stores that did not receive the promotion. The authors concluded that menthol is the lynchpin in a tightly integrated series of campaigns aimed at the urban poor, especially African Americans.

Anderson's (in press) analysis of tobacco industry documents highlighted the role of marketing in the growing popularity of menthol cigarettes among African American smokers. According to a history of menthol brands written by an R.J. Reynolds marketing official, Kool led this trend by advertising to African Americans before its competitors did: "*Kool ads were in Ebony consistently from at least 1962, when our records start….Kool became 'cool' and, by the early 1970s, had a 56 percent share among younger adult Blacks – it was the Black Marlboro*" (Burrows 1984, cited in Anderson in press). This sentiment was echoed in a 1968 document from Philip Morris, which observed that menthol cigarettes were "*especially suited to the needs, desires and tastes of Negro consumers*." (Philip Morris 1968, cited in Anderson in press). In a "Black Opportunity Analysis" conducted by R.J. Reynolds in 1985, the company's research observed that an "underclass" of African American smokers would remain reliable customers in spite of growing health concerns: "*Blacks simply have more pressing concerns than smoking issues*." (R.J.Reynolds 1985, cited in Anderson in press). A 1983 industry study of low-income African American smokers observed that recall of advertising for specific menthol brands had improved since 1979 and "*the use of menthol cigarettes among the 18–34 lower income Black segment is almost universal*" (Lorillard estimated 1983, cited in Anderson in press). The author concluded that heavy targeting of largely African American urban populations is reflected in the nearly exclusive preferences for menthol brands among these smokers. Indeed, survey data described in chapter 4 confirms that although more menthol smokers are non-Hispanic white than African American, African Americans disproportionately favor menthol brands.

All types of research methods are subject to limitations, including qualitative documents research. A separate peer-reviewed paper by Anderson et al. (in press) identified several limitations that pertain to the studies reviewed in this section and elsewhere in this chapter. The sheer volume of documents available (more than 60 million pages) makes it impossible for researchers to determine that all relevant data were included for each topic examined. Although researchers aim to identify the most important documents among similar results for combinations of related search terms, this "saturation" was not achieved in all studies. The prevalence of acronyms and evidence of code words for menthol suggests that researchers' understanding of the documents may be hampered if the context is unknown. In addition, evidence that the industry tried to conceal its findings and to destroy documents increases the chance that relevant documents could be missing and that a researcher's understanding of a topic might be incomplete. Despite these limitations, the studies reviewed here are noteworthy for a consistency of evidence about the tobacco industry's systematic efforts to promote menthol cigarettes to African Americans.

***Advertising environment***

The white paper by Rising (2010) identified six relevant peer-reviewed articles. In addition, this section included one peer-reviewed study that was published after the white paper (Seidenberg et al. 2010). The studies are organized by the type of advertising examined and then reviewed in chronological order.

Magazines

Three studies documented that advertisements for menthol cigarettes were overrepresented in magazines that are popular with African American readers. Cummings et al. (1987) compared ads that appeared in three magazines with a largely African American readership (Jet, Ebony, Essence) and four magazines with a largely non-Hispanic white readership (Newsweek, Time, People and Mademoiselle). Full-page ads appearing between June 1984 and May 1985 were classified according to product, and brand (menthol, non-menthol, or both). Compared to the other magazines, those targeting African Americans contained a larger proportion of cigarette ads (12.0 percent versus 9.9 percent) and larger proportion for menthol cigarettes (65.9 percent vs. 15.4 percent). Both comparisons were statistically significant.

Informed by hypotheses from an analysis of tobacco industry documents about R.J .Reynolds' Uptown brand, one study compared cigarette ads for R.J. Reynolds brands that appeared in the same three magazines targeted at African American readers (Jet, Ebony, and Essence) with those that appeared in People Weekly (Balbach et al. 2003). Ads were sampled from two time periods: the years surrounding the introduction of the Uptown brand (1989–1990) and one decade later (1999–2000). Compared to People Weekly, the magazines targeted to African Americans contained a significantly larger proportion of R.J. Reynolds' ads for menthol brands—100 percent vs. 31.6 percent in 1989-90 and 97.7 percent vs. 0 percent in 1999-2000.

Landrine et al. (2005) examined cigarette ads that appeared in one magazine targeted at African Americans (Ebony), one at Latinos (the Spanish language edition of People) and one at non-Hispanic whites (the English language edition of People). In issues sampled from January 1990 through August 2002, the proportion of ads for menthol cigarettes was 67.2 percent in the African American magazine, 35.3 percent in the Latino magazine, and 17.3 percent in the other magazine. Unadjusted odds ratios suggested that the African American magazine was 9.8 times more likely to contain a menthol ad than the white magazine; the Latino magazine was 2.6 times more likely to contain a menthol ad.

In a submission from Lorillard to FDA, the company stated that "Newport marketing expenditures have not been disproportionately weighted toward African American smokers or any other ethnic group or gender" (p. 44, Lorillard, July 2010). Although the company's advertising expenditures for general market magazines consistently exceeded its expenditures for African American magazines (see Figure 11, Lorillard July 2010), that difference does not preclude a pattern of targeted marketing that was documented in the studies of magazines. Assuming lower rates are paid to advertise in magazines with a smaller circulation, it would be possible to place a larger volume of ads in African American magazines at a substantially lower total cost. Lorillard increased its spending on African American magazines relative to general market magazines in 1993 (see Figure 11, Lorillard July 2010), but no studies examined the relative impact of that increase on the proportion of ads for menthol brands. Content analyses of magazine advertising for menthol and non-menthol brands after 2002 were not found.

Outdoor and retail advertising

All four studies on this topic found that menthol cigarettes were marketed disproportionately in areas with more African American residents. Altman et al. (1991) compared billboard advertising by the racial/ethnic demographics of census tracts in San Francisco, California. Each of the 901 billboards in the city was photographed between 1985 and 1987. Census tracts were categorized by the predominant racial/ethnic group and without regard to the proportion of non-Hispanic white residents. Thus, African American neighborhoods referred to census tracts where 30 percent of the residents were African American and they were the dominant ethnic/racial minority group, even if a

larger proportion of residents were non-Hispanic white. The proportion of all billboards that advertised menthol cigarettes was 22 percent in African American neighborhoods, 17 percent in Hispanic, 11 percent in white and 10 percent in Asian neighborhoods. African American neighborhoods were significantly more likely to contain billboards advertising menthol cigarettes.

Pucci et al. (1998) described outdoor advertising for cigarettes in six Boston neighborhoods—two with the highest median household income, two with the lowest, and two in the middle range. In the two of the neighborhoods, 89.2 percent and 62.3 percent of the residents were African American. All outdoor ads for tobacco, including billboards, placards, posters, stickers, banners, neon and freestanding signs, were counted and categorized by brand. Ads for exclusively menthol brands, Newport, Kool, and Salem, made up 49 percent of the outdoor advertising for cigarettes in the two African American neighborhoods, compared to 38 percent in the Latino neighborhoods, and 22 percent in the non-Hispanic white neighborhoods. The proportion of all ads for menthol, regardless of brand, was not coded.

Laws et al. (2002) visited all stores in 10 demographically contrasting areas of Boston, Massachusetts and compared the proportion of all cigarette ads for menthol brands. To identify predominantly Latino and African American neighborhoods, the researchers selected census tracts of similar per capita income but different ethnic compositions. The comparison areas were predominantly non-Hispanic white and more affluent. Field observations were conducted in all 128 stores that sold cigarettes in 1999. Stores in the area with the highest proportion of African American residents contained the highest concentration of cigarette ads for menthol brands—32 percent in that area compared to 13 percent overall. The difference between the proportion of ads for menthol in predominantly minority areas (29 percent) and non-minority areas (12 percent) was statistically significant.

Similarly, Seidenberg et al. (2010) compared the proportion of all cigarette ads for menthol on storefronts in two Boston neighborhoods, one with predominantly African American residents (50.1 percent) and one with few African American residents (2.7 percent). To eliminate the large discrepancy in the number of retailers that sold tobacco in the two areas, the researchers visited all 59 stores that sold cigarettes in one zip code in the African American neighborhood with all 43 stores that sold tobacco in the comparison community. The proportion of cigarette ads for menthol brands was significantly greater in the African American neighborhood (53.9 percent vs. 17.9 percent). Adjusting for other characteristics of the ads (including size, proximity to school, and the presence of a price), the odds of finding an ad for menthol cigarettes was five times greater on storefronts in the African American neighborhood.

One weakness of the studies about outdoor and retail advertising is that they were limited to small geographic areas. In addition, some of the analyses did not control for neighborhood income, making it difficult to discern whether neighborhoods were targeted because they were predominantly low-income, African American, or both.

*Summary*. All of the tobacco industry document reviews provide evidence that the tobacco industry developed specialized brands and tailored marketing strategies to promote menthol cigarettes to African Americans. Studies of the advertising environment that have compared menthol and non-menthol advertising provide corroborating evidence of the target marketing strategies that were identified in the industry documents research. In all three empirical studies on the subject, menthol cigarettes were advertised disproportionately more than non-menthol cigarettes in magazines aimed at African American readers, compared to magazines with low African American readership. Both studies of outdoor advertising and both studies of retail store advertising showed a higher proportion of menthol ads out of all cigarette ads, in neighborhoods with more African American residents than neighborhoods with lower proportions of African American residents.

**Targeting: Other Race/Ethnicity**

Although there are many studies that confirm African Americans to be a particular target audience for menthol marketing efforts, there are fewer industry document reviews and empirical studies that point to the use of menthol advertising targeted towards particular ethnic groups, such as Hispanics, Asian Americans and Hawaiian/Pacific Islanders. Nonetheless, available studies generally show purposeful targeting towards these ethnic groups.

***Industry document reviews***

A review of tobacco industry documents on targeting of Asian Americans and Pacific Islanders described many tobacco marketing campaigns to reach these population subgroups, but marketing strategies for menthol cigarettes were not specifically mentioned (Muggli et al. 2002). A tobacco industry document review by Anderson (in press) identified menthol marketing campaigns specifically aimed towards Asians and Hawaiians/Pacific Islanders. For example, a study of an R.J. Reynolds' Kool cigarette marketing campaign targeting Hawaiians in 1988 remarked that the use of ethnic models "*could provide an opportunity for Kool to capitalize on being the first to employ ethnic advertising in Hawaii*" and "*display what islanders call the aloha spirit*" (Anderson in press). Anderson (in press) also documented that Philip Morris' Marlboro promotion plan in 1992 included "*special programs to menthol Hispanic and Asian smokers*" to increase its market share among young adult smokers.

***Empirical studies***

Altman et al. (1991) conducted a descriptive analysis of billboards by census neighborhood demographic characteristics during 1985-1987 in San Francisco. Overall, 19 percent of billboards featured ads for tobacco (and 13 percent for menthol cigarettes). Menthol cigarette billboards were more likely in African American (22 percent) and Hispanic (17 percent) neighborhoods than in Asian (10 percent) and white (11 percent) neighborhoods. Although no statistical analysis was undertaken, the rates appeared disproportionately lower for non-menthol cigarette billboards in African American (2 percent) neighborhoods, while being around half the rate in Hispanic (8 percent), Asian (4 percent) and white (6 percent) neighborhoods.

Two studies focused on magazine advertising were located. Landrine et al. (2005), in the same study described above in the section on targeting African Americans, Landrine et al. (2005) examined tobacco advertising in issues of Ebony, People magazine and People in Spanish between 1988 and 2002. In this study, ads for menthol brands were significantly more likely in the Spanish-language edition of People (35 percent of cigarette ads), compared to 17 percent of ads in the English language version of People magazine. A more recently published study reported on a descriptive analysis of cigarette ads in the English- and Spanish-language versions of Cosmopolitan and Glamour magazines from 1988 to 2002 (Fernandez et al. 2005). Despite these magazines having the same publisher, content, length and advertising policies, there were significantly more ads for menthol brands in the magazines for Spanish-speaking women (51.1 percent of cigarette ads) than in the versions for English-speaking women (28.3 percent of cigarette ads). In fact, magazines targeting Spanish speakers were 2.64 times more likely than the English language magazines to contain ads for menthol cigarettes. Sixty percent of the cigarette ads in the Hispanic versions were for Kool and Newport, compared to only 26 percent of the cigarette ads in the white magazine versions. Although this study was looked at just two women's magazines, it focused on popular titles. These studies both provide evidence of targeting of Hispanics through menthol magazine advertising.

The point of sale advertising study by Laws et al. (2002), described in a previous section, audited stores in Boston neighborhoods for tobacco advertising. They found 32.3 percent of all interior and exterior advertisements for menthol brands were in neighborhoods with the highest percentages of minority (African American and Hispanic) residents while 10 percent of all menthol cigarette ads were in neighborhoods with the lowest minority populations—a statistically significant difference. Another retail-focused study by Glanz et al. (2006) reported on an audit of tobacco advertising in 184 tobacco retail outlets in Hawaii in late 2002. Overall, advertisements for Kool menthol cigarettes were the most common of all tobacco ads identified, irrespective of whether ads were a straight count or were weighted by size. Kool also had the most outdoor ads using both outcomes. It had the largest number of indoor ads when a straight count was used, and was second to Marlboro when adjusted for size of ad. This retail advertising for Kool was thought to reflect the preference among Hawaiian youth for menthol cigarettes (especially Kool), which differs from youth preferences for Marlboro on the mainland (Appleyard et al. 2006; USDHHS USSG report 2004).

*Summary*. Comparatively fewer reviews and empirical studies examined whether menthol marketing has been targeted to racial/ethnic groups other than African Americans. Although no tobacco industry document reviews were available on the topic, all four empirical studies examining menthol and non-menthol advertising found a higher proportion of menthol ads out of all cigarette ads in Hispanic neighborhoods (2 studies)/magazines (2 studies), than in non-Hispanic white neighborhoods/magazines. A tobacco industry document review provided evidence that Asian Americans and Hawaiian/Pacific Islanders were targeted in menthol marketing. One empirical study showed a high prevalence of retail advertisements for Kool cigarettes in Hawaii.

**Does menthol marketing influence perceived taste and/or sensory experience of menthol cigarettes?**

Throughout TPSAC meetings, tobacco industry representatives consistently pointed to taste as being the main driver of preference for menthol cigarettes among menthol cigarette smokers (July 2010). However, taste is a complex perception, since it is the product of both flavor and other sensory attributes. Consumers can also be quite unclear as to what they mean by taste, often simply echoing descriptions given to them by tobacco branding, labeling and advertising (Pollay & Dewhirst 2002). Furthermore, there is evidence that consumers use elements of taste to infer the healthiness and other attributes of products. This is likely to be a natural human tendency, with some evolutionary advantages. For example, a key element of unpleasant taste is the perception of bitterness, thought likely to have evolved in animals to help them avoid eating plants and other foods containing toxins and other harmful chemicals.

This section is organized into two parts. First, it summarizes consumer research from other domains related to taste perception to document how branding and labeling can influence consumer taste perception and sensory evaluation. Subsequently, this section summarizes studies specifically pertaining to messages about cigarettes in general and menthol cigarettes in particular.

It should be noted that additional literature on the sensory experience of smoking menthol cigarettes compared to non-menthol cigarettes is summarized in chapters 3 and 6.

**Role of branding and labeling in taste perception and sensory evaluation**

Consumers have generally poor ability to discriminate between tastes, due in part to our taste buds' ability to detect only sweet, sour, bitter, salty and umami tastes. Multiple other senses are involved in taste perception, including smell, sound (when bitten or chewed) and touch (texture in the mouth and temperature) (Elder & Krishna 2009). Visual cues also contribute to the sense of taste by generating expectations about flavor. Evidence from the consumer science literature about the

degree to which branding and labeling influence perceptions of the taste of food and drinks illustrates that taste perception is subjective and easily manipulated (Deliza & MacFie 1996). Use of branding, including use of color and descriptive names, results in an expectation or sensory halo effect, whereby the expectation halo influences how a person thinks a product might taste as well as taste perceptions and liking when the product is consumed.

There are several ways in which expectations might influence the sensory experience of products and their liking of the product (Deliza & MacFie 1996; Cardello 2007). One model predicts the existence of a contrast effect (or boomerang effect), which may occur if the consumer holds expectations that are vastly different from the eventual product performance. Under these circumstances, consumers who have very low (or very high) expectations about a product might be pleasantly surprised (or very disappointed) by the contrast when the product is actually consumed. However, contrast effects have rarely been observed in the literature, even when disconfirmation of expectation is arguably quite large (Cardello 2007). Another model, known as the assimilation model, predicts that evaluation of the product will change in the direction of expectations. In other words, an expectation can be a driver of sensory experience and liking. In studies where food and beverages have been used as test products, the vast majority of observed effects have been assimilation effects (Deliza & MacFie 1996; Cardello 2007).

For example, bitter coffee was appraised after sampling as tasting less bitter only among those consumers who were exposed beforehand to three advertisements asserting that the coffee was not bitter (Olson & Dover 1978). An early study found that a slice of turkey was rated more positively after tasting if consumers thought it was a popular brand rather than an unknown brand (Makens 1965). In a more recent study, people who were given an energy bar supposedly containing soy protein were more likely to rate it as 'grainy' and 'tasteless,' compared with identical bars that contained no mention of the word 'soy' (Wansink & Park 2002). In fact, neither bar contained soy. In another study in Illinois, evocative descriptive names of cafeteria meals (such as 'Succulent Italian Seafood Filet') led to meals being rated after consumption as more appealing, tastier and caloric, and eliciting more positive comments, than exactly the same meals with less descriptive names (such as 'Seafood Filet') (Wansink et al. 2005). Color and labeling influenced perceptions of otherwise identical M&M candies: brown M&Ms were rated as more 'chocolatey' than all other colors, and those labeled as *dark chocolate* were rated as more 'chocolatey' than those labeled *milk chocolate* (Shankar et al. 2009). Even children express the effects of branding on taste perception: a study of three to five year olds in California found that identical food products were appraised as tasting better when they were branded with McDonald's than when they were unbranded (Robinson et al 2007).

There is variability in the extent to which brand and label information influence evaluation of different types of products. For example, in another controlled cafeteria study, diet and health labels (e.g. , chocolate pudding vs. healthy chocolate pudding; pineapple soy muffins vs. diet pineapple soy muffins) improved the rated taste of desserts but not the rated taste of entrees (Wansink et al. 2004). In interpreting these findings, the investigators suggested that people might expect a dessert labeled as healthy or diet-related to not taste very good. When it tastes better than expected, it prompts an over-evaluation of taste ratings. By contrast, health labels had less ability to influence evaluation of the entrees offered, since they were already relatively healthy. This study suggests that for products that are less healthy, descriptive labels likely have greater capacity to promote positive taste evaluations.

In recent years, much progress has been made in understanding the neural basis of cognitive effects on taste and other sensory experiences. This research has used functional magnetic resonance imaging (fMRI) technology that measures blood flow in various regions of the brain in response to product consumption under varying conditions of expectation. In summary, these studies

demonstrate that expectancies can change both the subjective evaluation of the product and the neural response to these products (Cardello 2007; Cardello & Wise 2008). For example, McClure et al. (2004) found that Coke was rated higher in a subjective taste test when consumed from a cup bearing the Coke logo than from an unmarked cup. Consistent with these subjective ratings, the study also found that the image of a Coke can presented prior to Coke tasting resulted in greater brain activity in the dorsolateral prefrontal cortex (DLPFC), hippocampus and midbrain, compared to unbranded Coke delivery (McClure et al 2004). This finding is important because the hippocampus and DLPFC have both been previously implicated in processing emotion and affect as it relates to behavior change. The investigators suggested that branding information biases preference decisions through the DLPFC, with the hippocampus engaged to recall the associated information (McClure et al 2004). In a more recent study, Nitschke et al. (2006) found that when people tasted a highly aversive (bitter) fluid, the level of activation in the bilateral taste cortex in the brain was reduced when they were told it would be only mildly aversive, compared to when they were told that it would be highly aversive. This misleading information also led to people rating the bitter fluid as less aversive than that same fluid when it was tasted following the truthful cue. Together, these studies imply that branding and labeling can lead people to hold more favorable expectations about a product, and these expectations influence brain functions in ways that result in an enhanced sensory experience.

The influence of branding on sensed experience when products are consumed is automatic, in that consumers are largely unaware of these processes. In part, this is likely to be because when consuming a product, consumers have limited time to make their evaluation and tend to rely on short-cuts – easily available information which is processed quickly and efficiently to assist their decision-making and guide their evaluation (also known as heuristic processing). Most consumers do not think that branding or labeling prior to tasting would change their sensed experience of products and are, in fact, unable to correctly predict the results of taste tests in which expectancies are manipulated in the ways described (e.g., Lee et al. 2006).

It is important to note that branding and labeling are not the only information available to form consumer expectations: the shared experiences and recommendations of others and one's own experience with the class of product to be tasted will also influence expectations and therefore one's subjective perceptions of taste. Individuals who have less experience with the class of products to be tasted and low involvement with the product tend to rely more on branding and labeling information (Deliza & McFie 1996; Cardello 2007).

Overall, this body of consumer sensory research suggests that a product that people may find unremarkable or even aversive, or that they know may be unhealthy, can be manipulated to be experienced as more pleasant by strengthening consumer's expectations that the product will offer a positive experience. Branding and labeling therefore have a critical role to play in raising consumer expectations about a product. As suggested by Cardello (2007), "*the opportunity exists to improve the acceptance of a product and its market share through creative marketing that establishes a positive image and expectation for a product. Here lies the heart of all advertising strategies aimed at improving product image*" (Cardello 2007, p.230). Those who have less experience with a class of products, including young people, may be especially vulnerable to the effects of marketing on product liking and sensory experience, and therefore, on its consequent influence upon product acceptance and use.

**Branding and labeling effects on subjective experience of cigarettes**

There is good evidence to show that branding and labeling modify the subjective perception of tobacco when it is consumed. Most of this research has been undertaken using cigarette packaging as the medium for branding. In a review of internal tobacco industry documents on tobacco packaging made public through litigation filed against major U.S. cigarette manufacturers, Wakefield

et al. (2002) found that tobacco companies employed the concept of expectancy manipulation or 'sensation transfer' to assist them to design cigarette packaging. In the industry documents, the term 'sensation transfer' is used to refer to the phenomenon whereby brand elements on packaging create expectations of what the cigarette will be like when smoked—also referred to as the 'halo effect' of branding. Numerous tobacco industry studies were found whereby exactly the same cigarettes presented in different packs led consumers to evaluate them differently when they were smoked. Tobacco companies discovered that lighter colors on the pack promoted perceptions of lower cigarette strength. For example, identical cigarettes presented in blue packs were described after being smoked as 'too mild,' 'not easy drawing,' and 'burn too fast,' whereas when presented in a red pack, they were described as 'too strong' and 'harsher' (Wakefield et al. 2002).

A published empirical study randomly assigned 200 male and female smokers to smoke identical cigarettes that were branded either "April" or "Frontiersman" (Friedman & Dipple 1978). Female smokers who smoked the cigarettes with a feminine brand name rated all aspects of taste and enjoyment more favorably than the female smokers who tried the identical cigarettes with a masculine name. Similarly, male smokers favored the masculine brand, but the effect was less pronounced. In their industry document review on marketing imagery, Pollay & Dewhirst (2002) find that market researchers for the tobacco industry and its advertising agencies were not confident consumers knew what they were talking about when referring to 'taste' of a cigarette. As one document from 1975 detailed, *"[I]t is almost impossible to know if the taste smokers talk about is something which they, themselves, attribute to a cigarette or just a 'play-back' of some advertising messages."* (Marketing & Research Counselors Inc., cited in Pollay & Dewhirst 2002).

DiFranza et al. (2002) suggest that the process by which pack design communicates what consumers might expect from the cigarettes is subconscious. An R.J. Reynolds marketing department document indicated that "*on the first level a package serves to reinforce the brand's advertising in establishing a certain brand image or set of connotations, and in doing so it operates on a subconscious level. That is, the fact that it does this is not readily apparent to the consumer*" (Marketing Research Department 1969, cited in DiFranza et al. 2002). DiFranza et al. also note that the influence of pack design on the subjectively experienced qualities of the cigarette is of such a magnitude that when purely objective ratings of the cigarette qualities are desired, the test cigarettes are not branded (DiFranza et al. 2002). At the July 15, 2010 TPSAC meeting, tobacco industry representatives acknowledged that the presence of branding information does influence consumer evaluations of cigarettes when they are smoked (transcript p.183–185.) Thus, consumers' perceived taste and sensory evaluation of cigarettes are influenced not only by the product itself, but by related branding information, including color, pack design, and labeling.

In a review of tobacco industry documents, Wakefield et al. (2002) found that green colors in menthol packaging were predominantly used to influence expectations of menthol taste and sensory experience. For example, after smoking identical menthol cigarettes in a Philip Morris test, panelists consistently ascribed more menthol coolness to those presented in the darker of two shades of green, compared with the standard white paper cigarettes. There was no discernable difference between the lighter shade of green and white (Martin 1969, cited in Wakefield 2002). Another Philip Morris test found that the menthol brand Saratoga was perceived as having more menthol when the cigarette itself was wrapped with green paper than either production Saratoga, which had the same menthol level but was in a white wrapper, or the More brand, which had a higher menthol level but was in a brown wrapper—indicating that the green paper had an effect on the amount of menthol perceived (Howes 1976, cited in Wakefield 2002). A similar review of tobacco packaging by DiFranza et al. (2002) also commented on these sensation transfer tests, giving an example of an R.J. Reynolds pack test in which men strongly preferred the cigarette smoked when taken from an 'ice pack' over a cigarette smoked when taken from a 'green pack,' even though the cigarettes were identical in composition. The test concluded "*the cigarette related to the ice pack seems to be perceived as being*

*a milder cigarette by the respondents. The ice on the ice pack connotes a cool/refreshing cigarette to the respondents*" (Magnus 1969, cited in DiFranza et al. 2002). Thus, manipulating elements of package design is sufficient to change smokers' expectations and evaluations of menthol cigarettes when they are smoked regardless of how much menthol they contain.

Consumer testing of cigarette packs was also undertaken to ensure that expectations of menthol content remained stable when lower tar and nicotine brand extensions were introduced. DiFranza et al. (2002) point to a consumer study by R.J. Reynolds in 1975 for three pack design options for Salem menthol cigarettes. Overall, the report concluded that "*the 'Green Line' design was the most effective in connoting lower tar and nicotine, especially among Salem smokers and female smokers. This package was also the least likely of the three alternatives to connote less menthol*" (Daniel 1975, cited in DiFranza et al 2002).

*Summary*. There is strong evidence from the general marketing literature that branding and labeling influence consumer expectations about a product and the subjective experience of product consumption. Tobacco company research and empirical studies demonstrate that elements of packaging such as branding, color and use of descriptive labels influence consumer beliefs about cigarettes, as well as the sensory experience when the product is smoked. There have been no peer-reviewed experimental studies specifically on the effects of menthol branding on consumer taste and sensory evaluation. However, consumer testing conducted by tobacco companies demonstrates that manipulation of elements of menthol cigarette packaging influences consumer sensory experiences of perceived coolness, amount of menthol, mildness, and overall preference. Thus, menthol packaging reflects the tobacco industry's knowledge about how color, labeling and other elements of branding will improve the consumer experience of the product's characterizing flavor.

## DO CONSUMERS PERCEIVE MENTHOL CIGARETTES AS SAFER OR LESS HARMFUL THAN NON-MENTHOL CIGARETTES?

As indicated in the section on Packaging, for both menthol and non-menthol cigarettes, different shades of the same color and the proportion of white space are commonly used to distinguish between variants of the same brand family. Two studies illustrate that color and other branding features influenced adults' and adolescents' (ages 12–17) expectations about perceived health risk (Hammond & Parkinson 2009); Hammond, Dockrell, Arnott, Lee & McNeill 2009). Using a paired comparison study design with one element of packaging manipulated, adult smokers rated cigarette packs that featured lighter colors, sensory descriptors (smooth, light, mild), and pictures of filters as delivering smoother taste, less tar and reduced health risks (Hammond & Parkinson 2009). In addition, beliefs about taste were positively correlated with beliefs about tar delivery and health risk. These studies did not include menthol packs, but they illustrate the extent to which branding elements about taste and sensory experience may contribute to beliefs that some cigarettes are less harmful than others. This section examines evidence from qualitative analyses of tobacco industry documents, qualitative focus group research, and survey research that examined consumer perceptions about the health benefits and relative risks of menthol cigarettes.

### Industry document reviews

Reviews of tobacco industry internal documents made public as a result of legal proceedings against tobacco companies provide a wealth of information about consumer perceptions of menthol cigarettes. The limitations of industry document reviews have been outlined in a previous section.

Giovino and colleagues (2004) identified tobacco industry documents in the late 1960s and 1970s which suggested that menthol smokers, including African Americans, perceived menthol cigarettes to

be less hazardous than non-menthol cigarettes. Giovino et al. refer to a study from R.J. Reynolds called "Project Y" where menthol smokers were classified as 'more concerned' than smokers of non-menthol cigarettes. They point to a Philip Morris report on focus group discussions undertaken to assess the attitudes of African American smokers about menthol cigarettes, which states, "*There are indications that menthols tend to be considered generally better for one's health. That impression refers not only to the health of the respiratory tract, but the whole organism. The majority view is that menthols are 'less strong' than regular cigarettes, and that a cigarette which is 'less strong' is better for a person's health"* (Tibor Koeves, cited in Giovino et al. 2004). It was uncommon for consumers to openly assert that menthol cigarettes conferred an explicit health advantage; rather, that perception was more implicit and described indirectly by the use of terms such as strength, cooling, lower in tar, and less irritating. Consistent with the promises of early menthol marketing campaigns discussed in a prior section, tobacco industry documents indicated that individual sampling of menthol cigarettes often occurred because of a cold or sore throat, and during the winter months (Tibor Koeves, cited in Giovino et al. 2004), reflecting the higher seasonal rates of acute respiratory infection during this time. Another R.J. Reynolds document reported that African Americans were more likely than whites to believe menthol cigarettes were "*better when you have a cold,*" "*less likely to make you cough,*" and "*less irritating to the throat*" (R.J. Reynolds, cited in Giovino et al. 2004).

In their tobacco industry document review, Kreslake et al. NTR (2008) summarize some of the tobacco industry's extensive research to assess how product design influences consumer ratings of attributes of interest. They find that the way in which consumers describe product attributes differs between menthol and non-menthol smokers. For example, cigarette strength for menthol smokers is defined by menthol intensity, minty flavor and tobacco flavor, whereas for non-menthol smokers, it is defined by throat impact and throat scratch. Harshness is defined by amount of tobacco flavor for menthol smokers, but by throat impact, presence of a burnt or tarry flavor, and absence of added flavor for non-menthol smokers (Swaim, cited in Kreslake et al. NTR 2008). There was evidence in tobacco industry consumer research that consumers used menthol cigarettes as part of a purposive effort to change their smoking behavior in ways consistent with trying to reduce their exposure to the health harms. Kreslake et al. (NTR 2008) describe qualitative research with consumers undertaken by tobacco companies between 1972 and 1994. These studies suggest that some menthol smokers switched from non-menthols in an effort to maintain their smoking without the negative physical symptoms they attribute to non-menthols. These studies also describe consumers' use of menthols during a respiratory problem such as a cold, sore throat or bronchitis. Switching to menthols to try to cut down on the amount smoked was reported in qualitative interviews. Menthol cigarettes were perceived by consumers as milder than regular cigarettes, but were seen as distinct from 'light' cigarettes because they were viewed as not being compromised by the higher filter ventilation. A report by Roper (cited in Kreslake NTR 2008) on smokers of 'low tar' cigarettes concluded that "*menthol seems to compensate or make up for both few cigarettes and light cigarettes"* by providing *"an extra something.*" Kreslake et al. (NTR 2008) conclude that smokers who may otherwise quit because of the perceived harshness and health effects of 'higher tar' cigarettes, seek out menthol cigarettes for their 'substitute sensation' as they move to what they perceive is a lower tar cigarette with its associated implicit health reassurance. Tobacco industry document reviews on the role of menthol cigarettes in influencing quitting beliefs and intentions are discussed more fully in chapter 6 in the section on smoking cessation.

Anderson (in press) also analyzed industry documents on consumer perceptions of menthol cigarettes up to the mid 1990s. Consistent with Kreslake et al. NTR (2008) and Giovino (2004), Anderson also concluded that consumers view menthol cigarettes as safer, or less harmful, than non-menthol or full-flavor cigarettes. She notes that menthol smokers sometimes identify this perception explicitly (directly) and sometimes implicitly (indirectly), through the use of terms that suggest improved safety or health benefits, such as 'light,' 'mild,' 'cooling' or 'soothing.' For example, she

cites an American Tobacco focus group study, which observed that "*there were indications that the menthol smoker subconsciously perceived menthol cigarettes as being healthier. There was somewhat of a 'health image' associated with menthol, related to its masking of the tobacco taste and its association with medicine, colds and sore throats*" (American Tobacco, cited in Anderson in press). Anderson found that menthol cigarettes have been marketed as, and are often perceived by consumers to be, milder and less irritating than regular cigarettes and therefore less of a health threat, in the same way that light/low tar cigarettes are mistakenly perceived to be safer. She concludes that menthol cigarettes provide psychological reassurance to consumers without providing any real health protection. This is exemplified in an R.J. Reynolds analysis of potential for share growth of menthol in 1997: *"[t]he health concern was perhaps the primary motive for switching to menthol in the first place. In the hierarchy of product benefits/attributes desired by menthol filter smokers, throat concerns rank just behind generic taste and satisfaction*" (RJR, cited in Anderson in press).

Klausner's (in press) tobacco industry document review was consistent with the findings of these other reviews in concluding that some young people smoke menthol cigarettes because they perceive them to be less harmful than non-menthol cigarettes, a notion they point out was encouraged through menthol advertising. Documents referred to young smokers choosing menthol cigarettes because they found the menthol "*less harmful*" or "*moving away from the problem [of smoking a harmful product]*" and "*a guilt-reducing mechanism…it manages in some small measure to subtly disguise the sin*" (cited in Klausner, in press). Klausner also notes that some youth use menthols for the first time when they have a sore throat or a cold because they perceive them to be less irritating than non-menthols. For example, a British American Tobacco study from 1982 found some smokers "*ascrib[e] medicinal properties to the mentholation*" and believe that "*menthols are somehow less intrusive or even less harmful than regular cigarettes.*"

**Empirical and qualitative studies**

The White Paper by Rising & Alexander (2010) found no published empirical studies of youth beliefs about of menthol cigarettes. Studies of adults' beliefs about of menthol cigarettes are discussed below. After first considering contextual and methodological interpretation issues, this section presents studies grouped by population surveys, clinic surveys, and focus group studies.

Surveys that compared menthol and non-menthol smokers' beliefs about the overall harm of smoking or disease risks of smoking (referred to in Lorillard's submission, July 2010) were not reviewed in this chapter. These surveys assessed the perceived harm or risk from smoking cigarettes, but not menthol cigarettes in particular. Over the years, a growing proportion of smokers agree that cigarette smoking is harmful (e.g., NSDUH surveys), as might be expected from the considerable investment in media campaigns about this important public health concern. Menthol smokers differ from non-menthol smokers on many demographic and psychosocial traits that would influence their beliefs about the harms of smoking. Comparing the beliefs about smoking for menthol and non-menthol smokers does not inform the research question about the perceived harm of menthol cigarettes in relation to non-menthol cigarettes.

Research about the relative harm of menthol cigarettes must be interpreted within the context of increased mass media education about the risks of smoking. During the 1990s, several states implemented tobacco education campaigns and after the MSA many more state-funded campaigns publicized the serious health harms of smoking and encouraged smokers to quit (NCI 2008). Over the past decade, a national media campaign from the American Legacy Foundation (Legacy) also broadcast messages about the misleading and deceptive practices of tobacco companies. Another Legacy media campaign emphasized the difficulty of quitting smoking and encouraged smokers to seek help. Media coverage about the deceptive marketing of "light" and "low tar" cigarettes is also

relevant. A federal court order in 2006 prohibited the defendant tobacco companies from stating or implying any health benefits of a brand of cigarettes through the use of misleading terms such as "light," "mild," and "low tar." The FDA implemented a ban on these terms in the marketing and sale of cigarettes in June 2010. During the past decade, the public has been exposed to ongoing news coverage and media education that refutes tobacco marketing claims that some cigarettes are less harmful than others.

Against this backdrop it is increasingly unlikely that consumers would identify any cigarettes as offering explicit health benefits. In addition, questions that ask respondents about comparative risks are likely to elicit responses that different types of cigarettes are similarly risky. However, even in a population acutely aware of the harms of smoking, some studies reveal consumer perceptions that some cigarettes are safer than others (Hammond & Parkinson 2009; Hammond et al. 2010). When socially desirable responding is likely, studies that require consumers to choose between two or more products that differ on specific dimensions of interest are more sensitive indicators of consumer beliefs. Such studies typically compare two or more products with one element manipulated, or ask respondents to rank order products along particular dimensions. These kinds of comparative assessments are routinely used in consumer research, including in tobacco company consumer product testing, and in the cigarette pack testing studies by Hammond and colleagues (Hammond & Parkinson 2009; Hammond et al. 2010). To date, no published studies have used these methods to compare consumer perceptions of menthol and non-menthol cigarettes. However, reports from qualitative methods that permit more in-depth and indirect assessments of consumer beliefs about menthol cigarettes are included in this review. Assessment of implicit health benefits are particularly revealing, including aspects of taste and sensory experience, such as cooling, soothing, smoothness, mildness, low nicotine, lower strength, easing uncomfortable physical symptoms, or attributes such naturalness. As indicated earlier, smokers interpret these kinds of attributes to imply reduced harm (Pollay & Dewhirst 2002; Wakefield et al. 2002; DiFranza et al. 2002; Hammond & Parkinson 2009; Paek et al. 2010).

**Population-based surveys**

Two secondary analyses examined adults' perceptions of the explicit benefits or harms/risks of menthol cigarettes. Davis et al. (2010) examined responses of 4,556 adults to questions about menthol cigarettes from the HealthStyles survey that was mailed to a national consumer panel in 2009. The survey asked respondents "*Do you believe menthol cigarettes, such as Newport, Kool, Marlboro Menthol, Camel Menthol have beneficial health effects?*" Excluding 250 respondents who did not know what menthol cigarettes were or provided no answer, 76.8 percent of respondents (and 81.2 percent of smokers) believed menthol cigarettes had no health benefits, 18.9 percent (14.7 percent of smokers) did not know whether they did or not, and 4.3 percent (4.2 percent of smokers) thought they did have health benefits. African Americans (9.0 percent), those with up to high school education (8.6 percent) and those with annual incomes less than $25,000 (8.0 percent) were more likely to believe that menthol cigarettes had health benefits. However, there were no differences by age group.

The HealthStyles survey also asked whether "*menthol cigarettes such as Newport, Kool, Marlboro Menthol, Camel Menthol are: more harmful to my health than non-menthol/regular cigarettes; just as harmful to my health as non-menthol/regular cigarettes; less harmful to my health than non-menthol cigarettes or; I don't know*." The 248 respondents who did not know what menthol cigarettes were or gave no answer were excluded. Of the remaining respondents, 45.8 percent perceived menthol to be just as harmful as non-menthol cigarettes to their health, 40.9 percent did not know if menthol cigarettes were more or less harmful, 12.6 percent thought menthol cigarettes were more harmful and 0.6 percent, less harmful. Former smokers were more likely than never smokers to state that menthol cigarettes were more harmful (15.9 percent vs. 10.3 percent), but the

comparison for current smokers (14.9 percent) was not significant. African Americans were more likely than whites to state that they did not know whether menthol cigarettes are more or less harmful than non-menthol cigarettes, but no interactions with smoking status were tested. Differences by age group were not reported as being significant. Although the survey achieved a 65 percent response rate, which is acceptable for a mailed questionnaire, the study was limited by the fact that the sampling frame was a pre-existing national panel that may not be representative of the national population. Also, no information was available about respondents' past or current use of menthol cigarettes. Odds ratios that compared beliefs by demographics were unadjusted, so the associations could be confounded.

Around 13 percent responded that menthol cigarettes were more harmful to health, but it was difficult to know if a perception of more harm to health might be due to menthol cigarettes being perceived to be more addictive or harder to quit. The survey did ask these two additional questions, and while again a majority (55 percent) responded that it was equally easy to get hooked on menthol and non-menthol cigarettes, or that they didn't know, 24.2 percent thought menthol cigarettes were more addictive. Similarly, while 82 percent thought both types of cigarettes were equally hard to quit, 12.1 percent thought menthols were harder to quit than non-menthols. However, the study did not explore the relationships between perceived harm and these variables.

Wackowski et al. (2010) examined data from a 2005 telephone survey of New Jersey adults, of whom 17.4 percent were smokers and 40.4 percent of smokers were menthol cigarette smokers (Wackowski et al. 2010). Smokers were asked "*compared to regular cigarettes, how risky do you think the following products are? Somewhat less, about the same, or somewhat more risky?"* Menthol cigarettes were included on a list of eight tobacco products (e.g., cigars, kreteks, bidis and light, herbal and flavored cigarettes). Question order was rotated. Overall, 70.1 percent of respondents reported menthol cigarettes posed the same risk as non-menthol cigarettes, 25.9 percent (and 30.2 percent of menthol smokers) reported that menthol cigarettes posed somewhat more risk, and 4 percent reported that menthol cigarettes posed somewhat less risk. Among menthol smokers specifically, 35.2 percent of African Americans and 46.3 percent of young adults (ages 18 to 24) believed menthol cigarettes posed somewhat more risk than non-menthol cigarettes. Independent of other demographics, young adult smokers were significantly more likely than the referent group of older smokers (age 65 or older) to believe that menthol cigarettes were somewhat more risky than regular cigarettes. Among menthol smokers, 46.3 percent of 18–24 year olds indicated menthol cigarettes were somewhat more risky than regular cigarettes, but the comparable responses for older menthol smokers were not reported.

A limitation of this study was that the response rate was 20.7 percent and the sample was sourced from only one US state. The study contained only one item about explicit health benefits of menthol cigarettes, and the authors pointed out that it is unknown how respondents interpreted the meaning of "somewhat less risky" and "somewhat more risky" than regular cigarettes. The authors speculated that the perceived ease of inhalation permitted by menthol may lead smokers to inhale more deeply and although this is interpreted as a benefit, it may also partly explain why menthols are perceived to be more risky. In addition, as for the Davis et al. (2010) survey, an alternative interpretation of "more risky" could be that menthol cigarettes were perceived as being more addictive and/or difficult to quit.

Given the aforementioned contextual factors, it is unsurprising that the vast majority of respondents attributed no explicit health benefits to menthol cigarettes and a small minority thought that menthol cigarettes were different than non-menthol cigarettes in explicit harms to health.

Two studies examined data from the same survey about perceptions of menthol cigarettes among African American smokers. Allen et al. (2010) developed a questionnaire based on focus groups with

African Americans. Items were also informed by the Castro (2004) literature review of biological, social, and cultural influences on the use of menthol cigarettes among African Americans and Hispanics. She cited examples of culturally relevant beliefs about the medicinal properties of menthol, including ingesting a menthol product (Vicks VapoRub) to treat congestion and colds. Castro concluded that health-related beliefs about menthol shared by lower-income African Americans and Hispanics are consistent with a view of menthol cigarettes as less toxic and addictive than regular cigarettes. The questionnaire developed and used in the Allen et al. study contained five multi-item scales, two of which assessed medicinal benefits and relative harm. The Medicinal Effects scale included statements that menthols are better than non-menthols for a sore throat, help to loosen up a stuffed up nose, help to cool a fever, and ease asthma problems; the Less Harmful scale included statements that menthol cigarettes contain fewer chemical additives, less nicotine, are less harmful and more natural than non-menthols. In other words, the Less Harmful scale was mostly comprised of items that assessed implicit harm. Another scale measured positive evaluations about the taste, cooling sensation and smell of menthols (Taste/Sensation). The remaining two scales measured the extent to which respondents endorsed beliefs that menthol cigarettes present an African American or stylish image (Image) and beliefs about menthol being frequently smoked by African Americans now and in the past (Tradition).

Allen et al (2010) surveyed 720 smokers in Los Angeles County who were recruited via street intercept methods from regions with high percentages of African Americans and interviewed between late 2006 and early 2007. Respondents were categorized as exclusively menthol smokers (57 percent), exclusively non-menthol smokers (15 percent), or smokers of both cigarette types (28 percent). Scale scores were derived from item responses to a 4-point scale with higher numbers indicating stronger agreement. Analyses compared scale scores for the three groups of smokers, adjusting for age, gender, education, and cigarettes per day. The three groups of smokers were equally likely to endorse the Image and Tradition scales. On the Taste/Sensation scale, menthol-only smokers scored higher than smokers of both types, who scored higher than non-menthol smokers. It was noteworthy that the scale scores for Taste/Sensation were positively correlated with scores for Medicinal Effects and Less Harmful. This finding is consistent with consumer research undertaken by tobacco companies, and with the findings of Hammond & Parkinson (2009), indicating that the concepts of taste, sensory experience and harm are related in the minds of consumers.

Compared to those who smoked exclusively non-menthols, menthol-only smokers and those who smoked both cigarette types had significantly higher scores on the Medicinal Effects and Less Harmful scales. Older participants and those with less education were also more likely to hold these beliefs. Compared to those who smoked exclusively non-menthols, smokers of both cigarette types had higher scores on the Medicinal Effects but not on the Less Harmful scale. The pattern of results suggests that menthol smokers were more likely than non-menthol smokers to perceive that menthol cigarettes provide medicinal benefits and reduced implicit health harms. Smokers ages 40 and older and less educated smokers were more likely to endorse these beliefs.

Unger and colleagues (2010) undertook a more detailed analysis of these data, including a larger set of covariates, such as perceived discrimination, depressive symptoms, anxiety symptoms, sensation-seeking, stress and reported frequency of exposure to menthol marketing. This ancillary analysis found Taste/Sensation to account for just over half the variance between menthol and non-menthol smoker subgroups. When excluded in order to evaluate the influence of other variables, it was found that compared with non-menthol smokers and adjusting for many covariates, those who smoked any menthol cigarettes were more likely to perceive medicinal benefits than others. Additional subgroup analysis showed that this was particularly the case among males ages 40 and older, although it should be noted that this subgroup analysis had low power to detect effects, with an approximate sample size of only 25 people who were regular smokers in each age/gender subgroup.

**Surveys of smokers seeking cessation treatment**

Hymowitz et al. (1995) administered a questionnaire to menthol cigarette smokers attending a smoking cessation program in New Jersey. Of 213 menthol smokers, 97 percent indicated menthol cigarettes "taste better", 61 percent thought they were "more soothing to my throat" than non-menthol cigarettes, and 51 percent indicated that "I can inhale menthol cigarettes more easily than regular cigarettes." Although menthol smokers endorsed these implicit health benefits, few of them (8 percent) reported that menthol cigarettes "are better for you than regular non-menthol cigarettes." There were few significant differences between African Americans and whites, and the small sample size limited these subgroup comparisons. Another limitation is that a convenience sample of smokers who are sufficiently motivated to quit to seek formal smoking cessation treatment likely differs from the general population of smokers. Despite the study limitations, it is notable that its findings are consistent with conclusions from reviews of tobacco company internal documents that consumers hold beliefs that menthol cigarettes offer a form of implicit or apparent health protection. This especially applies to menthol's throat-soothing qualities when inhaled in tobacco smoke, and the reduction of sensory barriers to inhaling the smoke. By comparison, few menthol smokers endorsed the statement that menthol cigarettes were explicitly healthier/safer than non-menthols.

Bansal et al. (2004) assessed smokers' beliefs about menthol cigarettes as part of an educational intervention about cigarette products. Of the 982 smokers who agreed to enroll in a cessation trial, 34.2 percent smoked menthol cigarettes and the sample was predominantly non-Hispanic white (72.8 percent). Prior to randomization to different educational conditions, participants rated their agreement with six statements about menthol cigarettes: "give you less tar than regular cigarettes;" "are cleaner than regular cigarettes;" "are safer than regular cigarettes;" "are easier to quit smoking than regular cigarettes;" "are smoother on your throat than regular cigarettes" and "feel easier on your chest than regular cigarettes." Respondents who agreed or disagreed also indicated the strength of their belief (somewhat or strongly). Respondents who were uncertain were assigned a value of 2 on a scale that ranged from 0 to 4. Higher scores reflected greater disagreement with beliefs that menthol cigarettes are less harmful than regular cigarettes. A mean of 3.28 out of 4 (standard deviation was not reported) suggests that on average, smokers enrolled in a cessation trial disagreed that menthol cigarettes were less harmful than regular cigarettes. The high level of internal consistency of the scale suggests that ratings about sensory experience (smoother and easier on the chest) were positively correlated with other items about relative harm. In addition, lower scores were observed for the two items about sensory experience, indicating more agreement with these items than others. In this respect, the pattern of findings was consistent with other studies (Allen et al. 2010; Hymowitz et al. 1994). However, differences between item responses were not tested and separate scores for menthol and non-menthol smokers were not reported. As noted previously, a convenience sample of smokers seeking cessation treatment likely holds different perceptions of menthol cigarettes than the larger population of smokers.

**Focus groups**

Richter and her colleagues undertook two studies of health risk perceptions of menthol cigarettes. In 2002, Richter et al. (2006) conducted 16 focus groups in Dallas and Chattanooga with young adult smokers (ages 18–22 years) who had tried or currently used non-traditional tobacco products (NTPs), such as bidis, shisha, and herbal cigarettes. All participants rated light, regular and menthol cigarettes against each other and against each of the NTPs on a six-point scale from 'much safer' to 'much more harmful.' Non-Hispanic whites (the largest participant group), perceived menthol cigarettes as less harmful than regular cigarettes and more harmful than light cigarettes. Among Hispanics, light cigarettes were consistently rated as safer than regular cigarettes, but there was inconsistency in comparative menthol ratings. Among African Americans, light cigarettes were rated

as either the same or safer than regular and menthol cigarettes, whereas menthol and regular cigarettes were perceived to pose the same risk. A strength of this study was repeated use of the rating exercise in all groups. A limitation was that results were not presented overall, but rather by race/ethnicity and college/non-college attendance, which limited the stability of estimates. It was noteworthy that the group with the largest sample size (non-Hispanic whites) more clearly rated menthol cigarettes as being in between light and regular cigarettes on the harmfulness scale.

In 2005, Richter et al. (2008) conducted six focus groups with African American menthol smokers aged 45 to 64 years old in Atlanta. Among the main discussion themes was a belief that smoking menthol cigarettes leads to fewer negative health effects. Taste was described as a prime reason for smoking menthol cigarettes, although this appeared to be closely linked to perceptions of harm. Menthol cigarettes were commonly described as being 'refreshing,' 'soothing' or 'smooth,' while non-menthols were 'strong' or 'harsh.' As one participant explained: "*A regular cigarette is too strong. If I smoke that, I mean, I just start coughing because it's too strong. Menthol is lighter*." Some participants described unpleasant reactions to smoking non-menthol cigarettes in comparison with menthol cigarettes. "*I can't smoke non-menthol cigarettes because I wind up with a headache and a dry mouth. It dries my tongue out. And a menthol cigarette doesn't. I can enjoy it, especially after I eat,*" one said. Another person commented: "*It'll hurt your head and hurt your chest if you try to smoke a non-menthol.*" Participants in a group asked to rank brands from most to least dangerous placed full flavor menthol brands in an intermediate position between brands described as 'light' or 'slim,' which were perceived to be least dangerous, and full flavor non-menthol brands, perceived to be most dangerous. Two additional themes that were related to each other were that non-menthol smokers were considered to be hard-core smokers with less interest in quitting, and that switching to non-menthol cigarettes was perceived as a strategy that menthol smokers used to try to quit smoking. Participants' preference for menthol cigarettes were strong and non-menthol cigarettes were viewed as a cessation aid. Some described switching to non-menthols as a strategy to help them quit, whereas others indicated that switching to menthol delayed quitting. "*The reason I started smoking menthol was because the regulars were so strong and instead of me quitting, I was trying to find some means to get around that, so I went to menthol*," one participant said.

Limitations of focus groups are that individuals may be influenced by other group participants, and skilled group moderation is required to ensure that dominant views do not skew responses of other participants. Focus groups are unlikely to be representative of the population from which participants are drawn, but are designed to capture a range of views and permit in-depth discussion of concepts, which requires synthesis using careful qualitative analysis. Conducting focus groups in multiple cities is a strength of the research reported here. In addition, the results from the comparative ranking task and the qualitative findings are consistent with tobacco industry consumer research on perceptions of menthol cigarettes.

*Summary*. Taking the tobacco industry's document research and empirical studies into account, the evidence suggests that consumers perceive that menthol cigarettes offer some form of implicit health protection or medicinal benefit that non-menthol cigarettes do not provide. This was reported in all four industry document reviews. These reviews also pointed to consumer beliefs about explicit health benefits of menthol cigarettes, reflecting early advertising messages that more explicitly promoted the health benefits of menthol cigarettes (see messaging section). Evidence from focus groups and several surveys also suggested that consumers perceive implicit health benefits of menthol cigarettes (Hymowitz et al. 1994; Richter et al. 2006; Richter et al. 2008; Allen et al. 2010; Unger et al. 2010). Two studies that used multi-item scales (Allen et al. 2010; Bansal et al. 2004) also found positive correlations between beliefs about taste/sensation, medicinal benefits, and relative harm, as was found or suggested in other studies (Pollay & Dewhirst 2002; Wakefield et al. 2002; DiFranza et al. 2002; Hammond & Parkinson 2009).

In studies that addressed both implicit and explicit health benefits, smokers were more likely to endorse the former than the latter (Hymowitz et al. 1994; Bansal et al. 2004). Indeed, few smokers endorsed any statement that menthol cigarettes are explicitly safer or less harmful than non-menthol cigarettes (Bansal et al. 2004; Davis et al. 2010; Hymowitz et al. 1994; Wackowski et al. 2010). In the large population-based surveys, some smokers reported that menthol cigarettes were more harmful/risky than non-menthol cigarettes (Davis et al. 2010; Wackowski et al. 2010), but the meaning of this response is difficult to interpret.

Notably, much of this research focused predominantly or exclusively on African American smokers (Allen et al. 2010; Unger et al. 2010; Richter et al. 2008, Hymowitz 1994), which raises the question of whether these consumers are substantially more likely than others to endorse implicit health benefits of menthol cigarettes. The two survey studies of African Americans (Allen et al. 2010; Unger et al. 2010), together with the focus group study of older African Americans (Richter et al. 2008), and the earlier clinic population survey of Hymowitz et al. (1994) which included a large proportion of African Americans, all found the respondents to hold beliefs about the medicinal benefits of menthol cigarettes and other implicit health benefits pertaining to menthol cigarette strength, constituents, smoothness and ease of inhalation. These studies asked about implicit health benefits in addition to explicit health harms or risks, and employed research methods that entailed the completion of multi-item scales, required respondents to make comparative rather than absolute judgments about products, or used qualitative techniques. The studies that included sample sizes large enough to compare African Americans with other racial/ethnic groups did not use these methods.

**EVIDENCE SYNTHESIS**

Chapter 5 set out to answer six questions relating to the marketing and consumer perception of menthol cigarettes. The responses to those questions are provided below. These answers assisted TPSAC in addressing the nine overarching questions listed and discussed in chapter 1 that are the subject of this report. Specifically, these responses address TPSAC's population-based questions: *Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?* TPSAC considered this information, along with the other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

**How is menthol marketing different from and similar to non-menthol marketing, in terms of product, place, price, promotion and packaging?**

The evidence is sufficient to conclude that menthol cigarettes are marketed in similar ways to non-menthol cigarettes, in that the same general marketing principles are employed.

However, there may be an important difference in practice in relation to retail marketing and pricing. Overall, menthol cigarettes are slightly more expensive than non-menthol cigarettes, although a larger proportion of retail sales for menthol than non-menthol cigarettes are promoted. More menthol smokers than non-menthol smokers take advantage of such promotions and this difference was greater for African American smokers. There was limited information available on pricing and promotions by neighborhood demographics, in relation to tobacco tax increases, and in relation to brands. This precluded a more detailed understanding of how the tobacco industry and consumers use price promotions of menthol vs non-menthol brands to undermine the potential benefits of tobacco tax increases and other tobacco control policies on quitting, particularly among key population subgroups. While the prevalence of smoking has declined in the past several years, the proportion of smokers who prefer menthol cigarettes has increased. Thus, the rate of decline in smoking prevalence is slower for menthol than for non-menthol smokers. This phenomenon has

coincided with a substantially increased emphasis on tobacco marketing and price promotions at the point of sale. Existing evidence is insufficient to conclude that retail marketing practices may be responsible for recent increases in the proportion of smokers who smoke menthol cigarettes. Research is needed to examine the relationship between the move towards retail-based marketing, especially price promotions, and the increase in the proportion of smokers who smoke menthol cigarettes.

**What health reassurance messages were/are used in menthol marketing messages?**

The evidence is sufficient to conclude that menthol cigarettes have been and continue to be marketed with a set of associated branding elements and labels that connote health benefits. These originally included claims of explicit medicinal benefits such as soothing a sore throat or clearing a blocked nose, but moved over time towards more implied health benefits, with the use of powerful images of coolness and refreshment, the use of phrases and labels stressing sensory experience such as 'refreshing' and 'smooth,' and the use of the color green which is associated with nature and healthiness. While contemporary tobacco marketing efforts have been constrained by legislation that restricts advertising in traditional media, the powerful advertising messages used in the past are reinforced and continued by the ongoing use of menthol brand names and menthol marketing messages such as 'smooth' and 'fresh' that are implicitly linked to health benefits.

**What other messages were/are conveyed to potential consumers by menthol marketing messages?**

The evidence is sufficient to conclude that other menthol marketing messages feature youthful imagery and themes to appeal to youthful audiences, as well as socially and culturally relevant messages about in-group identity to appeal to different market segments. Different in-group identities are emphasized in marketing for different brand families, so there is no single brand image that signifies a menthol smoker.

**Who are the target populations for menthol marketing? Is there evidence to show that youth, women, and specific racial/ethnic groups were targeted?**

Identification of primary target groups for marketing is basic marketing practice. NCI's Monograph 19 provides abundant evidence of targeting of youth, young adults, racial/ethnic groups, women and other population subgroups in cigarette marketing (NCI 2008).

Evidence presented in this Chapter and chapters 4 and 6 indicates that menthol smoking is higher among youth and young adults, compared with older adults. There is sufficient evidence to conclude that menthol cigarettes are marketed disproportionately to younger smokers. There is evidence from tobacco industry documents that the tobacco industry designed menthol cigarettes with lower menthol yields, with an awareness that, at these lower menthol levels, the sensory effects of menthol reduce the harshness of cigarettes for new smokers. In addition to messages that implied health reassurance, menthol cigarette marketing has promoted a more youthful brand image than for non-menthol cigarettes, and has emphasized the role of menthol cigarettes in peer group acceptance.

Chapter 4 demonstrates that menthol use is higher among women than men. While there is evidence from industry document reviews and empirical studies that women have been targets of tailored menthol marketing efforts, there is insufficient evidence that menthol marketing was targeted proportionately more to women per se than non-menthol marketing.

The evidence is sufficient to conclude that menthol cigarettes are disproportionately marketed per capita to African Americans. African Americans have been the subjects of specifically tailored menthol marketing strategies and messages. Billboard advertising and point-of-sale advertising for menthol cigarettes has been over-represented in neighborhoods with a high percentage of African Americans and in magazines with high African American readership, and more so than non-menthol cigarette advertising. Consistent with these targeted marketing efforts, menthol cigarettes are disproportionately smoked by African American smokers. The evidence is sufficient to conclude that it is at least as likely as not that menthol cigarettes have also been disproportionately marketed to Hispanics. Menthol smoking is higher in Hispanics than in non-Hispanic whites. Although Asian Americans, Hawaiian/Pacific Islanders and females have been the subjects of tailored menthol marketing messages and menthol smoking is higher in all these population subgroups, there is insufficient evidence to conclude that they have been proportionately more targeted by menthol than non-menthol advertising.

**Does menthol marketing influence perceived taste and/or sensory experience of menthol cigarettes?**

The evidence is sufficient to conclude that menthol branding and messaging influences the perceived sensory experience of menthol cigarettes, contributing to consumer's overall subjective evaluation and liking of the product.

**Do consumers perceive menthol cigarettes as safer or less harmful than non-menthol cigarettes?**

The evidence is sufficient to conclude that, consistent with marketing claims, consumers hold beliefs about the medicinal benefits of menthol and beliefs about other implicit health benefits, and that this is especially the case among African Americans. However, in the context of widespread public education about the health harms of tobacco use, it is uncommon to state an explicit belief that menthol cigarettes are safer or less harmful than non-menthol cigarettes.

## CHAPTER 6: EFFECTS OF MENTHOL CIGARETTES ON INITIATION, ADDICTION AND CESSATION

### INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address " the impact of the use of menthol in cigarettes on the public health including such use among children, African Americans, Hispanics, and other racial and ethnic minorities." This chapter is concerned with the effects of menthol cigarettes on smoking initiation, addiction and cessation. Put another way, do menthol cigarettes—when compared to non-menthol cigarettes—make it more or less likely that someone will start smoking, become addicted, or quit?

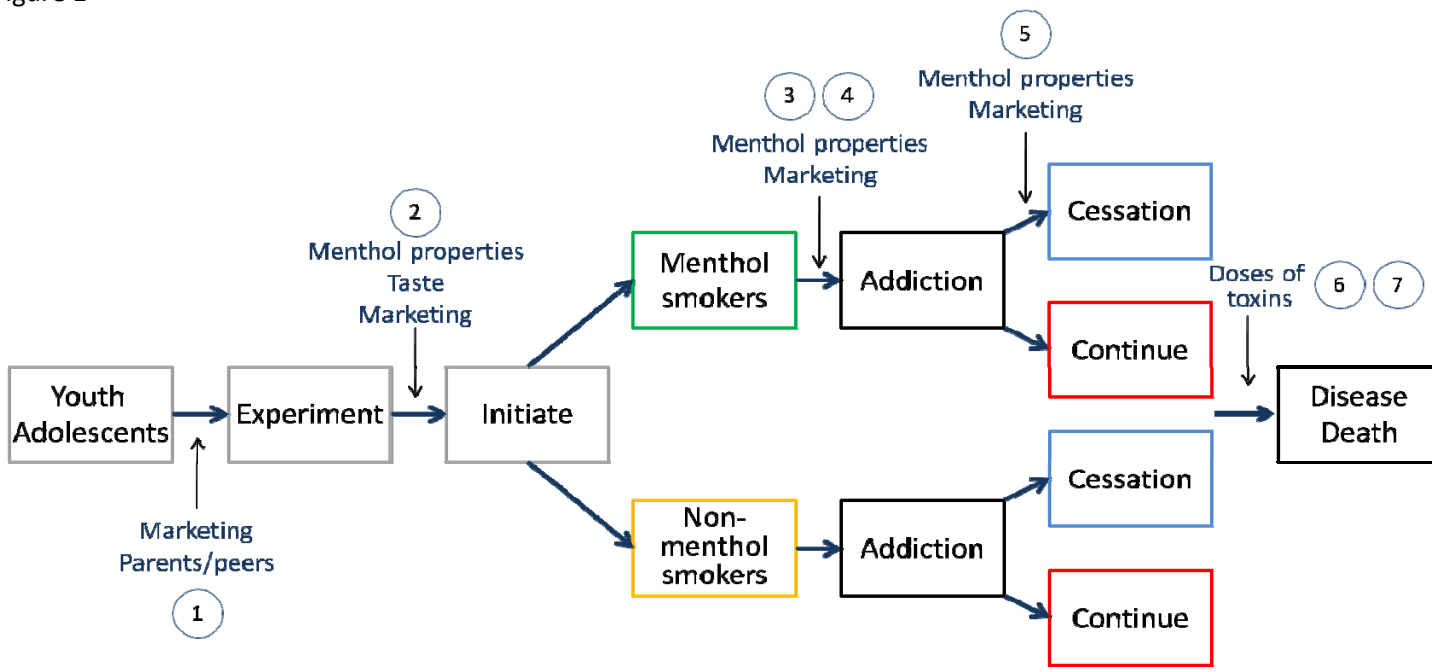
This chapter builds on information presented in previous chapters about the influence of menthol cigarette marketing (chapter 5) and the physiological effects of menthol cigarette smoking, including the cooling sensation that menthol imparts and the ability of menthol to counter the harshness of nicotine (chapter 3). Chapter 4 explored the broad patterns and trends of menthol cigarette use by age, race, gender and income. In order for TPSAC to execute its charge, it also addressed the impact of menthol cigarettes on smoking initiation, addiction and cessation.

The first chapter of this report presented nine questions relevant to TPSAC's consideration of the public health impact of menthol cigarettes; seven are related to individual menthol cigarette smokers and two are related to the population effects of smoking menthol cigarettes. The information and analysis provided in this chapter are relevant to five of the seven questions that relate to individual cigarette smokers. They are:

- Does availability of menthol cigarettes increase the likelihood of experimentation?
- Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?
- Does inclusion of menthol in cigarette increase the likelihood of the smoker becoming addicted?
- Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?
- Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?

In accordance with the public health model presented in chapter 1 (see Figure 1, below), this chapter is divided into three sections: (1) experimentation and initiation, (2) addiction, and (3) cessation. As indicated in Figure 1, several factors may moderate each stage within this model. The marketing of menthol cigarettes and their availability from peers or family members may influence experimentation with menthol cigarettes. Experimentation—and the continued influences of peers and marketing, coupled with the sensory effects of menthol cigarette smoking—may lead to smoking initiation. Nicotine pharmacokinetics, the sensory properties of menthol cigarettes (e.g., a cooling sensation) and beliefs transmitted by marketing messages or social groups about menthol cigarettes (e.g., relative safety), may promote regular smoking and eventually addiction. The same biological, social and commercial factors that lead to initiation and addiction may also affect the increased or decreased likelihood of menthol cigarette smoking cessation compared to non-menthol cigarettes.

Figure 1




**METHODS**

Chapter 2 provided the general framework for this report and the TPSAC's approach to gathering, reviewing and weighing the evidence. Using this framework, chapter 6 draws on sources that provide information about menthol cigarette smoking experimentation, initiation, addiction and cessation, or provide necessary background information. Four sources of documents were examined: (a) peer-reviewed articles obtained from the search conducted by the FDA and from additional studies identified from these articles; (b) white papers and secondary analysis of existing datasets either written or commissioned by the FDA; (c) tobacco company presentations and written submissions; and (d) public comments that provided relevant evidence.

**EXPERIMENTATION AND INITIATION**

The experimentation and initiation section covers five topics: (1) the rates of menthol vs. non-menthol cigarette use among youth and young adults compared to older adults; (2) the rates of menthol vs. non-menthol cigarette use in recent initiators and established smokers; (3) the age of cigarette initiation of menthol vs. non-menthol cigarette smokers; (4) switching between and among menthol and non-menthol cigarette smokers; and (5) the characteristics of menthol cigarettes that may enhance the abuse liability or appeal of the product (sensory experience, reduction of harshness, cooling sensation, beliefs about relative safety). This chapter draws on population-level information in chapter 4 in addition to multiple datasets, surveys and analyses that provide in-depth information about the experimentation and initiation of menthol cigarette smoking. This chapter also draws on information about the sensory experience of smoking menthol cigarettes presented in chapter 3.

**Patterns of smoking menthol cigarettes in adolescents and young adult smokers**

***Age gradient of proportion of menthol cigarette use across the age spectrum***

Most smokers start smoking during adolescence before the legal age for purchasing cigarettes or during their young adult years (Institute of Medicine, 1994; Substance Abuse and Mental Health Services Administration, 2009; U. S. Department of Health and Human Services, 1994). Thus, examining patterns of menthol cigarette smoking among adolescents and young adults is informative to understanding the role of menthol cigarettes in initiation.

In data collected in 2008, almost half of adolescent smokers between 12–17 years old (47.7 percent) reported past 30-day use of menthol cigarettes and 40.8 percent of young adults aged 18–25 years smoked menthol cigarettes (http://www.oas.samhsa.gov/2k9/134/134MentholCigarette.htm; Substance Abuse and Mental Health Services Administration, 2009). The rate of initiation with menthol cigarettes compared to non-menthol cigarettes is not well characterized. However, a greater pattern of menthol smoking has been observed among youth and younger adults compared to older adult smokers (Hymowitz et al. 1995; Substance Abuse and Mental Health Services Administration, 2009; Sidney, Tekawa, & Friedman 1989, among African Americans and Asians; Fernander et al. 2010; see chapter 4). For example, based on analysis of pooled cross-sectional 2004-2008 NSDUH data, a higher proportion (44.7 percent) of adolescent smokers ages 12–17 smoke menthol cigarettes than among young adults ages 18-25 years old (36.1 percent) or adults 26 years old or older (30.2 percent) (Rock, Davis, Thorne, Asman, & Caraballo 2010). When separated by different race/ethnicities, the proportion of menthol smokers is higher in adolescent smokers 12–17 years old compared to smokers 18–25 years or 26 years and older among whites (41.0 percent vs. 28.8 percent vs. 21.9 percent, respectively), Hispanics (47.0 percent vs. 38.2 percent vs. 29.5 percent), Asians (51.5 percent vs. 35.8 percent vs. 28.6 percent) and American Indian/Alaska Native (34.7 percent vs. 27.4 percent vs. 23.0 percent). By contrast in the African American population, 71.9 percent of adolescent smokers smoke menthol cigarettes compared to 82.2 percent of adult menthol smokers.

Giovino (2010, unpublished submission) conducted a fine grain analysis of NSDUH data to determine if an age gradient existed when smokers were divided into two categories: those who smoked fewer than 10 cigarettes a month (less established smoking) and those who smoked 10 or more cigarettes a month (more established smoking). He observed a statistically significant age gradient among those menthol smokers aged 12–34, with the highest prevalence observed among the 12–17 year olds for both categories of smokers.

As discussed in detail in chapter 4, TPSAC received public submissions that criticized and clarified NSDUH survey data. TPSAC reviewed these submissions and concludes that the issues raised in Curtin et al. (submission to the FDA, June 2010) are addressed in Giovino et al. (2010, unpublished submission) and do not affect TPSAC's interpretation of the NSDUH data.

***Age gradient of propotion of menthol cigarette use within youth***

Studies have also been conducted examining age gradients within an adolescent group. According to an analyses of the 2004, 2006 and 2009 National Youth Tobacco Survey (NYTS), a slightly higher portion of current middle school smokers than current high school smokers used menthol cigarettes within the past 30 days (49.4 percent vs. 44.9 percent; Caraballo & Asman, in submission). These results are concordant with the Appleyard et al. study (2001) using the 2000 NYTS and the study of Hersey et al. (2006), using the 2000 and 2002 NYTS among whites and Hispanics, but not among Blacks/African Americans (Appleyard, et al. 2001; Hersey, et al. 2006), and among Asian and Native Hawaiians/ Pacific

Islanders (Appleyard, et al. 2001). Giovino (2010, unpublished submission), analyzing the 2003 National Youth Smoking Cessation Survey, observed that menthol cigarette use was highest among smokers ages 12–15 years (53.5 percent), followed by ages 16–17 years (47.0 percent), ages 18–21 years (40.5 percent) and ages 22–25 years (34.6 percent). A statistically significant age gradient was observed overall and within males, females and whites. In an analysis of the 2006 NYTS, Curtin et al. (2010b) found a statistically significant higher percentage for "current smokers aged 9–13 years (59.3 percent) and lower percentage for current smokers aged 17–21 years (38.3 percent) reporting menthol vs. non-menthol cigarette smoking." The smoking rate among 14–16 year olds was 45.8 percent.

In an analysis of 2004–2008 pooled NSDUH data, (February 10, 2011 presentation (*Comparative Rates of Initiation of Menthol and Non-menthol Cigarette*s), Hersey observed that younger adolescents were more likely to smoke menthol cigarettes than older adolescents. The percentages of menthol smokers in each gradient, with confidence intervals in brackets, were: 12–13 years old, 48.6 percent (42.4, 54.8); 14–15 years old, 46.3 percent (43.6, 49.0); 16–17 years old, 43.9 percent (42.1, 45.6); 18–25 years old, 36.3 percent (35.5, 37.1). Age gradients were observed regardless of whether the groups analyzed were all current smokers or smokers who identified their menthol or non-menthol status. Similar age gradients were observed among whites (12–14 years old, 42.7 percent [39.0, 46.3]; 15–17 years old, 38.1 percent [36.4, 39.8]) and Hispanics (12–14 years old, 47.1 percent [37.3, 57.0]; 15–17 years old, 42.2 percent [37.5, 46.9]). The age gradients were reversed among African American adolescents (12–14 years old, 50.9 percent [40.8, 61.0]; 15–17 years old, 70.4 percent [65.3, 75.4]) and other racial/ethnic groups (12–14 years old, 37.2 percent [24.7, 49.7]; 15–17 years old, 46.4 percent [39.9, 53.0].

(See Table 1 for studies on age gradients associated with menthol smoking).

***Brand preference among youth: age gradient and trends***

The most popular menthol brand smoked by youth is Newport, which is manufactured by Lorillard. Along with the non-menthol brands Marlboro and Camel, Newport ranks among the top three brands purchased by adolescents. These brands are used by 81.3 percent of smokers aged 12–17 years old and 82.4 percent of smokers aged 18–25 years old (SAMSHA 2005, (see Caraballo & Asman, in submission). Internal tobacco documents show that as early as 1976, Lorillard had noted that Newport had a strong appeal among young or new smokers (Klausner, 2011 in press, page 16).

The findings from the product preference studies are congruent with the age gradients found in the prevalence of menthol cigarette users among adolescents. In the 1993 Teenage Attitudes and Practice Survey (TAPS), 70 percent of current smokers reported that they usually bought their own cigarettes and younger smokers (aged 12–15 years) were more likely than older smokers (aged 16–18) to purchase Newport cigarettes (19.4 percent vs. 10.6 percent) and less likely to buy Marlboro cigarettes (49.5 percent vs. 63.1 percent, Barker, 1994). Similarly, the 1999 Monitoring the Future Survey found fewer adolescents in higher grades compared to lower grades reporting preference for Newport cigarettes (eighth grade. 22.5 percent; tenth grade, 17.7 percent, twelfth grade, 13.3 percent) (Johnston, O'Malley, Backhan, & Schulenberg 1999).

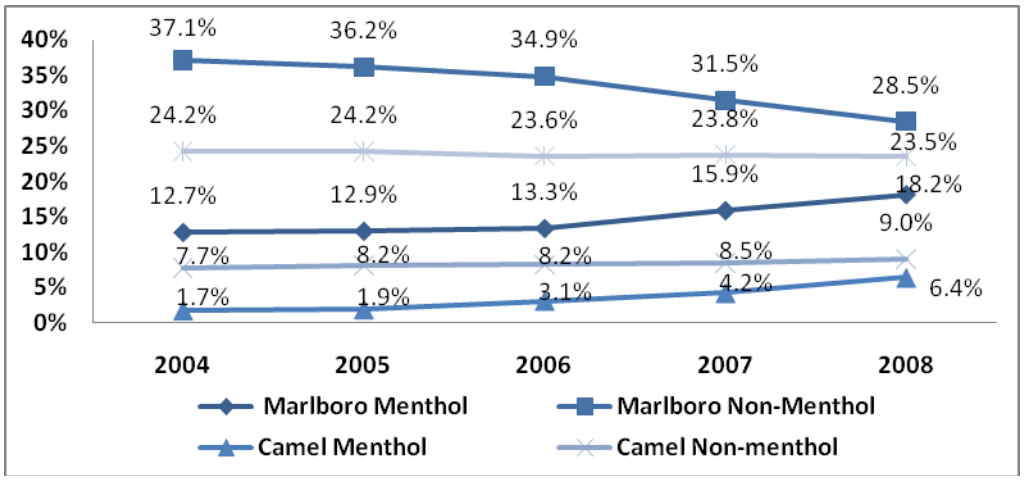
Giovino et al. (2004), in an analysis of 2000 NSDUH data by racial/ethnic group, found the age gradient was dependent on the brand of menthol cigarettes. Among African American smokers, more than three-fourths of adolescents (79.2 percent, ages 12–17) and young adults (76.7 percent aged 18–25 years) but less than one-third of those age 26 and older (31.5 percent) smoked Newport. African American smokers age 26 and older smoked Kool (14.1 percent) and Salem (6.9 percent) more than African American smokers ages 12–17 (2.1 percent and 1.6 percent for Kool and Salem, respectively) and

African American smokers ages 18–25 (4.6 percent and 1.6 percent for Kool and Salem, respectively). Among white smokers ages 12-17, nearly one of five (18 percent) smoked Newport but less than one of 10 older smokers smoked Newport (9.3 percent of 18–25 year olds and 2.9 percent of 26 years and older). White smokers ages 26 and older, smoked Kool (1.8 percent) and Salem (3.0 percent) more than white adolescent smokers ages 12–17 (0.7 percent and 0.3 percent for Kool and Salem, respectively). Among Hispanic smokers, nearly one of three adolescents age 12–17 (31.4 percent), one of six young adults ages 18–25 (16.7 percent) and less than one of fourteen adults ages 26 years and older (7.1 percent smoked Newport cigarettes. The age gradient for Kool (0.3 percent vs. 0.9 percent vs.3.6 percent for adolescents, young adults and adults, respectively) and Salem (no data vs. 0.2 percent vs. 3.4 percent for adolescents, young adults and adults, respectively) were the inverse of the gradient for Newport.

Studies suggest an increasing trend in menthol use among youth both historically and more recently, depending on the menthol brand (see Table 2 for trends in menthol smoking among youth). TAPS showed a substantial change in brand preferences among the adolescents from 1989 to 1993, with a 55 percent increase in the purchasing of Newport cigarettes (4.5 percentage points) in spite of the unchanged market share for Newport and a decrease in Newport advertising expenditures to $35 million from $49 million during this time (Barker, 1994). Similarly, Kaufman et al. (2004), analyzing data from three nationally representative cross-sectional surveys of adolescents (1996 National Survey of Tobacco Price Sensitivity, Behavior, and Attitudes Among Teenagers and Young Adults; and the 1989 and 1993 TAPS), found that percentages of white and Hispanic adolescents who usually bought Newport doubled between 1989 and 1996, The percentage of white adolescent Newport buyers grew to 10.4 percent from 5.3 percent and the percentage of Hispanic adolescents who usually bought Newport increased to 25.9 percent from 12.8 percent, with dramatic increases among those ages 12–14 (from 4.8% percent to 19.2 percent). Increases in Newport purchases were observed among both males and females. More recent data show that the percent of past month Newport smokers in grades 8, 10 and 12 has remained stable from 1998 to 2008 (see Caraballo & Asman, in submission, FDA white paper), although a decreasing trend has been observed with Marlboro cigarettes (see Figures 3–5 in paper).

Hersey presented an analysis of the percent of 12–17 year olds smoking different brands of menthol cigarettes from 2000 to 2008 using the NSDUH survey (Presentation to TPSAC February 11 2011; see Figure 2). Although the percent of this age group who used Newport cigarettes did not increase between 2000 and 2008 (23.4 percent and 23.5 percent, respectively), the percent who smoked Marlboro Menthol increased to 18.2 percent from 12.7 percent and Camel Menthol increased to 6.4 percent from 1.7 percent. On the other hand, non-menthol Marlboro cigarettes decreased to 28.5 percent from 37.1 percent.

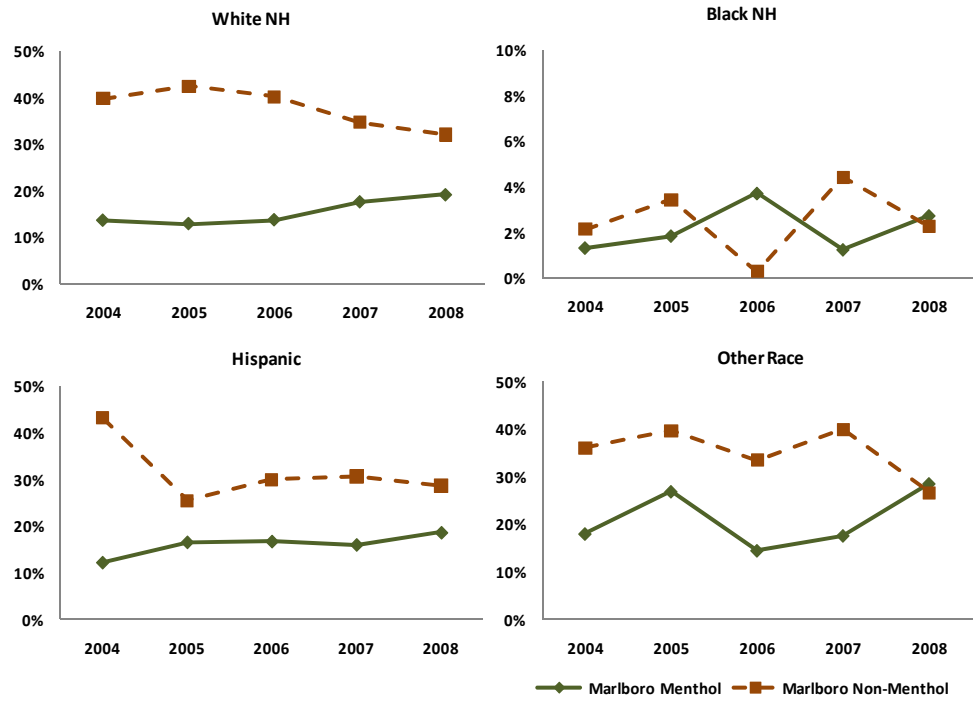
**Figure 2. Trends in the Percentage of Brand Use among 12-17 Year-Old Current Smokers in the National Household Survey of Drug Use and Health (NSDUH): 2004 to 2008**




**Note: This figure shows percentage of current smokers aged 12 – 17 who smokeda particular brand and type of cigarettes. Data were analyzed by RTI from the National Household Survey on Drug Use and Health (NSDUH). The number of current smokers aged 12-17 in this analysis by year was 2004: 2,225; 2005: 2,221; 2006: 1,996; 2007: 1,907; and 2008: 1,759. Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008**

In their analysis of the NSDUH surveys from 2004 to 2008 among 12–17 year olds across different racial/ethnic groups, Hersey et al. observed an increase in Marlboro menthol use and decrease in Marlboro non-menthol use among whites, Hispanics and the other category, but not among African Americans (Presentation to TPSAC February 11 2011, see Figure 3).

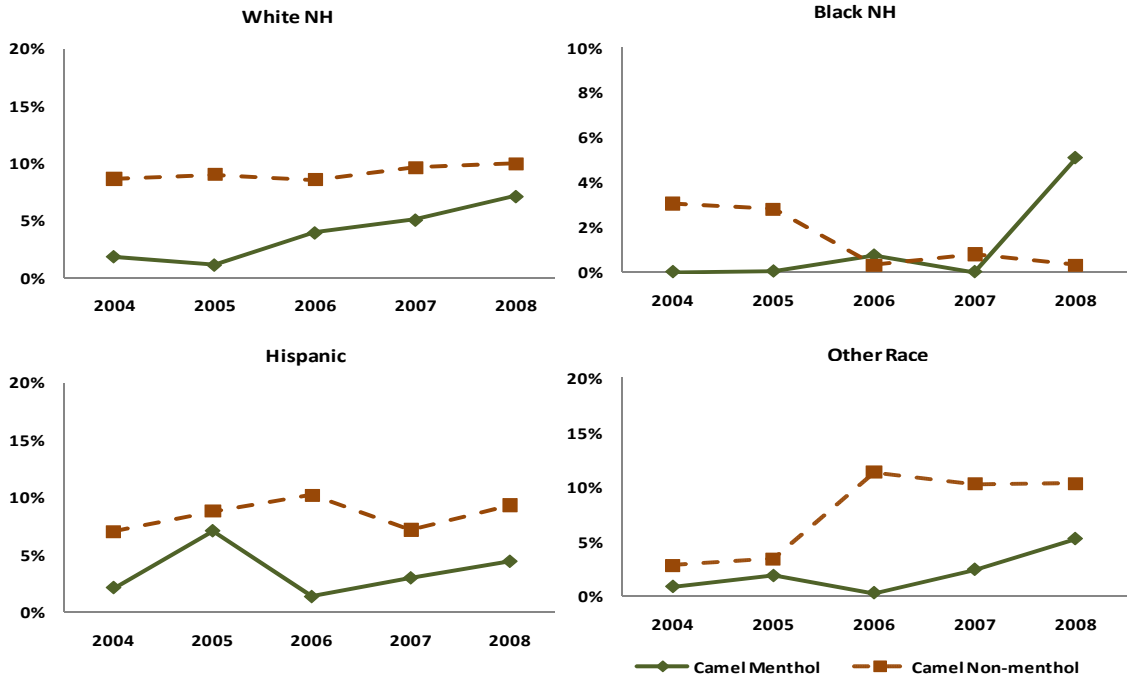
**Figure 3. Percent of Smokers, Aged 12 – 17, Smoking Marlboro Menthol and Marlboro Non-Menthol from 2004 to 2008 by Race/Ethnicity**




**Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008**

For the Camel menthol brand, increases were seen for all racial/ethnic groups, whereas non-menthol Camel use decreased among African Americans, did not change among whites and Hispanics, and increased among smokers in the other category (see Figure 4). On the other hand, Newport cigarette use remained relatively flat between 2004 and 2008, as observed by Caraballo and Asman (in submission, FDA white paper).

**Figure 4. Percent of Smokers, Aged 12 – 17, Smoking Camel Menthol and Camel Non-Menthol from 2004 to 2008 by Race/Ethnicity**




**Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008**

The data were also examined by age and level of experience with smoking, as assessed by those who had smoked less than 100 cigarettes (novice smokers) and those who had smoked 100 cigarettes or more (experienced smokers). The percentage of Marlboro Menthol smokers increased among novice and experienced smokers ages 12–17 (+6.1 percentage points and +4.1 percentage points, respectively) and among novice and experienced smokers ages 18–25 year olds (+5.6 percentage points and +3.3 percentage points). Greater increases were observed in the youngest group.

Altria Client Services provided information intended to counter the hypothesis that the availability of menthol cigarettes increases cigarette initiation. In a June 30, 3010 submission (Page 100), Altria said the rate of cigarette purchases among underage adolescents had decreased dramatically since 1995. According to the Youth Risk Behavior Survey, 54.5 percent either purchased (38.7 percent) or had someone else purchase cigarettes (15.8 percent) compared to 42.1 percent who either purchased (14.0 percent or someone else purchase cigarettes ( 28.1 percent) in 2009. This document also refers to studies indicating that most adolescents obtain their cigarettes from peers and potentially family members, rather than purchasing the cigarettes themselves (articles cited include: Croghan, Aveyard, Griffin, & Cheng, 2003; Emery, Gilpin, White, & Pierce, 1999; Forster, Chen, Blaine, Perry, & Toomey,

2003; Harrison, Fulkerson, & Park, 2000; Ma, Shive, Legos, & Tan, 2003; Substance Abuse and Mental Health Services Administration, 2007; S. S. Williams & Mulhall, 2005). Concordant with these findings, Allen and Unger (2007) examined factors associated with menthol and non-menthol cigarette use among a convenience sample of 432 adult African American smokers in lower income neighborhoods in Los Angeles in 2001. After controlling for age and employment, and significant correlates of menthol use, including parents' menthol cigarette smoking (among females) and among both men and women, the belief that most African American smokers smoke menthol, suggesting that social and cultural norms contribute to menthol cigarette smoking. As noted in chapter 5, "Menthol marketing…uses socially and culturally relevant messages about in-group identity to appeal to different market segments." Marketing cigarettes as part of the youthful or African American culture would be increase the appeal and availability of cigarettes among peers within this social network.

A submission by Altria (June 30, 2010, page 30) showed a significant increase in the market share of Marlboro menthol cigarettes from 1975 to 2005 (5.4 percent share of US market in 2005, see Figure 5) as well as Newport cigarettes (9.8 percent of market share in 2005). It was noted that this increase in market share could not be explained by any change in levels of menthol yield in cigarettes (Lorillard Tobacco Company, submission, June 30, 2010 for Newport Full Flavor, Lights and Mavericks). Although the menthol content in cigarettes has increased, the yield has stayed the same through increased ventilation of cigarettes.

Figure 5. Trends in market share of menthol cigarettes

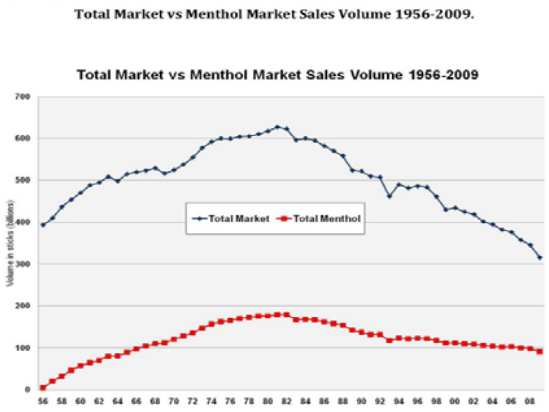



In order to examine the association between market share and youth smoking rates, the June 30, 2010 submission from Lorillard correlated menthol market share with youth smoking rates by state (2009 data of youth smoking rates obtained from Campaign for Tobacco Free Kids, Key State-Specific Tobacco-Data and Rankings). The data show an inverse association of menthol market share with youth smoking rates (see page 49 and 50, Figures 13 and 14). This analysis did not explore potential ecological confounding by such factors as race.

To further support the lack of relationship between youth smoking and the availability of menthol cigarettes, the June 30, 2010 document submitted by Altria points to the significant declines in underage smoking since peak levels in the late 1990s. However, by contrast, Giovino (2010 unpublished submission) showed that the rate of decrease is less among menthol cigarette smokers compared to non-menthol cigarette smokers. In fact, among young adults (18–25 year olds), no change in the rate of menthol use has been observed from 2004 to 2009 (14.0 percent vs. 14.5 percent) compared to a

decrease in non-menthol use (25.7 percent vs. 20.4 percent). This finding follows the market share pattern observed for menthol vs. non-menthol cigarettes (see Figure 6, [Figure 9 from Lorillard June 2010 submission]). Furthermore, while the rate of smoking has been declining among adolescents (although the most recent Monitoring the Future report shows that smoking rates have stopped declining, with a slight increase in eighth and tenth graders from 2009 to 2010, www.monitoringthefuture.org), the proportion of adolescent cigarette smokers who report using menthol cigarettes increased significantly from 2004 to 2008 (Rock, et al., 2010). Specifically, Rock et al. (2010) noted that the 2004 to 2008 NSDUH data showed that menthol cigarette use increased significantly among white smokers aged 12–17 (from 40.3 percent in 2004 to 46.0 percent in 2008, $p < 0.01$) and among menthol smokers aged 18–25 years old for both Hispanics (from 33.9 percent in 2004 to 42.4 percent in 2008) and in whites (from 26.7 percent to 32.5 percent, $p < 0.01$).

Figure 6.




Finally, the suggestion has been made that menthol cigarettes are not likely to contribute to the initiation of smoking because African American youth have a higher prevalence of smoking menthol cigarettes compared to whites, yet they experience a lower rate of smoking and a later age of onset compared to whites (presentation by Hunt, July 15-16, 2010, Altria). Hunt did not address other factors such as the role of cultural norms and ethnicity and race, which needs to be taken into consideration. Menthol cigarettes may still facilitate initiation of smoking in the African American culture even if they experience different patterns of initiation than whites.

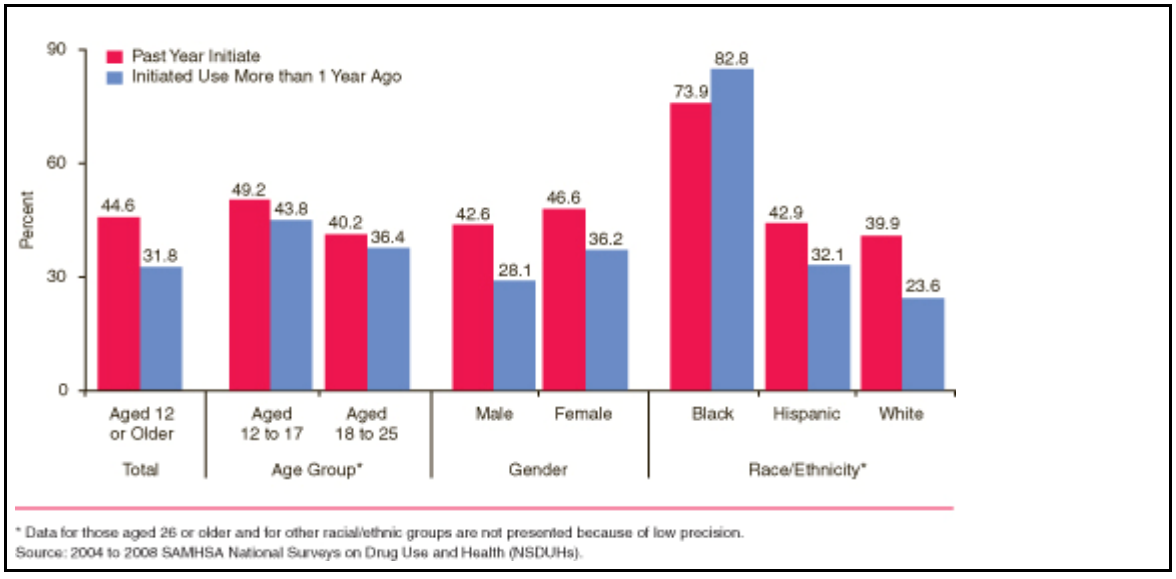
*Summary:* The evidence strongly suggests a higher prevalence of menthol cigarette use among adolescent smokers compared to adult smokers, except among African Americans. This finding is concordant with the trend and prevalence data presented in chapter 4. The discrepant results observed in some studies using national surveys, particularly in the analysis presented by Curtin et al. 2010 (see chapter 4), may be reflect the small subject sample (e.g., NHANES had only 20 menthol smokers in the 12-17 year old category) or subjects less than 18 years and older were not interviewed (e.g., NHIS). The results also show that a higher proportion of younger adolescent smokers tend to smoke and prefer menthol cigarettes compared to older adolescent smokers. The data show that while adolescent smoking has been declining among menthol and non-menthol smokers, the rate of decline is greater among non-menthol smokers and the proportion of adolescent smokers smoking menthol cigarettes, particularly Camel and Marlboro menthol cigarettes, has been increasing among both experimenting smokers (<100 cigarettes in a lifetime) and more established smokers (smoking 100 or more cigarettes

in a lifetime). It is unclear whether a greater proportion of younger adolescents initiate and experiment with cigarette smoking with menthol cigarettes compared with older adolescents.

**Pattern of menthol smoking in recent smokers versus established smokers**

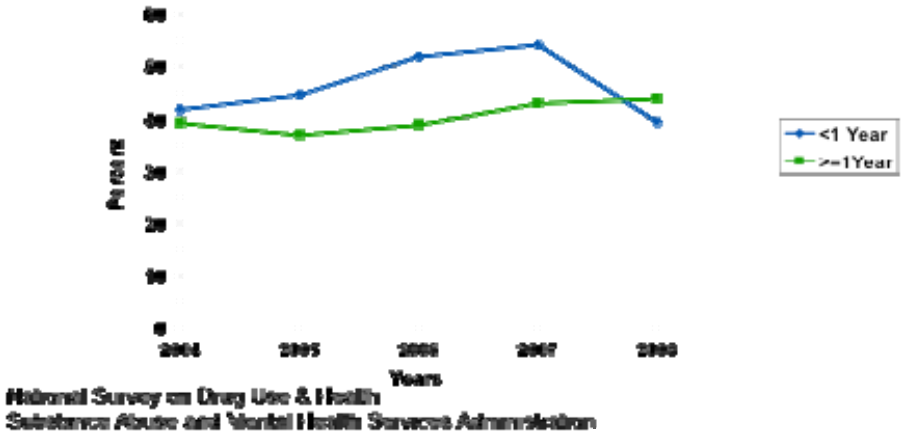
Two peer-reviewed articles, three white papers and three public comments were identified and reviewed by TPSAC. Peer-reviewed studies of national survey data show that recent adolescent smokers are more likely to smoke menthol cigarettes than more established adolescent smokers (Hersey, et al., 2006; Substance Abuse and Mental Health Services Administration, 2009), although the trend was reversed in 2008 among smokers aged 12–21 (Rising et al. 2010). Hersey et al. (2006) analyzed data from the 2002 NYTS that examined middle and high school students who smoked for one or more times in the past 30 days and who described the brand and/or the menthol status of the cigarettes they usually smoked. A significantly higher percent of menthol smokers was found among middle school students who had been smoking for less that 1 year compared with middle school students who had been smoking for more than 1 year (62.4 percent vs. 53.3 percent, $p < 0.002$). This same pattern was observed for high school students, but the difference was not statistically significant (45.9 percent vs. 41.9 percent, respectively). In an analysis of the 2004 to 2009 NSDUH data, the proportion who smoked menthol cigarettes compared to non-menthol cigarettes among those who had been smoking less than 1 year was higher among smokers aged 12–17 years (49.2 percent vs. 43.3 percent) and among smokers aged 18–25 years (40.2 percent vs. 36.4 percent) as well as among whites (39.9 percent vs. 23.0 percent), Hispanics (42.9 percent vs. 32.1 percent), but not among African Americans, although no statistical analysis was provided (See Figure 7, NSDUH Report Menthol Cigarettes,2009).

**Figure 7. Past Month Menthol Cigarette Use among Past Month Cigarette Smokers Aged 12 or Older, by Recency of Cigarette Initiation and Demographic Characteristics: 2004 to 2008**




In the white paper submitted by Rising et al. (2010), unpublished data on the use of menthol cigarettes by young smokers (aged 12–21 years) from the 2004 to 2008 NSDUH was described that showed a higher prevalence of menthol use among smokers who smoked less than one year compared to smokers who smoked for more than one year, but this pattern was reversed in 2008 (see Figure 8).

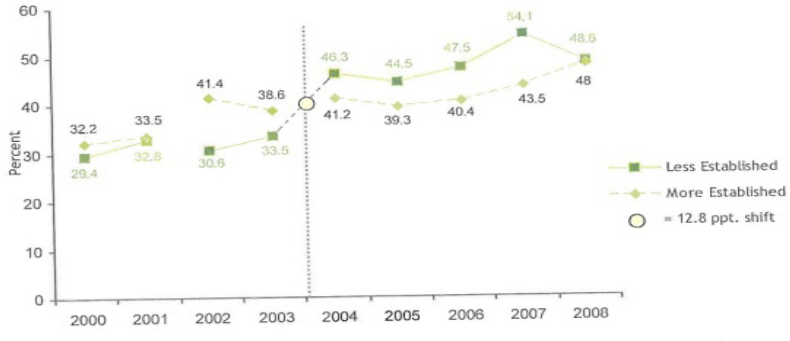
**Figure 8. Menthol cigarette use by new smokers (age: 12-21)**




In the submission dated June 30, 2010 (page 110), Altria raised the issue that the findings from the 2004 to 2008 NSDUH may reflect how the question is phrased. They pointed out that prior to 2004, the question was phrased as: *During the past 30 days, did you smoke (insert brand name if identified) menthol or regular cigarettes* ***most often***. After 2003, the question was phrased: *Were the (insert brand name if identified) cigarettes smoked during the past 30 days menthol* (which thereby assessed any use of menthol cigarette smoking). Altria contended that few differences were observed in the percent of menthol smokers among current initiates (current smokers who had indicated that they had smoked for the first time in the past year) vs. prior initiates (current smokers who said they initiated smoking in prior years) prior to 2004, but after the change in phrasing, higher rate of recent smokers were observed to smoke menthol compared to more established smokers. TPSAC found it is difficult to attribute the differences in the data after 2003 to changes in the survey question. Even before the change, menthol smokers were beginning to account for a larger percentage of recent smokers. However, Altria (June 2010) pointed out that the jump in percentage was more than expected after the change in how the question was framed (see Figure 6.6, page 109). On the other hand, as pointed out by Giovino (2010, unpublished submission), Altria failed to note that the survey after 2003 included a question prior to the menthol cigarette inquiry which asked for the brand ***most often used*** and then an inquiry was made as to whether this brand of cigarettes (most often) smoked during the past 30 days was menthol. Relatively few smokers do not answer the question about the cigarettes most often smoked. For example, in 2008, only 4 percent of the sample responded to the question of whether they smoked menthol cigarettes in the past month without naming a usual brand of cigarettes.

Altria (June 2010 submission) conducted another analysis in which adolescent subjects were divided into those who had smoked less than 100 cigarettes cumulatively (novice smokers) and those who had smoked more than 100 cigarettes cumulatively (experienced smokers) (see Figure 9). The results showed a lower percentage of menthol smokers vs. non-menthol smokers in the novice smoker category during the earlier time period. However, it is important to note that the more recent survey data showed a higher percentage of menthol smokers in the novice smoker category, except in 2008.

Rates of reported past 30-day menthol cigarette use by 12 to 17 year olds reporting Less vs. More than 100 lifetime cigarettes[15]




In a study combining data from the 2004, 2006 and 2009 NYTS, differences were not observed in potential stages and prevalence of smoking menthol cigarettes (Caraballo & Asman, in submission). Among adolescents who smoked <1 cigarette per day (CPD) on 1–5 days of the past 30 days, 30.9 percent reported smoking menthol cigarettes, a rate similar to or slightly lower than among adolescents who smoke 1–5 CPD on 1–5 days, 6–9 days, 20–29 days and all 30 (45.3 percent to 49.7 percent). These data suggest that adolescents are not more likely to initiate smoking with menthol cigarettes. Similarly, using the NSDUH 2004-2008 surveys, Giovino (2010, unpublished submission) also found no differences in proportions of use of menthol cigarettes among smokers of all ages who smoked 1–5 days in the past 30 days (36.1 percent), 6 to 9 days (38.3 percent) or 10 days of more (31.9 percent). Among those aged 12–17 years, the proportions were 52.8 percent, 54.5 percent and 46.3 percent, respectively.

Another way to examine whether or not greater initiation in smoking occurs with menthol smokers is to compare the rate of menthol cigarette use vs. non-menthol cigarette use among less established smokers. In the February 11th presentation, Hersey examined data from 2000 to 2008 using the NSDUH survey and observed that a higher percent of menthol vs. non-menthol smokers smoking fewer than 100 cigarettes among youth. For example, 51.7 percent of Marlboro menthol smokers aged 12–17 reported smoking fewer than 100 cigarettes in their life vs. 38.1 percent of Marlboro non-menthol smokers. Similarly, 62.1 percent of Camel menthol smokers reported smoking fewer than 100 cigarettes versus 40.3 percent of Camel non-menthol smokers. For Newport, the rate was 46.8 percent. Because of the cross-sectional nature of the study, the causal direction is hard to interpret (smokers initiating on menthol cigarettes vs. those smoking menthol cigarettes tend to smoke fewer cigarettes).

(See Table 3 for rates of recent vs. established smokers among menthol smokers.)

*Summary:* These studies are limited by being cross-sectional and we can only infer that recent users as opposed to more established users are representative of those who initiated smoking with menthols. Nonetheless, there is some evidence to show that more recent smokers have a higher prevalence of smoking menthol cigarettes than established smokers in studies of adolescents that examined duration of smoking. However, there is mixed evidence to show that smokers of a few cigarettes (who might represent experimenters) tend to smoke more menthol cigarettes than smokers of a higher number of cigarettes.

**Age of initiation for menthol vs. non-menthol cigarettes**

Nine peer-reviewed articles, two unpublished submissions, and one white paper on internal tobacco documents were identified. Nine peer-reviewed studies and one unpublished secondary analysis

showed no differences in age at which the first cigarette was smoked (Allen & Unger, 2007; Okuyemi, Ebersole-Robinson, Nazir, & Ahluwalia, 2004; Pletcher et al., 2006), age of initiation (Cubbin, Soobader, & LeClere, 2010) or started smoking (Hyland, Garten, Giovino, & Cummings, 2002; Hymowitz, et al., 1995)(Hyland November 2010) or age of regular smoking (Lawrence et al., 2010; Okuyemi, et al., 2004; Okuyemi, Faseru, Sanderson Cox, Bronars, & Ahluwalia, 2007), comparing smokers of menthol and non-menthol cigarettes. The types of studies examined ranged from cross-sectional surveys (Cubbin, et al., 2010; Lawrence, et al., 2010; Okuyemi, et al., 2004), multicenter cohort studies (Hyland, et al., 2002; Hymowitz, et al., 1995; Pletcher, et al., 2006) to a treatment study (Okuyemi, et al., 2007). Two studies specifically examined African American populations (Okuyemi, et al., 2004; Okuyemi, et al., 2007). Three of the studies used the COMMIT database but with analyses of different time periods (Hyland, et al., 2002; Hyland & Rivard, 2010 b; Hymowitz, et al., 1995). One study that examined risk factors for menthol status showed marginal statistical significance for age of regular smoking, with delayed initiation associated with menthol status (Fernander, Rayens, Zhang, & Adkins, 2010). Tobacco documents also do not reveal any evidence to show the menthol smokers start earlier than non-menthol smokers (Klausner, 2011 in press).

In a submission from R.J. Reynolds, Curtin et al. (2010b) examined self-reported age of initiation in four national surveys: first whole cigarette smoked (NHANES <20 years old; NYTS), age started smoking regularly (NHANES, age < 20 years; NHIS), age first began smoking cigarettes (NSDUH) or age at first cigarette (NSDUH). The authors concluded that in general, based on NHANES, NHIS and NSDUH data, older age of initiation was observed among current menthol compared to non-menthol smokers, especially among females and individuals 30 years or older. However, significant differences were not observed with control for race, age and gender. On the other hand, the NYTS showed the age of first whole cigarette smoked was younger among the menthol compared to the non-menthol smokers, even when controlling for race, age and gender. The average initiation age was 0.52 years younger in current menthol smokers vs. non-menthol cigarette smokers ($p<0.05$).

*Summary:* The preponderance of evidence shows that menthol cigarette smokers do not report an earlier age of initiation of cigarette use (age of onset of first cigarette or regular smoking). However, the one study that examined an adolescent sample observed an earlier age of first smoking a whole cigarette among menthol vs. non-menthol smokers.

**Rate of switching from menthol to non-menthol cigarettes and from non-menthol to menthol**

Switching rate was considered important to consider because greater switching from menthol to non-menthol compared to non-menthol to menthol suggests that menthol may serve as a starter product. Two peer-reviewed articles, four unpublished secondary analysis (one of which was a public comment and submission) were identified for this topic and one white paper on internal industry documents. Data are conflicting on the extent of switching from menthol to non-menthol compared to non-menthol to menthol cigarettes. In the 15-year CARDIA cohort study that enrolled 1,535 healthy African American and European white men and women aged 18 to 30 years old in 1985, no differences were observed in the percent of young adult smokers (18 to 30 years old at the time of enrollment) who switched types of products (12 percent menthol to non-menthol switchers, 11 percent non-menthol to menthol switchers; Pletcher, et al., 2006). In another study of 29,037 current smokers and members of the Kaiser Permanente Medical Care Program followed for 4.5 years, more African American smokers under the age of 40 years switched from non-menthol to menthol cigarettes (14.6 percent) than from menthol to non-menthol cigarettes (3.6 percent), even when adjusting for age and sex (Sidney, et al., 1989); however, this study was conducted in the early 1980s and the follow-up rate was quite low (28 percent to 32 percent).

Hyland and Rivard (submission to FDA, November 2010b) explored the characteristics of menthol smokers and rates and correlates of switching to and from mentholated products using data from the COMMIT (Community Intervention Trial for Smoking Cessation) study. The percentage of 2,095 smokers using menthol tobacco in 1988 through 2001 by different demographic and smoking-related characteristics was calculated. Like other studies, they found that switching between menthol and non-menthol cigarettes is uncommon for all smokers, regardless of race. About 6.4 percent (out of 2,095) switched from menthol to non-menthol and 4.2 percent switched from non-menthol to menthol. Logistic regression was used to examine the correlates of switching from menthol to non-menthol cigarettes and vice versa in 1993 and in 2001. Smokers age 55 and older, as well as those who started smoking at 15 years or younger, were most likely to switch from menthol to non-menthol cigarette in 1993 or 2001. Smokers who report smoking fewer than 25 cigarettes per day were most likely to switch from non-menthol to a menthol cigarette in 1993 or in 2001.

Hyland and Kasza (November 2010 a submission) conducted another secondary analysis of epidemiological studies using the International Tobacco Control Four Country Survey (ITC-4), which collected information from 7,532 subjects 18 and older between 2002 and 2008 (annual assessments) from four different countries. Current smokers were defined as having smoked at least 100 cigarettes during their lifetime, and currently smoking at least monthly, and menthol status was determined by the brand that they presently smoke. Among whites, the probability of switching from menthol to non-menthol cigarettes (7.63 percent) was higher than switching from non-menthol to menthol (1.74 percent). Similarly, among Hispanics, the probability of switching from menthol to non-menthol cigarettes was higher (17.39 percent) than switching from non-menthol to menthol (6.72 percent). Among African Americans, the probability of switching from menthol to non-menthol (7.8 percent) was lower than non-menthol to menthol (14.78 percent).




Two studies examined adolescents or young adults. One report analyzed the 2003 National Youth Smoking Cessation Survey. This survey examined 2,582 16-24 year olds who had ever smoked 20 lifetime cigarettes and had smoked at least once during the previous 30 days. After 24 months, 1,045 out of the 2,582 initially enrolled participants were still smoking. Menthol status was determined at baseline and at follow-up. Results showed that more 16-24 year old smokers switched from smoking menthol cigarettes to non-menthol cigarettes than vice versa after a two-year assessment period (15.0 percent vs. 6.9 percent, Giovino, 2010 unpublished submission). Nonnemaker et al. (November2010 submission to the FDA) analyzed a three-year longitudinal cohort school-based study of 12-18 year olds

using the American Legacy Longitudinal Tobacco Use Reduction Study. This school-based survey of 47,237 middle school and high school youth was conducted in three waves from 2000 through 2003 in 83 schools in seven communities and five states. The analyses were restricted to youth who participated in all three waves of the survey (N=16,396 out of 35,352 interviewed at baseline). Youth who initiated smoking prior to baseline or who were older than 18 were dropped from the study. Analyses were estimated using weights that account for baseline characteristics as well as attrition. Data was analyzed excluding and then including youth who initiated smoking in Wave 3. Including Wave 3 initiates because of the larger sample size, the results showed that 5.9% switched from menthol to non-menthol and 8.0 percent from non-menthol to menthol, a direction opposite from that observed from Giovino (2010).

(See Table 4 for rates of switching)

*Summary:* There is some evidence to suggest that more menthol smokers switch to non-menthol cigarettes within certain populations of smokers. This may help explain some of the age trends in menthol smoking (lower prevalence among older adults), where more subjects are are switching from menthol to non-menthol. It is notable that relatively few smokers switch brands thereby demonstrating brand loyalty even among yIt is notable that relatively few smokers switch brands thereby demonstrating brand loyalty even among youth and young adults.

**Sensory experience of menthol cigarettes**

Several articles have described characterizing menthol as facilitating the uptake of cigarettes because it reduces the harshness of tobacco and provides a cooling sensation thereby increasing the appeal of the product (Henningfield et al., 2003) (Lawrence, Cadman and Hoffman, white paper 2010). As described in chapter 3, these effects from menthol makes it biologically plausible that menthol enhances the addictiveness of cigarettes.

Because of the limited amount of research in this area, internal tobacco industry documents may reveal the industry's thinking about menthol cigarettes as a product for initiators or non-established smokers. In research that assesses relevant documents from 1965 to 2000, two types of menthol smokers emerge—those who cannot tolerate the harshness and irritation of non-menthol cigarettes, and those who seek out the flavor and physical sensation of menthol (Kreslake et al. 2008).

For the first type, menthol reduces the negative sensory characteristics associated with smoking. This type includes a large proportion of occasional smokers or young smokers, or smokers who switched to menthol cigarettes because the harshness or perceived negative health effects of their non-menthol cigarettes. The tobacco industry documents show that they were aware of how to manipulate menthol levels to appeal to cigarette smoking initiates. The author (Cnatrell, 1987 in Kreslake 2008, page 710) of an internal Brown & Williamson memo noted that a "successful starter cigarette would need to provide a low tobacco taste, low impact and irritation, low tobacco aftertaste and low menthol content." A Lorillard document noted that among younger subjects (aged 21-29), ratings of overall satisfaction were lower when the levels of menthol increased. Thus, Newport Lights, which had less menthol loading, was more appealing to younger respondent than cigarettes with higher menthol loading (Kreslake et al., 2008, page 711). The second type of smoke includes individuals who seek out specific menthol flavors associated with physical sensation. These established menthol smokers appear to be tolerant of or seek out stronger sensory characteristics and tend to be African American and male.

A search of internal tobacco industry documents commissioned by the FDA using the Legacy Tobacco Document Library addressed properties of menthol and the smoking experience. The review found properties menthol contribute to the that "menthol has cooling and anesthetic properties that are dose-sensitive and that can moderate the harshness and irritation of tobacco." (conclusion from R.J.Reyonlds Tobacco Co. study, page 8, Yerger, in press). This finding is congruent with a search conducted by Wayne and Connolly (2004) who reviewed the archival database maintained at Tobacco Documents Online, ranging in date from 1920s through1990s. These authors reported that documents indicate that tobacco companies thought that mentholation led to "altered perception of tobacco smoke and its constituents via cooling, smoothing and anesthetic effects; increased impact through stimulation of trigeminal receptors and interaction with nicotine controlling its perception, delivery and uptake." The FDA commissioned report (Yerger, in press) page xx) further observed, "By making cigarettes smoother and less harsh, menthol alleviates nicotine's irritating effect. For decades, the tobacco industry has known that younger, inexperienced smokers have lower tolerance for irritation and tobacco taste than do older and more experiences smokers."

The white paper commissioned by the FDA (Klausner, 2011 in press) on menthol initiation concluded that their analyses indicate that youth and experimenters choose menthol cigarettes because they are easier to smoke, are more soothing on the throat and cooler, milder and less harsh or burning. Further, the author describes an early study that was conducted by Philip Morris, which showed that what menthol smokers report they like about menthol is due to effect rather than taste. The key effects that appear to appeal to menthol smokers include "cooling effects clean, antiseptic effects, slightly numbing, anesthetic effects and heady, lifting effects (page 6)." The author points to a Brown & Williamson document that surmised the beginning smoker's familiarity with mint-flavored candies contributed to the acceptance of menthol. Similar to the Kreslake study, the author describes the tobacco companies' knowledge that initiators of smoking prefer cigarettes with a hint of menthol but as the smokers age, they prefer cigarettes with more menthol. In addition, the documents also showed that some youth smoke menthol cigarettes because they perceive them to be less harmful than non-menthol cigarettes. The tobacco companies also found the family and peer influences to be important in determining use of menthol cigarettes by young and new smokers. Other tobacco companies believed that the choice of menthol was haphazard. Industry presentations and associated documents suggest that individuals have different taste preferences and taste is what drives them to smoking mentholated cigarettes (July 2010 TPSAC meeting).

*Summary:* Based on review of internal tobacco documents, the evidence suggests that youth choose menthol cigarettes, particularly at lower menthol yields, mainly because of the relative ease of smoking a menthol cigarette for the naive smoker and because they perceive menthol to be less harmful than non-menthol cigarettes. These internal document findings converge with the studies on the physiological effects of menthol conducted both internally and externally to the tobacco companies and possibly the finding that adolescent smokers tend to prefer Newport cigarettes, which tend to have lower menthol in cigarette as percent of tobacco weight and lower menthol in smoke than brands like Kool or Salem (June 30, 2010 Altria submission, Table 1.3). Taken together, the various lines of evidence support an appeal of menthol cigarettes to youth and starting smokers because of their sensory effects.

**REGULAR SMOKING AND ADDICTION**

This section examines whether menthol cigarette use is more likely to lead to regular smoking or nicotine addiction compared to non-menthol cigarette use. TPSAC looked at evidence in three relevant areas: abuse liability, the trajectory of addiction, and the intensity of addiction. Abuse liability addresses whether menthol interacts with nicotine or enhances the experience of smoking to make menthol

cigarettes more addictive than non-menthol cigarettes. Trajectory of addiction explores the likelihood and speed with which menthol cigarette smokers become addicted to nicotine compared to non-menthol cigarette smokers. Intensity of addiction assesses whether menthol cigarette users are more or less dependent on nicotine or cigarette smoking than non-menthol cigarette users.

**Abuse liability assessment**

***Menthol's effects on the nicotine pharmacokinetics***

Nicotine pharmacokinetics are important because the reinforcing strength of cigarettes is based on the amount and speed of nicotine delivery as well as the rate of nicotine clearance (U. S. Department of Health and Human Services, 1988, 2010). As noted in chapter 3, the preponderance of evidence shows no differences in the amount of acute nicotine delivered by a single cigarette to menthol vs. non-menthol cigarette smokers. Although evidence presented in chapter 3 suggests menthol may slow the clearance of nicotine from the bloodstream, the effect is small and not likely to affect pharmacokinetics significantly. Therefore, most likely, menthol does not alter the pharmacokinetics of nicotine in a way that would enhance the development addiction beyond that of a non-menthol cigarette. Chapter 3 reports that menthol may act on nicotinic receptors and may modulate pharmacologic effects of nicotine, but the functional consequence of such effects with respect to addiction is unknown.

***Abuse Liability Laboratory Studies***

To date no formal animal or human abuse liability assessment has been conducted with menthol cigarettes. In the absence of such research, TPSAC examined four peer-reviewed studies on smoker responses to menthol and non-menthol cigarettes; one peer-reviewed analyses of internal tobacco company documents, and two peer-reviewed studies on behavioral economic analysis of menthol and non-menthol cigarette smokers.

<u>Smoker responses to menthol and non-menthol cigarettes</u>

Several studies have examined the effects of menthol containing cigarette substitutes and cigarettes on subjective response, which may provide insight into whether a product containing menthol may be more rewarding. The within-subject, laboratory studies and their findings are summarized below.

Levin et al. (1990) used cigarette substitutes to examine smokers' taste reactions to five flavors, three tobacco flavors and two menthol-like flavors. Each flavored cigarette substitute was rated on several dimensions and compared to placebo. Cigarette substitutes with menthol-like flavors received statistically significantly higher ratings on liking and satisfaction than placebo and were among the highest ranked in both menthol and non-menthol smokers.

Pickworth et al. (2002) examined smokers' reactions to high-nicotine yield (2.5 mg nicotine yield) and low-nicotine yield (.2 mg nicotine yield) menthol and non-menthol laboratory cigarettes and two menthol (Kool, Newport) and two non-menthol (Winston, Marlboro) commercial cigarette brands. Menthol cigarette smokers used menthols in the study; non-menthol cigarette smokers used non-menthols. No statistically significant differences in most subjective responses (strength, satisfaction, psychological reward, negative effects) were observed between the menthol and non-menthol smokers. Nicotine yield, not menthol, had effects on subjective measures.

Pritchard et al. (1999) compared responses of smokers to "denicotinized" (0.06 mg nicotine yield) menthol (4.1 mg menthol/cigarette) and non-menthol cigarettes. In this study, menthol and non-

menthol smokers tested both types of cigarettes. As in Pickworth et al. (2002), no significant differences in subjective responses (mental alertness, anxiety/nervousness, muscular relaxation) were observed between menthol and non-menthol cigarettes. In addition, little evidence of pharmacological effect, as assessed by EEG and heart rate, were observed between menthol and non-menthol cigarettes.

These laboratory studies are limited by their small sample sizes, unbalanced distribution of race/ethnicity among menthol and non-menthol smokers, and focus on established smokers and other inclusion criteria, limiting the generalization of these finding.

Only one study has examined reactions associated menthol vs. non-menthol cigarettes during the first smoking experience. No differences in subjective reaction to the first inhaled cigarettes by mentholation were observed (DiFranza et al., 2004). The DiFranza et al. study is limited due to the small sample size and retrospective recall of their experiences with their first inhaled cigarette. Furthermore, just over half could recall the brand of their first inhaled cigarette.

Analyses of internal tobacco company documents

One recent peer-reviewed study of internal tobacco industry documents reveals experiments that indicate menthol has a significant impact on low-nicotine and denicotinized cigarettes.

Yerger (in press) writes that during the late 1980s, Philip Morris scientists conducted tests on various prototypes of "alkaloid (nicotine) reduced tobacco" (ART). The non-mentholated ART prototypes were described as lacking impact (e.g., "kick" or "grab" in the back of the mouth and throat when inhaling a cigarette, a sensory experience believed to contribute to immediate smoking satisfaction). Yerger writes (page 8): "Phillip Morris found the mentholated prototypes of ART to be 'subjectively superior' to non-mentholated versions because they were the only ART prototypes that provided any impact." She further states, "When further testing the mentholated ART prototypes, Phillip Morris scientists found menthol provided this perceived impact because it produced some nicotine-like effects."

Yerger (in press) additionally writes that Philip Morris conducted a study that combined four levels of menthol with three levels of nicotine. The results showed that cigarettes without nicotine were preferred more when menthol was added; low or intermediate menthol levels were preferred over high menthol levels in cigarettes. Yerger describes other Phillip Morris studies that confirmed the observation that "menthol increased impact for the low-nicotine delivery cigarettes…The effect of menthol was most pronounced for the cigarette with the lowest nicotine delivery" (page 11, quote by Gerry Nixon from Phillip Morris).

Yerger (in press) further describes tobacco industry studies conducted by Phillip Morris and Brown and Williamson in the 1970s of different menthol concentrations on low-tar delivery cigarettes to maximize customer appeal and increase market demand for these cigarettes. During that time, these low-tar/nicotine brands were believed to address concerns about the health effects of smoking and were considered to represent a growth area.

Yerger (in press) also writes of human studies conducted by Phillip Morris that found menthol produces some nicotine-like central nervous system and subjective effects (e.g., mental alertness, muscular relaxation), making menthol a "partial replacement" for nicotine (page 15). This observation is likely to be due the stimulation of the trigeminal nerve or nerve fibers, which is considered "essential to eliciting 'liking' response to tobacco products" (page 15). Yerger writes that because of the nature of the documents, no information was provided on the specifics of study designs or who comprised the subjects for this study.

Behavioral economic models

The relative abuse liability of a product can be determined by the extent to which another product can be substituted for it. Tauras et al. (2010) observed that smokers do not find menthol and non-menthol cigarettes to be close substitutes. Using data from the 2003 and 2006/07 Tobacco Use Supplements to the Current Population Survey (n=57,387, aged 18 and older), they developed a regression model that estimated the probability of being a menthol smoker, conditional on being a current smoker who reported a preference for menthol or non-menthol cigarettes. Cigarette prices, smoke-free air laws and socioeconomic and demographic characteristics were examined as covariates. The results showed that non-menthol cigarettes were less of a substitute for menthol cigarettes than vice versa. A 10 percent increase in menthol cigarette prices would cause 2.36 percent of menthol smokers to switch to non-menthol cigarettes. By contrast, a 10 percent jump in non-menthol cigarette prices would cause 4.75 percent non-menthol cigarette smokers to switch to menthol cigarettes. This difference was more pronounced among African Americans and young adults. Furthermore, these investigators found relatively more use of menthol cigarettes in states that have stronger laws restricting smoking. Both these findings suggest that menthol cigarettes may be more reinforcing or addicting than non-menthol cigarettes.

Farrelly et al. (2007) examined the effect of price increases on the purchase of stronger cigarette types (cigarettes with higher tar and nicotine yields). Scanner data (ScanTrack licensed from ACNielsen) on cigarette prices and sales were obtained from supermarkets (with at least $2 million in annual sales) across the United States from 1994 to 2004. Using multivariate regression models, price elasticities suggest that the average inflation-adjusted price increase of 55.8 percent for menthol cigarettes was associated with an increase of 1.73 percent in sales-weighted tar yields and 1.28 percent increase in sales-weighted average nicotine yields. A 50.5 percent price increase of non-menthol types of cigarettes over the same period produced an estimated increase of 1 percent in tar per cigarette but no statistically significant increase in nicotine yields. Thus, these findings show that an increased probability that stronger cigarettes are smoked as price of cigarettes is increased and this effect is larger among menthol than non-menthol smokers. Concordant with the prior study, these results also suggest addiction to cigarettes may be stronger among menthol smokers, although the study results do not show if more exposure to tar and nicotine occurs as a result of the smoking higher tar and nicotine yield cigarettes. However, one of the strengths of these studies is that they are nationally representative samples and examine actual behavior of consumers.

*Summary:* No animal and relatively few human studies have been conducted directly examining the relative abuse liability of menthol vs. non-menthol cigarettes. Reviews of internal tobacco industry documents show studies conducted by the tobacco industry that demonstrate that menthol is associated with greater impact or “throat grab” when added to denicotinized or lower nicotine yield cigarettes. As suggested in chapter 3, abuse liability of menthol cigarettes may be higher because of potentially strong conditioned cue response with menthol cigarettes. Finally, studies using behavioral economic models, which have been used to assess abuse liability of other drugs, suggest greater reinforcing effects from menthol cigarettes.

**Trajectory from initiation to regular smoking or dependence**

To date, only Nonnemaker et al. (2010) has examined if early menthol cigarette use was more likely to be associated with regular smoking or dependence than early non-menthol cigarette use. As previously described, this unpublished research analyzed data from the American Legacy Longitudinal Tobacco Use Reduction Study, a three-year longitudinal cohort school-based study of 12–18 year olds. Progression to

greater smoking was determined in three ways: (1) a transition from smoking less than 100 cigarettes to smoking more than 100 cigarettes; (2) a transition from smoking on less than 20 days per month to smoking 20 or more days per month; and (3) a transition from non-daily smoking to daily smoking. Nicotine dependence was measured in response to the following questions: (a) *How soon after you wake up do you usually smoke your first cigarette on weekdays? during the weekend?* (b) *If you are sick with bad cold or sore throat, do you smoke cigarettes?* (c) *How true is this statement for you? When I go without a smoke for a few hours, I experience cravings*; (d) *How true is this statement for you? I sometimes have strong cravings for cigarettes where it feels like I'm in the grip of a force that I can't control*. The higher the score on this dependence measure, the greater the extent of dependence. Key explanatory variables included an indicator for reporting the first cigarette smoked was menthol (n=1100), and indicators for pattern of menthol use: menthol to menthol (n=3930): menthol to non-menthol (n=55); non-menthol to menthol (n=82); and non-menthol to non-menthol (n=459). Analysis includes adolescents who initiated in Wave 3 to provide a larger sample size and also because some ethnic/racial groups do not start smoking until a later age. All regression analysis was controlled for gender, age, and race/ethnicity. Key findings follow (see Appendix A for tables).

Among Wave 3 smokers, 43.0 percent reported menthol use at initiation. A large majority of current smokers at Wave 3 maintained a preference for the type of cigarette they started on across survey waves—36.8 percent began smoking menthols and still smoked menthols at Wave 3, and 49.3 percent began smoking non-menthols and still smoked non-menthols in Wave 3. As previously noted, only a small percentage reported going from menthol to non-menthol (5.9 percent) and from non-menthol to menthol (8.0 percent).

Initiation to menthol is positively associated with smoking daily (OR: 1.99, 95% CI: 1.42–2.80), established smoking (OR: 1.94, 95% CI 1.41–2.66) and lifetime cigarette smoking (OR:1.94, 95% CI: 1.40–2.68) at Wave 3 compared to non-menthol reference group initiators.

Respondents who switched from menthol cigarettes to non-menthol cigarettes were significantly more likely to qualify for smoking daily (OR: 3.30, 95% CI 1.59–6.87), established smoking (OR:3.25, 95% CI: 1.58–6.66) and lifetime cigarette smoking (OR: 3.41, 95% CI: 1.59–7.31) compared with the non-menthol reference group initiators. The greater likelihood of smoking regularly or lifetime smoking may be a function of switching rather than menthol status. For example, respondents who switched from the non-menthol to menthol group were also significantly more likely to qualify for established smoking (OR: 2.05, 95% CI: 1.08–3.87) and Lifetime Cigarette Smoker (OR:1.98 95% CI: 1.03–3.78). However, menthol to menthol respondents were also more likely to qualify for daily smoking (OR: 2.09, 95% CI: 1.45–3.03), established smoking (OR: 2.07, 95% CI: 1.47–2.93) and lifetime cigarette smoking (OR: 2.08, 95% CI: 1.47–2.94) than for the non-menthol reference group.

Most importantly, for all three outcomes—daily smoking, established smoking and lifetime cigarette smoking—the models that include Wave 3 initiators reveal a positive and statistically significant association between menthol at initiation and transitions to higher levels of smoking (smoking daily, OR: 2.11, 95% CI: 1.47–3.03; established smoking, OR: 2.02, 95% CI: 1.44–2.84; and lifetime cigarette smoking, OR: 2.32, 95% CI: 1.64–3.28)

Respondents who switched from menthol cigarettes to non-menthol cigarettes were statistically significantly more likely to transition to increased smoking for each transition outcome compared with the non-menthol reference group (smoking daily, OR: 3.65, 95% CI: 1.46–9.16; established smoking, OR: 4.72, 95% CI: 1.86–11.99; lifetime cigarette smoking; OR: 7.42, 95% CI: 2.73–20.22). Transitions for each outcome were also more likely for menthol-to-menthol respondents (smoking daily, OR: 2.12, 95% CI: 1.44–3.12; established smoking, OR: 2.09, 95% CI: 1.45–3.00; lifetime cigarette smoking, OR: 2.27, 95% CI: 1.57–3.28). Respondents who switched from non-menthol to menthol were not more likely to transition to increased smoking for any of the transition outcomes.

Menthol cigarette use at initiation is positively and statistically significantly associated with nicotine dependence, according to the results of the ordinary least square regressions for the nicotine dependence (OR:1.04, 95% CI: 0.26–1.82). Menthol-to-non-menthol smokers were significantly more likely to have higher dependence scale scores (OR: 2.33, 95% CI: 1.08–3.59) than non-menthol to non-menthol smokers. However, menthol to menthol smokers have significantly lower scale scores (0.96, 95% CI: 0.08–1.83) than the non-menthol reference group. This latter finding is not robust. No statistically significant results were found in the non-menthol to menthol group.

Klausner (2011 in press) found no evidence in internal tobacco company documents to indicate that people who start smoking menthols compared to non-menthols progress more quickly toward established smoking. No study has primarily examined the rapidity with which people initiate smoking and become regular smokers. Okuyemi et al. (2004), in a study of African American treatment seekers found menthol smokers report three years between their first cigarette and the start of regular smoking was compared to two years for non-menthol smokers. The generalizability of this data is limited.

*Summary*: In order to specifically determine if menthol cigarettes play a significant role in the initiation of smoking, the best study would be to examine the rates of continued or established smoking and dependence among those who initiated smoking with menthol vs. non-menthol cigarettes. There are limitations to the Nonnemaker et al. (2010) study including: (a) a small sample size of ethnic/racial minority groups, (b) inclusion of subjects who only completed all three waves of the study, (c) the lack of national representativeness of the sample, and (d) long intervals between assessments. While replication of these results would be important and an establishment of a longitudinal cohort study would be valuable, the currently presented evidence is persuasive in demonstrating that initiating with menthol cigarettes is associated with increased risk for transitioning to more established smoking**.**

**Degree of addiction**

There are several ways to assess the degree of addiction to a tobacco product. These include examining the (1) the number of cigarettes smoked, with higher levels of smoking denoting greater dependence,(2) biomarkers of exposure (e.g., urinary total nicotine equivalents (NE), plasma or saliva cotinine, total NE/cigarette, cotinine/cigarette), (3) alterations in the 3 hydroxycotinine (3OH) to cotinine ratio, with higher ratio potentially indicating greater risk for dependence, and (4) self-report measures of dependence which include using the Fagerstrom Test for Nicotine Dependence, a component of the FTND (time to first cigarette or TTF), other measures of dependence, waking up in the middle of the night to smoke and severity of withdrawal symptoms. The majority of these measures have been validated with each other or other indicators of addiction (USDHHS 2010). The section reviews studies

using these indices of addiction to assess whether adults and adolescents who smoke menthol cigarettes are more addicted to nicotine than those who smoke non-menthol cigarettes.

***Adults***

Cigarettes per day

The number of cigarettes smoked per day (CPD) has been found to be a strong indicator of nicotine dependence (U. S. Department of Health and Human Services, 2010). TPSAC identified 28 studies that measured CPD by cigarette type. Of these studies, one was excluded because of its small sample size (Ahijevych, Dai, & Chan, 2002). Of the remaining 27 studies, 16 found no CPD differences between menthol and non-menthol cigarette smokers. The studies are summarized below.

Eleven peer-reviewed studies found that menthol cigarette users reported smoking fewer cigarettes per day. The statistical significance of the results varied by race/ethnicity in some of the studies, but the results related to race/ethnicity were not consistent from one study to the next. A limitation of many of the studies is that they did not control for age, race/ethnicity, or income. Results of the 11 studies follow.

- Wang et al. (2010), analyzing a cross-sectional, multi-site, observational study, reported 15.0 vs. 16.3 CPD for menthol vs. non-menthol cigarette users, respectively ($p < 0.01$). Although CPD was statistically significantly higher in white menthol vs. non-menthol cigarette smokers (18.1 vs. 17.2 CPD), there was no difference in African Americans (10.9 menthol vs. 12.1 non-menthol CPD).

- Giovino et al. (2004), analyzing the U.S. component of the International Tobacco Control Policy Evaluation survey, found a statistically significant difference of 18.1 vs. 19.8 CPD ( $p<0.01$) in white menthol vs. non-menthol smokers, respectively. No difference was observed in African Americans.

- Curtin et al., (2010 dependence) analyzing 2003 NHIS, found borderline significance for lower intensity of smoking among menthol vs. non-menthol cigarette smokers overall ($p=0.06$), a statistically significant difference in white menthol vs. non-menthol cigarette smokers (15.5 vs. 16.98 CPD, respectively, $p < 0.05$), but not among African Americans or "other" ethnic group. In an analysis of 2007 NSDUH, white menthol cigarette smokers also showed a lower smoking intensity than white non-menthol cigarette smokers ($p < 0.01$), but this difference was not seen among African Americans or other racial/ethnic groups.

- Stahre et al. (2010), analyzing the 2005 National Health Interview Survey, found 14.6 vs. 17.5 CPD ($p < 0.0001$) in menthol vs. non-menthol cigarette smokers, respectively.

- Analyzing data from the 2002 and 2006/07 Tobacco Use Supplement-Current Population Survey (TUS-CPS), Fagan et al. (2010) found 13.1 vs. 15.0 CPD ($p < 0.001$) in menthol vs. non-menthol cigarette smokers, respectively; Lawrence et al. (2010) found 51.9 percent of menthol cigarette smokers consumed fewer than 10 cigarettes per day compared to 42.3 percent of non-menthol cigarette smokers.

- Pletcher et al. (2006), examining a longitudinal cohort study with young adults examining risk in cardiovascular disease (CARDIA) reported 10 vs. 15 CPD ($p < 0.001$) for menthol and non-menthol cigarette smokers, respectively

- Hyland et al. (2002) examining a national community-based intervention trial found menthol smoking was associated with smoking five cigarettes or less a day compared to smoking more than this amount at baseline after controlling for covariates.

- Gandhi et al. (2009), examining a large sample of treatment seekers, reported 19.0 vs. 23.1 ($p< 0.001$) overall, 15.7 vs. 20.3 CPD ($p<0.001$) in African American menthol vs. non-menthol cigarette smokers, respectively, and 17.0 vs. 22.1 CPD ($p=0.017$) in Hispanic menthol vs. non-menthol cigarette smokers, respectively. No differences were observed in whites ($p=0.09$) or "other" ethnic group.

- Fu et al. (2008), in a multi-site study of Veterans Administration multi-ethic treatment seekers, observed 20 vs. 30 CPD ($p < 0.001$) in menthol vs. non-menthol cigarette smokers, respectively. Subjects were asked to recall CPD for the two years prior to study entry.

- Muscat et al. (2002), in a cross-sectional analysis of a case-control study on smoking and lung cancer, found 28.0 vs. 29.3 CPD in white menthol vs. non-menthol cigarette smokers, respectively (prevalence odd ratio, POR, for smoking $\geq$ 21 CPD vs. smoking $\leq$ 20 CPD= 0.9, 95% CI=0.8-1.0), and 18.2 vs. 20.9 CPD in African American menthol vs. non-menthol cigarette smokers, respectively (POR for smoking $\geq$ 21 CPD vs. smoking $\leq$ 20 CPD= 0.7, 95% CI=0.3-0.9).

Ten peer-reviewed studies showed no differences in CPD between menthol and non-menthol cigarettes. These studies included:

- Treatment studies (Fu, et al., 2008; Mustonen, Spencer, Hoskinson, Sachs, & Garvey, 2005; Okuyemi et al., 2003; Okuyemi, et al., 2007). Okuyemi et al. (2003; 2007) were conducted only in African Americans.

- Community based, cross-sectional studies (Hyland, et al., 2002 at follow-up; Muscat et al., 2009; Okuyemi, et al., 2004 ). Okuyemi et al. (2004) was conducted only in African Americans.

- A cross-sectional analysis of longitudinal cohort and intervention study for smoking and lung health (Murray, Connett, Skeans, & Tashkin, 2007).

- National surveys, including a secondary analyses of the 2005 NHIS and Cancer Control Supplement (Cubbin, et al., 2010) and the 2006/07 TUS-CPS (Ahijevych & Ford, 2010). The latter study found no differences in CPD by menthol status among daily and non-daily cigarette smokers.

Two non-peer-reviewed secondary analyses of cross-sectional surveys also found no CPD differences in menthol vs. non-menthol cigarette smokers.

- Hyland et al. (2010 a) examined the International Tobacco Control Four Country Survey (ITC-4) involving data collection from 7532 individuals between 2002 and 2008. No differences were observed in number of cigarettes within racial/ethnic and gender strata.

- Curtin et al. (2010c) conducted cross-sectional secondary analyses of 2005/06, 2007/08 NHANES and 2007 NSDUH. After controlling for sex, race/ethnicity and age, no overall differences in smoking intensity between menthol and non-menthol smokers were observed with NHANES and no differences were seen with NSDUH. When examining the NHANES data within racial/ethnic groups, no CPD differences were found among whites, African Americans or the "other" ethnic group.

Four non-peer-reviewed treatment-related studies also found no CPD differences between menthol

and non-menthol cigarette smokers. The first study examined the response to pharmacological treatments for nicotine addiction (King, Cao, & Matthews, 2010), the second study looked at the efficacy of a motivational treatment for smoking-relapse prevention in pregnant mothers, the third study examined the efficacy of palmtop computers for smoking cessation and the fourth study probed the social determinants of smoking cessation. The latter three studies involved both unadjusted and adjusted analyses (Reitzel, 2010 a, 2010 b) (2010c)

*Summary:* The evidence for differences in number of cigarettes smoked between menthol and non-menthol smokers is mixed. There some evidence to support the finding that menthol cigarette smokers consume fewer cigarettes per day than non-menthol cigarette smokers, particularly in some race/ethnicity groups compared to others, but the evidence within races is also mixed.

Biomarkers of exposure

Cigarettes per day may not be the most precise measure of actual exposure to nicotine (Caraballo et al., 1998). Determining actual nicotine exposure requires measurement of either total nicotine equivalents or cotinine (a metabolite of nicotine). These biomarkers of nicotine exposure can be examined in two ways: overall levels or per cigarette smoked.

*Biomarkers of exposure overall*

As described in chapter 3, TPSAC identified 14 peer-reviewed studies that measured and compared overall levels of biomarkers of nicotine exposure in menthol and non-menthol cigarette smokers. Results of these studies are summarized below.

Four studies found menthol cigarette smokers had statistically significantly higher levels of cotinine compared to non-menthol smokers. These studies were primarily experimental laboratory studies conducted with African American and white smokers (342 vs. 230 ng/ml, p=0.019, Ahijevych, Tyndale, Dhatt, Weed, & Browning, 2002; 239 vs. 180 ng/ml, p=0.02, Ahijevych & Parsley, 1999), smokers with schizophrenia as well as normal smokers (294 vs. 240 ng/ml, p=0.041, J. M. Williams et al., 2007) or African American and white smokers (478.2 vs. 249.1 ng/ml, significant even after adjusting for race, cigarettes per day and mean amount of each cigarette smoked, p=0.03, Clark, Gautam, & Gerson, 1996).

One study (Benowitz, Herrera, & Jacob, 2004) found higher cotinine levels in African American when they smoked menthol compared to non-menthol cigarettes, and lower cotinine levels in white smokers when the smoked menthol vs. non-menthol cigarettes. Cigarettes smokers who had experience in smoking both menthol and non-menthol cigarettes smoked menthol or non-menthol cigarettes with same machine-determined yield and nicotine content for one week before crossing over to smoke the other cigarette type for the second week. Subjects were confined to a residential unit 3 days out of each week. During this stay, subjects were instructed to smoke 20 CPD every 45 min, blood levels of nicotine were measured throughout the day and an intravenous infusion of deuterium labeled nicotine and cotinine were administered to determine rate of rate and pathways of nicotine clearance. Systemic intake of nicotine was not affected by menthol cigarettes. Plasma cotinine averaged over 24 hours was not significantly different between menthol and non-menthol smokers overall. However, there was a condition x race interaction, where $AUC_{nicotine}$ and average cotinine concentrations were higher in African Americans when smoking menthol cigarettes compared to non-menthol and the opposite was observed for whites. Although the sample size in this study was very small (n=14), the results emphasize the importance of examining race x menthol interactions.

Two studies detected a trend toward higher cotinine levels in menthol cigarette smokers compared to non-menthol cigarette smokers. Mustonen et al. (2005) found that African American and white menthol smokers had higher levels of cotinine compared to respective non-menthol smokers in a treatment study, but the differences were not significant (p=0.18). Muscat et al. (2009), in a cross-sectional, community-based study, observed slightly higher plasma cotinine in African American menthol vs. non-menthol smokers, but results were not statistically significant (p=0.09).

Seven studies found no differences in levels of cotinine and total nicotine equivalents (NE) between menthol and non-menthol smokers. These studies are:

- Wang et al. (2010), a cross-sectional, observational multi-site study, involving 24-hour urine collection and adjusted for covariates (lower NE levels were found in unadjusted analysis, 12.8 mg/24 hr vs. 13.5 mg/24hr, $p < 0.05$);
- Heck (2009), a parallel-arm study with subjects matched for machine-measured tar and balanced for sex, age and race, involving 24 hour urine collection;
- Signorello et al. (2009), a community-based cohort study on cancer occurrence;
- Murray et al. (2007), a community-based cohort intervention study among smokers at risk for COPD;
- Allen and Unger et al. (2007), a cross-sectional survey of African Americans living in an urban area (stratified by gender and controlled for age and employment status);
- Okuyemi et al. (2003; 2007), treatment studies with African American smokers; and
- Ahijevych et al., (1996) a laboratory smoke-exposure studies with female African Americans and whites, balanced for menthol status and race.

*Biomarkers of exposure as measured per cigarette*

The above studies measure overall levels of nicotine exposure; it is also possible to measure nicotine exposure per cigarette. Higher cotinine or nicotine equivalent levels per cigarette may be associated with greater reinforcing effects from each cigarette and subsequently a higher potential for addiction. TPSAC identified six peer-reviewed studies that measured and compared either cotinine per cigarette (cotinine/cigarette) or nicotine equivalents per cigarette (nicotine/cigarette) in menthol and non-menthol smokers.

Four studies showed higher levels of nicotine exposure per cigarette in menthol cigarette smokers compared to non-menthol cigarette smokers.

- Mustonen et al. (2005) found higher cotinine/cigarette in a treatment study of 307 white and African American smokers (23.3 ng/ml vs. 19.4 ng/ml, p=0.004), particularly black male menthol vs. non-menthol smokers.
- Ahijevych et al (2002) reported cotinine/cigarette levels of 20.7 ng/ml vs. 12.4 ng/ml (p=0.05) in an experimental laboratory study of a small number of African American and white female smokers. In a similar sample stratified for race and menthol status, Ahijevych et al. (1999) reported cotinine/cigarette levels of 17.8 ng/ml vs. 13.1 ng/ml, but found no race x menthol interaction.

- Wang et al (2010), using unadjusted statistical analysis, found higher nicotine equivalents (NE)/cigarette overall (0.96 vs. 0.90 mg/cigarette, $p < 0.05$) and within the African American (1.10 vs. 1.00 mg/cigarette, $p<0.05$) but not white (0.86 vs. 0.89 mg/cigarette) menthol cigarette smokers compared to non-menthol cigarette smokers, in a large cross-sectional, observational, ambulatory, multi-site study. When data was adjusted for covariates, no significant differences were observed.

Two studies found no differences in cotinine/cigarette in menthol vs. non-menthol cigarette smokers. One of these studies examined African American and white female smokers enrolled in smoke-exposure laboratory study (Ahijevych, et al., 1996). The other study examined smokers with schizophrenia and smokers without mental illness. These subjects were participants in either a treatment or experimental study in which cotinine/cigarette was adjusted for cigarettes per day, group (with and without mental illness) and ethnicity (J. M. Williams, et al., 2007).

*Summary:* There is conflicting evidence regarding the effects of menthol on nicotine exposure levels as measured by cotinine or 24-hour nicotine equivalents. Four studies found menthol cigarette smokers had statistically significantly higher cotinine levels; one study found higher cotinine levels in African American but not white menthol smokers; two studies detected a trend toward higher cotinine levels in menthol smokers; and seven studies found no difference in nicotine exposure between menthol and non-menthol smokers. The results are also mixed for the effects of menthol cigarette smokers on nicotine levels per cigarette (four of six studies supportive of higher levels, with one study finding effects in unadjusted analysis). Unfortunately, the majority of these studies did not control for race, income or gender, factors that may the affect number of cigarettes smoked or extent of nicotine exposure. In addition, as described in chapter 7, smokers who smoke fewer than 10 cigarettes per day may be a group where menthol effects may be observed.

Subjective measures of dependence

*Fagerstrom Test for Nicotine Dependence (FTND)*

The Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is the most widely used dependence measure (U. S. Department of Health and Human Services, 2010). TPSAC identified seven studies with FTND measures—five peer-reviewed, one unpublished secondary analysis, one unpublished submission by Altria. Six found no differences in FTND scores between menthol and non-menthol cigarette smokers. These studies were a cross-sectional survey of African American smokers seen at an inner-city health center generally catering to a low income population (Okuyemi, et al., 2004), a cross-sectional survey of African Americans living in an urban area (Allen & Unger, 2007), a community-based, cross-sectional study aimed at studying smoke exposure and nicotine dependence, adjusted for age, race, sex and education (Muscat, et al., 2009), a community-based, cohort study examining interventions for smoking cessation and lung health in smokers with mild and moderate airflow obstruction (Murray, et al., 2007), a cross-sectional , observational, multisite study (findings after adjusting for age, race, gender, education and tar yields; Altria Client Services on behalf of Philip Morris USA, 2010, June 2010 submission, p. 135) and a treatment study of African American smokers (Okuyemi, et al., 2003).

One study found statistically significantly higher FTND scores in menthol versus non-menthol smokers participating in a treatment study (5.56 ± 1.83 vs. 4.97 ± 1.81 years, $p = 0.007$). This study also found a greater smoking urge at baseline (first study visit) using the Brief Questionnaire of Smoking Urge in menthol vs. non-menthol cigarette smokers (total 33.32 ± 13.79 vs. 30.17 ± 12.63, $p = 0.043$) (King, et

al., 2010 secondary analysis, November ). This study was limited by its small sample of African American non-menthol cigarette smokers and white menthol cigarette smokers.

*Time to first cigarette (TTFC)*

A potentially better measure of dependence than FTND is time to first cigarette (TTFC)—the amount of time that lapses between waking and smoking the first cigarette of the day. This item has been found to be highly associated with physical dependence measures such as withdrawal symptoms and relapse to smoking after a cessation attempt (Piper et al., 2008; U. S. Department of Health and Human Services, 2010). Sixteen studies were identified with TTFC measures. Seven of them—six peer-reviewed studies and one unpublished secondary analysis—showed a shorter TTFC with menthol cigarettes. Eight studies—four peer-reviewed and four unpublished secondary analysis—showed no difference in TTFC between menthol and non-menthol cigarette smokers. One unpublished secondary analysis showed menthol cigarette smokers had a longer TTFC than non-menthol smokers.

The seven studies showing a shorter TTFC among menthol vs. non-menthol cigarette smokers follow.

- Ahijevych et al. (1999), in an experimental, laboratory smoke-exposure study in African American and white females, found TTFC of 19.9 vs. 37.4 minutes for menthol vs. non-menthol cigarette smokers, respectively, (p=0.02). The sample was stratified for race and menthol status.

- Okuyemi et al. (2003), in a smoking cessation treatment study in African Americans, found 81.7 percent of menthol vs. 69.8 percent of non-menthol cigarette smokers endorsed smoking $\leq$ 30 minutes after waking.

- Gandhi et al. (2009), in a smoking cessation treatment study in African American and white smokers, found 24.3 percent of menthol vs.19.9 percent of non-menthol cigarette users smoked within five minutes of waking.

- Muscat et al. (2009) measured TTFC in a community-based, cross-sectional study of smoke exposure and nicotine dependence in African American and white volunteers. Menthol cigarette smokers were more likely than non-menthol cigarette smokers to have a first cigarette 30 minutes or less after waking (OR: 2.1, 95% CI: 1.0-3.8). The results were adjusted for age, sex, race and education.

- Fagan et al. (2010), in a secondary analysis of pooled 2003 and 2006/07 TUS-CPS data on smokers of six to 10 cigarettes per day, found menthol cigarette smokers were more likely than non-menthol cigarette smokers to have a first cigarette within 5 minutes of waking (OR: 1.22, 95% CI: 1.05, 1.43 after controlling for a number of covariates such as gender, age, race/ethnicity and income).

- Ahijevych and Ford (2010), in a secondary analysis of the 2006/07 TUS-CPS among young adult, non-daily smokers using random effects model, found first cigarette within 30 minutes of waking associated with menthol smoking ($p<0.05$). Non-daily smokers were defined as those who smoked between one and 29 days in the last 30 days.

- Hyland and Kasza (2010 a November submission), in a non-peer-reviewed secondary, multivariate analysis of adult smokers who were interviewed as part of the International Tobacco Control Four Country Survey (ITC-4), found that when considering all respondents, menthol smokers reported fewer minutes to first cigarette compared to non-menthol smokers ($p < 0.01$). The analysis was adjusted for age, education, income, and quitting indicators. The strength of this relationship differed between racial/ethnic groups, with Hispanic respondents (particularly men), experiencing the greatest

difference between menthol and non-menthol smokers (significance for menthol X white/Hispanic interaction term <.05).

No differences were observed in eight studies:

- A secondary analysis of the 2006/07 TUS-CPS among daily, young adult smokers (using random effects model, Ahijevych & Ford, 2010); a secondary analysis of pooled 2003 and 2006/07 TUS-CPS among smokers who smoked fewer than six cigarettes per day or more than 10 cigarettes per day (after controlling for a number of covariates such as gender, age, race/ethnicity and income; Fagan, et al., 2010); and a secondary analysis of the pooled 2003 and 2006/07 TUS-CPS when using multivariate logistic regression model (Lawrence, et al., 2010).

- A cross-sectional, multisite observational study (first cigarette < 5 minutes or within 30 minutes, after adjusting for gender, age, race, income, tar yield, smoking amount, etc., Altria Client Services on behalf of Philip Morris USA, 2010 June submission).

- A large multi-site clinical trial comprised of a multi-ethnic sample to test a repeat tobacco cessation treatment found no differences between menthol and non-menthol cigarette smokers who had their first cigarette 30 minutes or less after waking. The study used retrospective recall of both menthol status and TTFC two years prior to study enrollment (Fu, et al., 2008).

- Three studies conducted by Reitzel (2010 a, 2010 b; 2010 c November submissions) also showed no difference by menthol status in time to the first cigarette of the day $\leq$ 5 minutes using adjusted analysis. These studies include research on the efficacy of a motivationally-based treatment for smoking relapse prevention in racially diverse pregnant mothers (Reitzel, 2010 c November) and palmtop computers used for smoking cessation among African American smokers (Reitzel, 2010 b November). The third study examined social determinants of smoking cessation in a racially diverse population (Reitzel, 2010 a November). In the randomized pregnant female smokers of diverse race, menthol was nearly statistically significantly associated with the time to the first cigarette of the day $\leq$ 5 minutes in unadjusted analyses (OR : 0.73, 95% CI: .54-1.00, p=0.05; (Reitzel, 2010 c November).

Conversely, in a secondary analysis of the 1988 telephone use surveys from COMMIT (Hyland, et al., 2002), increased menthol use was associated with greater than 60 minutes compared to less than 10 minutes to the first cigarette in the morning (OR: 1.16, 95% CI: 1.00-1.35 after adjusting for such covariates as for sex, age, race/ethnicity, education, amount smoked). Menthol users were slightly less likely to report smoking with 10 minutes after waking (RR: 0.90, 95% CI: 0.81- 0.99).

*Waking up in the middle of the night*

A recently validated measure of dependence is whether a smoker wakes up in the middle of the night. This measure has been related to smoking within 30 minutes of awakening, number of cigarettes per day and has been shown to be a predictor of treatment outcome (Bover, Foulds, Steinberg, Richardson, & Marcella, 2008; Foulds et al., 2006). Two studies have shown an association between menthol smoking and this measure. Gandhi et al. (2009) examined smokers who attended a specialist smoking cessation service and found a higher percent of menthol cigarette smokers vs. non-menthol cigarette smokers endorsed waking up in the middle of night to smoke (55.3% vs. 44.9%, p<0.001). Bover et al. (2008) also examined cigarette smokers who sought treatment as a specialist smoking cessation clinic. In multivariate analysis, night smoking was associated with smoking menthol cigarettes (AOR: 1.50; 95% CI: 1.20-1.87, p=0.0004).

Other dependence measures

Five treatment studies (two peer-reviewed studies and three unpublished secondary analyses) use two other dependence measures to analyze nicotine addiction by menthol status: Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). None of these studies showed a consistent menthol effect.

The Nicotine Dependence Syndrome Scale is multidimensional validated measure for nicotine dependence that provides a total score and score for several factors: Drive (craving and withdrawal and compulsion to smoke), Priority (behavioral preference of smoking over other reinforcers), Tolerance (reduced sensitivity to the effects of smoking); Continuity (regularity of smoking) and Stereotypy (invariance of smoking) (Shiffman, Waters, & Hickcox, 2004). Okuyemi et al. (2007) used NDSS to assess dependence in a treatment study of African American light smokers. No significant difference was observed between menthol vs. non-menthol cigarette smokers. In another survey (Florida Behavioral Risk Factor Surveillance System), using six items from the NDSS, non-menthol cigarette smokers reported greater dependence compared to menthol cigarette smokers, but multivariate analysis showed that the odds of menthol smoking were not related to nicotine dependence (Hooper et al., 2011).

The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) is a comprehensive, multi-dimensional measure of dependence that yields an overall smoking dependence score (WISDM-68 total score) as well as subscale scores for critical dimensions of dependence, including non-physical indices of dependence e.g., affiliative attachment, automaticity, social/environmental goals (Piper et al., 2004). Higher scores on the WISDM-68 are indicative of greater tobacco dependence. Three non-peer-reviewed secondary analysis of treatment studies using WISDM-68 were conducted by Rietzel (2010 a, 2010 b; 2010 c November).

In the first study, Reitzel (2010 b November) used WISDM-68 to measure dependence in a smoking cessation trial designed to determine the efficacy of using palmtop computers for cessation in African American smokers. Menthol cigarette use was not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, sex, partner status, income, employment status, and educational achievement. When examining each of the 13 subscales of the WISDM-68, in unadjusted analyses, menthol cigarette use was significantly associated with WISDM-68 Craving ($\beta$= .46, SE = .21; $p$ = .03) and marginally associated with Taste/Sensory Processes ($\beta$= .41, SE = .22; $p$ = .06). Specifically, menthol cigarette use was associated with more craving and taste/sensory-related dependence than non-menthol use. In adjusted analyses, the only significant association was between menthol cigarette use and WISDM-68 Taste/Sensory Processes ($\beta$= .52, SE = .24; $p$ = .03).

Reitzel (2010 c November) also examined dependence with the WISDM-68 in a study that randomized racially diverse pregnant female smokers of diverse race in clinical trial designed to test the efficacy of a motivationally based treatment for smoking relapse prevention. Menthol cigarette use was not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, race/ethnicity, partner status, income, and educational achievement. When the association between menthol use and each of the 13 subscales of the WISDM-68 was examined, in unadjusted analyses, menthol cigarette use was significantly associated with WISDM-68 Cue Exposure/Associative Processes ($\beta$= -.52, SE = .21; $p$ = .01) and Tolerance ($\beta$= .38, SE = .20; $p$ = .05). Specifically, menthol cigarette use was associated with less dependence in response to cue exposures/associative processes, but more tolerance-related dependence relative to non-menthol use. However, these significant associations were not maintained in adjusted analyses.

In the third study that utilized the WISDM-68, Reitzel (2010 a November submission) conducted a longitudinal cohort study designed to examine the social determinants of smoking cessation in 424 racially/ethnically diverse adult smokers. Menthol cigarette use was again not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, sex, race/ethnicity, partner status, income, employment status, and educational achievement. None of the 13 subscales of showed any significant relationships in unadjusted or adjusted analyses.

Withdrawal symptoms

Another measure of physical dependence is the extent to which menthol vs. non-menthol cigarette smoking leads to more severe withdrawal symptoms. Only one study examined this topic. Okuyemi et al. (2007), in a treatment study of African American smokers, found no differences in reported withdrawal symptoms between menthol and non-menthol cigarette smokers.

*Summary*: The evidence is conflicting regarding the effects of menthol on subjective measures of dependence in adult smokers. This conflicting evidence is observed whether they studies are population-based surveys, longitudinal cohort studies or treatment studies.

***Adolescents***

TPSAC identified six peer-reviewed articles and three unpublished secondary analyses that examined indications of nicotine dependence in adolescent menthol and non-menthol smokers. Five peer-reviewed studies and the three unpublished secondary analyses showed higher indicators of dependence.

Hersey et al. (2006), who examined data from 2000 and 2002 NYTS, conducted one of the most solid adolescent studies. This study controlled for demographic background (i.e., age, gender and race/ethnicity) and smoking behavior (i.e., length, frequency, and level of smoking) and used the validated Nicotine Dependence Scale for Adolescents (NDSA). Smokers were classified as menthol or non-menthol cigarette smokers based on their usual brand. The study found that adolescent menthol cigarette smokers were 45 percent more likely to score above the median on the NDSA than adolescent non-menthol cigarette smokers (p=0.006).

In another recent study, Hersey, Nonnemaker and Homsi (2010) examined the 2006 NYTS, using a logistic regression model that controlled for background (i.e., school level, gender, race/ethnicity) and smoking behavior (i.e., length, frequency, and level of smoking). Smokers whose usual brand was menthol had a significantly greater likelihood of endorsing needing a cigarette within 1 hour than among non-menthol smokers (OR=1.86, p=0.003). This relationship was also observed among established smokers (smoking > 100 cigarettes in a lifetime; OR=2.06, p=0.001). Among established smokers, smoking a menthol brand was significantly associated with feeling restless and irritable without smoking (OR=1.39, p=0.049) and with experiencing craving after going without smoking for a few hours (OR=1.35, p=0.035).

Wackowski and Delnevo (2007) also analyzed 1345 “established” adolescent smokers (smoked in the past 30 days and smoked at least 100 cigarettes in a lifetime) from the 2004 NYTS. Those who usually smoked menthol cigarettes had higher odds of endorsing two of four dependence related statements, even after controlling for demographic characteristics and smoking pattern. Compared to non-menthol cigarette smokers, menthol cigarette smokers were 2.6 times more likely to go less than an hour before needing a cigarette and 1.6 times more likely to experience cravings after not smoking for a while (p<.05). No significant differences were found for items inquiring the extent to which they feel restless

or irritable after not smoking for a while and their perception about their ability to quit smoking now if they wanted to.

Muilenburg and Legge (2008) surveyed middle and high school students in six public institutions in a large metropolitan area in southeastern U.S. Respondents included 2068 adolescents who had used or at least experimented with smoking. Compared to non-menthol cigarette users, menthol cigarette users smoked significantly more cigarettes based on various indicators of amount (total cigarettes smoked ever, days smoked in month, cigarettes smoked in month and ever smoked daily, OR: 3.41 to 5.35, $p \leq 0.01$), irrespective of race. Menthol cigarette smokers were statistically significantly more likely to report a shorter length of time since their last cigarette (OR=3.22, $p \leq 0.01$). It was important to note that only 18.6 percent of respondents reported smoking menthol cigarettes, though the population was predominantly African American. African American adolescent smokers have a much higher prevalence of menthol cigarette smoking (see chapter 4).

Collins and Moolchan (2006) assessed adolescent smokers (531 menthol and 41 non-menthol smokers) who were being recruited for a smoking cessation study. A higher percentage of menthol cigarette smokers endorsed smoking within the first 5 minutes of awakening compared to non-menthol smokers (45 percent vs. 29 percent). No differences were observed for FTND scores or smoking rate. This study did not describe the racial/ethnic composition of the menthol and non-menthol groups, which could be a potential confounding factor.

A non-peer-reviewed study, Nonnemaker et al. (2010) analyzed a three-year longitudinal cohort, school-based study of 12–18 year olds using the American Legacy Longitudinal Tobacco Use Reduction Study. As noted above (see *Trajectory from initiation to regular smoking or dependence*), this study demonstrated that initiation to menthol cigarettes was positively associated with smoking daily (OR: 1.99, 95% CI: 1.42-2.80), established smoking (OR: 1.94, 95% CI 1.41-266) and lifetime cigarette smoking (OR: 1.94, 95% CI: 1.40-2.68). Menthol use at initiation was also positively and statistically significantly associated with nicotine dependence (Beta: 1.04, 95% CI: 0.26-1.82).

Hersey, Nonnemaker, Homsi and Allen (November 2010) examined a 2002 survey of 5,511 youth in 48 U.S. schools sponsored by Legacy for Health. Analyses were conducted with 587 youth who had smoked cigarettes over the past three days and had a cotinine level of 5 ng/ml or higher. The study provided descriptive analysis and used multiple regression to model cotinine levels, or score on the Nicotine Dependence Scale for Adolescents controlling for age, sex; race/ethnicity, and the length, frequency, and level of smoking. Some of the more interesting results were the following: (1) Over all youth, in models that included cigarettes per day smoked, smoking menthol cigarettes did not have greater association with cotinine levels than smoking non-menthol cigarettes. (2) Among youth who smoked for less than one year, there was a statistically significant interaction between menthol use and the mean number of cigarettes smoked per day—menthol cigarette use was associated with increased cotinine levels among youth who smoked more heavily ($p=0.048$ to $p <0.001$). (3) Among youth who smoked for less than one year, smoking menthol cigarettes rather than non-menthol cigarettes was associated with statistically significantly higher levels of nicotine dependence ($p=0.049$). (4) Findings were similar for whites and non-whites, although samples sizes were quite small in some ethnic/racial groups.

Curtin et al. (June 2010c) conducted cross-sectional secondary analyses of NYTS. With regard to smoking intensity, current menthol cigarette smokers compared to non-menthol cigarette smokers were significantly ($p < 0.001$) more likely to be overrepresented in the higher use categories (>20 cigarettes, 13.1 percent vs. 5.1 percent) and less represented in the lower use categories ($\leq$ 10 cigarettes per day, 73.3 percent vs. 82.9 percent). This observation was statistically significant in both genders and among

whites and other racial/ethnic groups, but not African Americans. When controlling for age, gender and race/ethnicity, current menthol cigarette smokers were more likely to smoke 11–20 cigarettes (OR: 1.43, 95 percent CI: 0.97-2.10) and >20 cigarettes (OR: 2.25. 95 percent CI: 1.32-3.85) compared to non-menthol smokers.

DiFranza et al. (2004) found no differences in dependence measures between menthol and non-menthol smokers in a study that followed 267 seventh graders in the Boston area for 30 months. Students were asked at the end of the study if the first cigarette they had smoked was menthol or non-menthol. There were no differences in responses to the Hooked on Nicotine Checklist between menthol and non-menthol smokers. It is important to note that about 50 percent of this population did not know if the first cigarette they smoked was menthol or non-menthol. It was not known what cigarette type subjects continued to smoke.

(See Table 5 for summary of results on adolescence and dependence.)

*Summary*: There is strong evidence to support that adolescent menthol cigarette smokers are more dependent on nicotine than adolescent non-menthol cigarette smokers. Seven of the nine studies reviewed by TPSAC involved multivariate analysis that controlled for demographic characteristics and smoking history. Differences were found on a dependence measure (Hersey, et al., 2006) and on items related to smoking urgency (e.g., needing a cigarette within 1 hour, shorter time to needing a cigarette, inability to go for less than one hour before feeling like they need a cigarette, shorter length of time since last cigarette), and craving or feeling irritable/restless for a cigarette after not smoking for a while (among established smokers) (Hersey, Nonnemaker, & Homsi, 2010; Muilenburg & Legge, 2008; Wackowski & Delnevo, 2007). Furthermore, studies showed greater cigarette use among menthol smokers (Curtin, et al., 2010c June 2010 Muilenburg & Legge, 2008; Nonnemaker, et al., 2010). Hersey et al. (November 2010) observed greater cigarette use among specific populations of menthol smokers, but less cigarette use among menthol smokers overall. A study that did not conduct a multivariate analysis found more menthol cigarette users smoked within five minutes of waking than non-menthol cigarette users—a measure of smoking urgency (Collins & Moolchan, 2006). Only one small study did not find significant differences on a dependence measure, but this study was limited by problems of recall and small sample size (DiFranza, et al., 2004).

**CESSATION**

This section examines whether menthol cigarette smokers are more or less likely to successfully quit than non-menthol cigarette smokers. Three types of research were reviewed: cross-sectional population surveys, longitudinal cohort studies (e.g., community tobacco intervention, health effects) and clinical trials of cessation treatments. TPSAC also assessed the effectiveness of approved pharmacologic treatments in menthol cigarette smokers compared to non-menthol cigarette smokers. This section first presents the evidence on cessation in adults, followed by the evidence on cessation in adolescents.

**Cessation in adults**

Twenty-five studies were identified and based predominantly on the results that adjusted for confounding factors, 13 showed no effect on cessation rates by menthol status, two studies showed a better outcome among menthol smokers, and 12 studies showed a detrimental effect. These studies are summarized below.

***Studies showing no significant differences in cessation between menthol vs. non-menthol smokers***

Population surveys

Alexander et al. (2010) used the 2006 TUS-CPS (n=30,146 current everyday or some day smokers 18 years or older) to determine differences in quitting behaviors between menthol and non-menthol cigarette smokers among groups with different occupational status. The results showed a trend toward a greater number of menthol cigarette smokers ever quitting smoking for one day or longer (70.9 percent vs. 69.5 percent, p=0.09), a statistically significantly higher number of menthol smokers quitting smoking for one day or longer *in the past 12 months* (55.0 percent vs. 50.3 percent, p<0.001). No differences between menthol and non-menthol cigarette smokers were seen in number of quit attempts in the past 12 months (mean=4.0, SE=0.2 vs. mean=3.8, SE=0.1) or longest length of time (months) they stopped smoking (mean=2.0, SE=0.2 vs. mean=2.2, SE=0.2). For blue-collar workers, menthol smokers were more likely to ever stop smoking for one day or longer compared to non-menthol smokers (71 percent vs. 65 percent, p=0.0008) and to stop smoking for one day or longer *in the past 12 months* (56 percent vs. 49 percent, p=0.002). Among service workers, menthol smokers were less likely to ever stop smoking for one day or longer compared to non-menthol cigarette smokers (65 percent vs. 71 percent, p=0.007). Using logistic regression to control for occupational status and workplace policies, no significant difference was seen in the likelihood of menthol vs. non-menthol cigarette smokers ever to quit smoking for one day or longer (OR: 0.98, 95% CI: 0.83-1.15).

Fagan et al. (2010) conducted a secondary analysis with the pooled 2003 and 2006/07 TUS-CPS. Data was analyzed among current daily smokers (n=46,273, 18 years or older). Statistically significant differences were observed for number of quit attempts made for one day or longer among those who made quit attempts in the past 12 months, with the higher number observed for the menthol cigarette smokers (mean=2.23, SE=0.04 vs. mean=2.14, SE=0.02, p <0.05). There were no differences in the length of abstinence in the past 12 months between menthol and non-menthol cigarette smokers who tried to quit (mean=0.32, SE= 0.01 for both groups). Bivariate and multivariate models did not show any significant association between usual cigarette brand (either menthol vs. non-menthol) and quit attempts in past 12 months (OR: 0.92, 95% CI: 0.83-1.02 to OR: 1.10, 95% CI: 0.91-1.34) or duration of quit attempts > 2 weeks in the past 12 months across various number of cigarettes categories (OR: 0.93, 95% CI: 0.79-1.12 to OR: 1.05, 95% CI: 0.82-1.36).

Longitudinal cohort studies

Murray et al. (2007) examined smokers (n=5,887 smokers aged 35-60 years) with evidence of mild to moderate airflow obstruction who enrolled in the Lung Health Study from 1986 to 1989. Menthol status was determined by inquiring whether the type of cigarettes they smoked was plain or menthol. Participants were randomly assigned to one of three intervention groups to determine their effects in preventing COPD: (a) smoking cessation and ipratropium, an inhaled bronchodilator, (b) smoking intervention and placebo inhaler and (c) usual care. For the smoking cessation analysis, data for the five years after enrollment was examined. At annual follow-up visits, an inquiry was made on whether participants had smoked cigarettes in the past 12 months. Menthol vs. non-menthol differences were examined for three classifications: (a) sustained quitters (participants who were biochemically confirmed as quitters at the five annual visits and could recall no month with mean smoking greater than one cigarette/day at any annual visit; (b) intermittent smokers (participants who were biochemically confirmed as quitters at some annual visits and as smoking at other annual visits, (c) continuing smokers (participants who were identified as smoking at all annual visits). No significant differences between menthol vs. plain cigarette smokers were observed in the percentage of participants who were sustained quitters (male: 16.6 percent vs. 17.2 percent; females: 13.8 percent vs. 15.4 percent) intermittent (male: 26.0 percent vs. 26.9 percent; females: 30.4 percent vs. 28.7 percent)

or continuous smokers (male: 57.3 percent vs. 55.9 percent; female: 55.9 percent vs. 55.9 percent) by use of menthol cigarettes.

Hyland et al. (2002) examined smokers (n=13,268 smokers 25-64 years old) enrolled in the Community Intervention Trial for Smoking Cessation (COMMIT), which involved selecting a random sample of smokers from a representative sample. COMMIT was a randomized community-based intervention trial for smoking cessation in 11 matched pairs of communities. These smokers completed a telephone tobacco use survey in 1988 and were re-interviewed in 1993. Use of menthol cigarettes (determined by report of whether the type of cigarettes of the brand that the participant smoked was menthol or plain) was analyzed at baseline and in 1993 when six-month cessation was assessed. Successful cessation was measured by a no response to the questions, *Do you smoke now?* and *Have you smoked any cigarettes in the past 6 months?* Multivariate regression was used to assess association with menthol use with outcomes controlling for other factors related to dependence (e.g., age, sex, education, cigarettes per day, time to first cigarette, history of past serious quit attempts). No association was observed between menthol and cessation both overall (RR: 1.00, 95% CI: 0.90-1.11) and in race-specific analysis (whites RR: 0.94, 95 percent CI: 0.83-1.05; African Americans RR: 1.04, 95 percent CI: 0.73-1.47; Hispanic RR: 1.22, 95 percent CI: 0.80-1.87). However, the data showed greater number of more than two quit attempts among menthol smokers (OR: 1.16, 95% CI: 1.03-1.30).

In a non-peer-reviewed study, Hyland et al. (2010 b submission to FDA) conducted another analysis of the COMMIT data set. A total of 2,095 cohort members was included in the analysis. The association between cessation as determined in 2005 and use of menthol cigarettes in 1988 through 2001 was examined using logistic regression models which controlled for gender, age, race, education, frequency of alcohol consumption, age started smoking, amount smoked, time to first cigarette, number of past quit attempts, other smokers in the household, and desire to quit smoking. There were three key cessation indicators.

> (a) Quit Attempts in 2005: *Since 2001, how many times have you made a serious attempt to quit smoking?* A response of 1 or greater was considered a quit attempt.
>
> (b) Cessation in 2005*: Have you smoked any cigarettes in the last six months?* A current smoker was defined as a person who smoked in the six months before the survey; a quitter was defined as a person who was a current smoker in 2001 and a former smoker in 2005.
>
> (c) Cessation in 2005 among those who attempted.

Menthol smokers were equally as likely as non-menthol smokers to try to quit smoking in the overall population (OR: 0.91, 95% CI: 0.72-1.15, 57.5 percent vs. 60.3 percent), among African Americans (OR: 1.24, 95% CI: 0.27-5.67, 55.3 percent vs. 62.5 percent) and among whites (OR: 0.91, 95% CI: 0.71-1.17, 58.8 percent vs. 61.0 percent). Menthol smokers were equally likely to be successful in quitting in the overall population (OR: 0.84, 95% CI: 0.61-1.15, success rates 14.7 percent vs. 18.5 percent) and in whites (OR: 0.79, 95 percent CI: 0.56-1.11, 14.7 percent vs. 19.1 percent). The odds ratio for successful quitting could not be calculated for African Americans because of the small sample size. For African Americans, success rates we were 17.0 percent for menthol and 9.4 percent for non-menthol. Menthol smokers were also equally likely as non-menthol smokers to be successful in quitting among those who had made a quit attempt as observed in the overall population (OR: 1.03, 95% CI 0.71-1.48, success rates 22.1 percent vs. 24.5 percent) and among whites (OR: 0.96, 95% CI: 0.65-1.41, success rates 22.0 percent vs. 25.2 percent). Among African Americans, the success rate was 26.9 percent for menthol vs.

10.0 percent for non-menthol smokers. Unfortunately, in this study, the number of blacks was quite low (n=91 total, and lower when examining the effects of menthol).

Muscat et al. (2002) examined adult smokers (19,545 current and ex- smokers, 16,540 non-menthol smokers and 3,005 menthol smokers) enrolled in a case-control study on smoking tobacco-related cancers between 1981 and 1999. Ever smokers were defined as having smoked at least one cigarette each day for one year. Current smokers smoked at least one cigarette each day for the preceding year. Ex-smokers were smokers who did not smoke at least one cigarette each day for the preceding year. Menthol status was based on whether the subject reported the last brand smoked as menthol. The results from this cross-sectional dataset showed that a higher percentage of former smokers among African American non-menthol smokers vs. menthol smokers (35.7 percent vs. 29.4 percent, $p < 0.01$) and white non-menthol smokers vs. menthol smokers (52.9 percent vs. 43.7 percent, < 0.01). Unconditioned logistic regression analysis was used to estimate the prevalence odds ratio (POR) of current vs. ex-smoker by menthol status. The models adjusted for sex, education, case-control status, years of smoking and cigarettes per day. Menthol was not associated with continued smoking. The POR was not significant among African American (POR: 1.1; 95% CI: 0.8-1.4) or white (POR: 1.1, 95% CI: 1.0-1.3) smokers. The main weakness of this study was the use of a convenience sample rather than a random population based sample. In addition, the sample was mostly older adults. Furthermore, the criterion for ex-smokers was quite unusual (not smoking each day for the past year).

In an in-press article, Blot et al.(Blot et al., in press) analyzed data from the Southern Community Cohort Study (SCCS), a prospective study of 85,806 racially diverse adults to examine racial disparities in cancer and other chronic diseases. Adults ages 40–70 years residing in 12 southern states were predominantly recruited through mailings to stratified random samples of the general population and at a community health center. Subjects were followed from March 2002 to September 2009. Subjects were classified as smokers (defined as those who smoked 100 cigarettes in their lifetime) or former smokers. Menthol status was determined by whether or not they usually smoked menthol cigarettes. During follow-up, subjects were classified as quitting or continuing to smoke. Results from data collected at the time of enrollment showed that African American, menthol and non-menthol cigarette smokers had equal odds of quitting after adjustments for age, income, education, recruitment source, pack years smoked, BMI) (OR=1.03; 95% CI: 0.96 to 1.11). White menthol cigarette smokers were statistically significantly more likely to quit than non-menthol cigarette smokers (OR=1.55, 95% CI: 1.41 to 1.70). Among smokers who were followed for an average of 4.3 years (7,886 and 4,487 current smokers of menthol and non-menthol during baseline, respectively), the odds (adjusted for the same variables above plus race) of quitting were similar among menthol and non-menthol smokers (OR=1.02, 95% CI: 0.89 to 1.16). This is a large study, but one of the weaknesses is that older age of this population, which may limit the generalizability of results.

Treatment studies

Cropsey et al. (2009) examined differences in treatment outcome among white and African American female prisoners (N=233; white=109, 38.1 percent menthol while in prison; African American=124, 81.3 percent menthol while in prison) who underwent a 10-week nicotine replacement and group psychotherapy intervention. Some were randomized to a wait list for six months before entering the cessation component. Smoking cessation was assessed across the 12-month follow-up period (weeks 1-10 and 1 week and 3, 6 and 12 months post-treatment). Seven-day point prevalence abstinence (not smoking in the past seven days) was determined at each assessment period. Although whites had statistically significantly higher overall smoking cessation rates across time compared to African American women, menthol cigarettes were not associated with these differences in quit rates.

Interaction between race and smoking menthol was not significant. This study was limited by the relatively young age of participants (mean age was early to mid-thirties) and the select population of smokers.

Fu et al. (2008) examined the effects of menthol cigarette smoking on cessation among a multi-ethnic sample of smokers (N=1,343, white=76%, African American=14%, other=10%, 342 menthol users, 19 years and older) enrolled in a multi-site, randomized controlled trial of an intervention designed to facilitate repeat tobacco cessation treatment. Subjects who had received a prescription for NRT or bupropion for smoking cessation from one of five Veterans Administration Medical Centers were assigned to usual care or intervention. The intervention consisted of phone calls to patients with the aid of a computerized provider prompt to assess smoking status, interest in making another quit attempt and in preferences for tobacco treatment. The primary outcome was seven-day point prevalence abstinence at six months post-randomization. Menthol status was assessed with a follow-up survey by inquiring if subjects smoked menthol cigarettes two years ago (one year prior to the index quit attempt). Analysis on the effect of menthol was adjusted for covariates including predictors of abstinence as well as ethnicity, gender, site and time to first cigarettes. No significant effects of menthol on smoking cessation rates were observed, using multivariate analysis (OR: 1.31, 95% CI: 0.95-1.82) and unadjusted logistic regression analysis (OR: 1.14, 95% CI:0.85-1.53). Although a significant interaction between the intervention and menthol cigarettes was observed (p=0.02), with greater success among menthol smokers in the treatment condition (OR: 1.80, 95% CI: 1.18-2.76), this interaction was no longer statistically significant after Bonferroni correction for multiple comparisons. Therefore, this study found menthol did not decrease smoking cessation among older smokers during a quit attempt aided by pharmacotherapy. No differences were found in number of 24-hour quit attempts in the past month. The primary weaknesses of this study was the two-year recall for the assessment of menthol cigarettes with no brand switching information during this period, and the older age of the smoking population (mean age=56 years old).

Harris et al. (2004) examined predictors for successful quitting among 600 African Americans participating in a smoking cessation trial. This cessation study involved a double-blind, placebo-control randomized trial examining bupropion vs. placebo prescribed for seven weeks. Outcome variable was seven-day biochemically confirmed abstinence among 535 participants who completed the seven-week medication phase. Although the univariate analysis showed that not smoking menthol cigarettes was a predictor of cessation success (p=0.0062; 41.53 percent vs. 28.3 percent), menthol cigarette use was not a predictor in the logistic regression analysis. It should be noted that this is the same population of smokers used in the Okuyemi et al. (2003) study described below.

In a non-peer-reviewed secondary analysis of data, Reitzel (2010 a, 2010 b; 2010 c November) examined the menthol cigarette effects in three treatment studies, two of which found no differences in treatment outcome. One study (Reitzel, 2010 a), Project CARE, was a longitudinal cohort study designed to examine the social determinants of smoking cessation and included 424 adult (21 years or older) treatment-seeking smokers (34 percent non-Latino African Americans, 33 percent Latino, and 33 percent non-Latino white) recruited from the Houston, TX area and enrolled from 2005–2007. Menthol status was determined by asking participants if their regular brand of cigarettes was menthol or non-menthol. All subjects received six weeks of nicotine patch treatment, six brief smoking cessation counseling sessions and self-help materials. Treatment success was defined as biochemically verified continuous abstinence from smoking since the quit date through week 26 post-quit. Both unadjusted and adjusted analyses were conducted. Menthol cigarette users had lower rates of continuous abstinence than non-menthol cigarette users at all follow-up points. However, menthol cigarette use did not statistically significantly predict continuous abstinence from smoking in analyses adjusted for time (*p*

=0 .73; *n* =680), or in analyses adjusted for age, sex, race/ethnicity, partner status, income, employment status, educational achievement, time, cigarettes smoked per day, and time to the first cigarette of the day ($p$ = 0.84; $n$ = 607). Continuous abstinence rates within each racial/ethnic group did not differ by menthol cigarette use status in unadjusted or adjusted analysis.

In the other non-peer-reviewed paper, Reitzel (2010 b November) conducted a secondary analysis of Project BREAK FREE, a randomized clinical trial that examined the efficacy of smoking cessation treatment delivered on palmtop computers. This trial recruited 399 treatment seeking, African American smokers from 2005–2007 from the Houston, TX area. Menthol status was determined by asking participants if their regular brand of cigarettes was menthol or non-menthol. Outcome variable and analysis was similar to the previously described study (Reitzel, 2010 a November). Menthol users had higher rates of continuous abstinence than non-menthol users at all follow-up points. However, menthol cigarette use did not significantly predict continuous abstinence from smoking in analyses adjusted for time and treatment group ($p$ = .40; $n$ = 573), or in analyses adjusted for age, sex, partner status, income, employment status, educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day ($p$ = .30; $n$ = 457).

***Studies showing a better rate of cessation among menthol smokers***

Population surveys

Cubbin et al. (2010) conducted a secondary data analysis using 2005 NHIS and Cancer Control Supplement of current smokers (those who smoked at least 100 cigarettes and currently smoke some days or everyday) and former smokers (those who smoked at least 100 cigarettes but did not smoke right now) (n=31,428, ages 25-65). Menthol status was determined by asking whether the usual cigarette brand was menthol (in the 12 months before quitting for former smokers). All analyses were weighted for income and education. No statistically significant differences were observed for quit attempts in the past year by cigarette type among current everyday smokers by gender and racial/ethnicity. There was, however, a trend for menthol smokers for both genders and all racial/ethnic groups to have higher levels of quit attempts than similar subgroups of non-menthol smokers (e.g., as great as 10–20 percent difference). When examining quit duration among former smokers, statistical significance was observed only in white female menthol smokers. They had abstained about 2.5 years longer than white female non-menthol smokers (15.0 vs.12.5 years, $p<0.01$).

In a non-peer-reviewed study, Hyland and Kasza et al. (November 2010 submission) conducted a secondary analysis of a nationally representative sample of adult smokers (N=7532) who were interviewed as part of the International Tobacco Control Four Country Survey (ITC-4) between 2002 and 2008. ITC-4 is an ongoing prospective cohort survey conducted with nationally representative respondents from four countries, including the United States. Current smokers were defined as persons who reported having smoked at least 100 cigarettes in their lifetime and who currently smoked on at least a monthly basis. Menthol cigarette use status was determined by the brand of cigarettes smoked. Cessation behaviors were defined as:

> (a) Making a quit attempt. Respondents were asked: *Have you made any attempts to stop smoking since we last talked with you?*
>
> b) Successful smoking cessation, defined as no longer smoking on at least a monthly basis; and
>
> c) Successful cessation among those making a quit attempt.

Adjusted association between menthol cigarette use and cessation behaviors were estimated for respondents overall, as well as for separate racial/ethnic groups and genders. The menthol x race/ethnicity and menthol x gender interaction terms were specifically tested in the overall models. Multivariate analyses included an adjustment for respondent gender and race/ethnicity (unless stratified on these variables), age, education, income, ever made a quit attempt before baseline, and intention to quit. Additionally, outcomes were also adjusted for the heaviness of smoking index. Results showed white respondents (particularly women) who smoked menthols were less likely than those who smoked non-menthols to report making quit attempts (OR: 0.84, 33.5 percent vs. 38.4 percent in both sexes and OR: 0.81, 34.3 percent vs. 40.1 percent in females, $p<0.05$), while African American women who smoked menthols were more likely to report successful cessation (OR:3.58, 12.8 percent vs. 8.5 percent, $p<0.05$) and successful cessation among those who attempt to quit (OR:3.96, 24.6 percent vs. 15.8 percent, $p <0.05$) than non-menthol cigarette smokers.

***Poorer cessation among menthol vs. non menthol cigarette smokers***

Population surveys

Gundersen, Delnevo and Wackowski (2009) analyzed data from the 2005 U.S. National Health Interview Survey (NHIS) to determine the relationship between race/ethnicity, menthol smoking and cessation in a nationally representative sample. The sample included 7,815 white, African American and Hispanic current and former cigarette smokers who did not use other tobacco products and who had made a quit attempt. Menthol status was determined by whether or not the usual brand of cigarettes in the past 12 months or the 12 months prior to quitting were menthols. Outcome variables were current smokers (having smoked 100 cigarettes in a lifetime and now smoking everyday or some days) vs. former smokers (having smoked 100 cigarettes in a lifetime but not currently smoking). Multiple logistic regression analysis was used to test the relationship of menthol smoking with cessation, controlling for various demographic, smoking behavior and risk perception factors (e.g., sex, age, cigarettes per day, education, perceived likelihood of getting cancer). Overall, menthol smokers were less likely than non-menthol smokers to be former smokers (56.9 percent vs. 61.5 percent, $p < 0.01$). This relationship was statistically significant among African Americans (43.7 percent vs. 62.1 percent, $p < 0.01$) and Hispanics (48.5 percent vs. 61.2 percent, $p < 0.01$), but not among whites (62.8 percent vs. 61.6 percent, $p=0.44$). In the multiple logistic regression analysis, when African Americans and Hispanics were collapsed into non-whites, non-white menthol smokers were statistically significantly less likely to have quit smoking compared to non- menthol smokers (AOR: 0.55, 95% CI: 0.43-0.71, $p<0.01$). This result was largely driven by the Hispanic group (AOR; 0.61, 95% CI: 0.39-0.97, $p=0.04$) and not by African Americans (AOR; 0.78, 95% CI: 9.56-1.00, $p=0.15$). Among white smokers, menthol cigarette smokers were more likely to be former smokers than non-menthol smokers (AOR; 1.17, 95% CI: 1.00-1.36, $p<0.05$).

Similarly, Stahre et al. (2010) conducted a secondary analysis of cross-sectional data from the 2005 National Health Interview Survey Cancer Control Supplement examining current smokers (n=6511, 1,700 menthol; 4,355 non-menthol) and former smokers (n=6774, 1,515 menthol smokers; 4,434 non-menthol smokers). Univariate analysis of the data was conducted to determine variables that differed significantly by menthol status. Menthol status was determined by whether or not the respondent's usual brand of cigarettes was menthol. Multiple logistic regression analysis modeled the relationship between menthol smoking status, demographic characteristics and smoking-related characteristics on the population quit ratio and utilization of quit aids. In the univariate analysis, the quit ratio was significantly higher among non-menthol vs. menthol smokers (50 percent vs. 47 percent, $p=0.014$). When examining quit ratios within races, no significant differences in quit ratios for menthol vs. non-menthol smokers were observed for whites (52 percent vs. 50 percent), Asian Americans (38 percent vs.

42 percent), American Indian/Alaska Native (52 percent vs. 35 percent) or Hispanics (40 percent vs. 45 percent). However, quit ratios were significantly lower for African American menthol vs. non-menthol smokers (34 percent vs. 49 percent, $p < 0.001$). In multiple logistic regression analysis, there was a significant interaction between race and menthol smoking status. African American menthol smokers were significantly less likely to quit smoking than white non-menthol smokers (OR: 0.72, 95% CI: 0.53-0.97). No analysis was done with menthol status alone. No differences were found in utilization of quit aids.

Trinidad et al. (2010) conducted a secondary data analysis of the 2003 and 2006-07 TUS-CPS that examined current smokers and their interest in seriously quitting in the next six months and former smokers (ever smokers) who had successfully quit for at least 6 months at the time of the survey. In a multiple logistic regression analysis, African American menthol smokers were significantly less likely than white non-menthol smokers to have quit smoking (AOR: 0.72, 95 percent CI: 0.53-0.97, p=0.031). Among African Americans (OR: 1.62, 95% CI: 1.35-1.95) and Hispanics/Latinos (OR: 1.21, 95% CI: 1.00-1.47), those who currently smoked menthol cigarettes were more likely to be seriously considering quitting in the next six months than non-menthol smokers, after adjusting for socio-demographic variables. Among former smokers, those who smoked menthol compared to non-menthol cigarettes were less likely to have successfully quit for at least six months within various racial/ethnic groups: African Americans (AOR: 0.23, 95% CI: 0.17-0.13); Asian Americans/PI (AOR:0.22, 95% CI: 0.11-0.45); Hispanics/Latinos (AOR:0.48, 95% CI: 0.34-0.69) and non-Hispanic Whites (AOR:0.28, 95% CI: 0.25-0.33).

In a non-peer-reviewed submission, Delnevo et al. (November 2010) conducted a secondary analysis of the 2003 and 2006/7 TUS-CPS. In this analysis, they attempted to address the limitations of Gundersen et al. (2009), that is, the inadequate control of socioeconomic variables, and the potential lack of statistical power among the African American population. The sample consisted of white, African American and Hispanic current smokers and former smokers who quit in the past five years. In addition this study examined two subpopulations of Hispanics: Mexican vs. Puerto Rican in origin. Current smoker was defined as meeting two conditions: having smoked 100 cigarettes in a lifetime and now smoking “everyday” or “some days.” Former smoker was defined as meeting two conditions: having smoked 100 cigarettes in a lifetime and now smoking not at all. With regard to assessing menthol status, current smokers self-reported whether or not their usual brand of cigarettes in the past 12 months was menthol. Former smokers, who quit in the past five years, reported whether or not their usual brand 12 months prior to quitting was menthol. Because the relationship between menthol and cessation may be impacted by sample restriction decisions, the authors examined five samplerestrictions:

1. Current and former smokers who quit within the past 5 years, regardless of past quit attempts or current other tobacco product (OTP) use;

2. Current and former smokers who quit within the past 5 years who did not report current OTP use;

3. Current and former smokers who quit within the past 5 years who reported ever having made a quit attempt;

4. Current and former smokers who quit within the past 5 years who did not report current OTP use and have ever made a quit attempt (replicates Gundersen, et al., 2009); and

5. Past 12-month cigarette smokers who made a quit attempt or had quit.

Multiple logistic regression was used to estimate the odds ratio of being a former smoker for menthol smokers relative to non-menthol smokers while controlling for other independent variables (education, household income, gender, age, seasonality and for restriction 5, exposure in the past 12 months to cigarette excise tax increase. Using sample restriction 1, menthol smokers were less likely to be former smokers than were non-menthol smokers (AOR=0.914, 95% CI: 0.868-0.961) overall. This relationship held among whites (AOR: 0.928, 95% CI: 0.877-0.982) and African Americans (AOR: 0.810, 95% CI: 0.670-0.979). The magnitude of the relationship among Hispanics was similar to whites, but was not statistically significant (AOR=0.936, 95% CI:0.793-1.105). Statistically significant findings were observed across various sample restrictions, with overall AOR ranging from 0.902 for sample restriction 3 to 0.932 for sample restriction 2. Only in sample restriction 5 was the finding not statistically significant. Similarly, the relationship between menthol smoking and cessation was statistically significant across sample restrictions among whites except in sample restriction 5. Among African Americans, the relationship was statistically significant across all restrictions, with an AOR ranging from 0.684 in sample restriction 4 to 0.810 in sample restriction 1. Among Hispanics, the relationship was statistically significant in sample restriction 5 only. However, when examining Hispanics by origin, menthol smokers of Mexican origin are substantially more likely to have quit smoking, though this was statistically significant only in sample restrictions 2 (AOR=1.338, 95% CI: 1.039-1.722) and 4 (1.349, 95% CI: 1.016-1.790). In contrast, menthol smokers of Puerto Rican origin were substantially *less* likely to have quit relative to non-menthol smokers across all categories, with adjusted odds ratios ranging from 0.421 in sample restriction 5 to 0.63 in sample restriction 2. Because of the number analyses, the data is provided in the Appendix. This study offers evidence that smoking menthol cigarettes leads to less cessation among smokers, in particular among African Americans and Puerto Rican Hispanics.

(b) (4)



Longitudinal cohort studies

Pletcher et al. (2006) used the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a longitudinal study of risk factors for coronary artery disease, to determine the effects of menthol cigarettes on smoking cessation and health outcome measures. Using this dataset, 1,535 smokers (952 menthol and 563 non-menthol) ages 18–30 and healthy were identified in 1985. Participants underwent baseline examination and then follow-up at years 2, 5, 7, 10 and 15 with 74 percent retention at year 15. At each examination, participants were questioned on four items: recent quit attempts, success in recent quit attempts, no current smoking since the past two times they were examined, and any relapses. After adjusting for ethnicity, sex, age, demographic and social factors, a trend toward menthol smokers experiencing lower cessation (OR: 0.71, 95% CI 0.49-1.02, p=0.06) and a lower likelihood of recent quit attempts (p=0.11) compared to non-menthol smokers was found. The results were not statistically significant. However, a statistically significant increase in the risk of relapse, that is, non-sustained quitting, was observed in menthol vs. non-menthol cigarette smokers (OR: 1.89, 95% CI, 1.17-3.05, p=0.009). Results were similar among African Americans and whites, after additional adjustment for cigarettes smoked daily at baseline. Baseline menthol cigarette smokers were more likely to still be smoking during follow-up examinations compared to baseline non-menthol cigarette smokers (69 percent vs. 54 percent, p <0.001), but stratification by ethnicity attenuated this association. The main weakness of this study was that it was difficult to tease apart the effects of ethnicity and menthol preference due to the limited number of white menthol smokers (N=189) and African American non-menthol smokers (N=95). The authors pointed out that differences in nicotine levels in cigarettes may confound results.

Treatment studies

Foulds et al. (2006) conducted a retrospective cohort analysis of 1,021 patients (670 white, 219 African American, 80 Hispanics, 52 other) who attempted to quit tobacco at a specialist tobacco dependence treatment outpatient clinic in New Jersey during 2001–2003. Treatment was comprehensive and multidisciplinary; it included assessment of the smoker, an individualized treatment plan that recommended medication and group treatment (six weekly 90-min. sessions), and establishment of a target quit date. A four-week follow-up was conducted in person (39 percent) or on the telephone (61 percent). Biochemical verification was obtained among those who attended in-person follow-up. Six-month follow-up was collected by telephone contact or by mail. Outcome measure was tobacco abstinence over the past seven days. Although univariate analysis demonstrated that menthol compared to non-menthol cigarette smoking had a significant effect on abstinence success (lower rates at four weeks, 35.4 percent vs. 42.3 percent and at 26 weeks, 24.9 percent vs. 35.8 percent), multivariate analysis (which took into account various demographic and tobacco history variables) showed trend toward significant menthol affects, p=0.053). Similarly, Gandhi et al. (2009) conducted a retrospective cohort analysis of 1,688 participants (778 smoked menthol cigarette smokers: 302 African American, 348 white, 99 Latino, 20 other; and 910 non-menthol cigarette smokers: 72 African American, 499 white, 50 Latino, 59 other) who attended the same specialist smoking cessation service in New Jersey during 2001–2005 and who set a quit date and attempted to quit smoking. This study extended the sample size of the Foulds et al. (2006) study. Outcome measure was self-reported seven-day point prevalence abstinence from tobacco products. Biochemical verification was available on some people, but accuracy of self-reported abstinence ranged from 99.4 percent to 100 percent. Average age was late 30s to early 40s. Unadjusted abstinence rates were lower with menthol vs. non-menthol cigarette smokers at the four-week follow-up overall (no values given) and among whites (43 percent vs. 50 percent, p=0.031), African Americans (30 percent vs. 54 percent, p <0.001) and Latinos (23 percent vs. 50 percent, p=0.001). At the six-month follow-up, similar observations were made overall (no values given), and among African Americans (18 percent vs. 36 percent, p=0.001) and Latinos (11 percent vs. 28

percent, p=0.009), but not whites. At four-week follow up, African Americans, Latino and white non-menthol smokers had similar quit rates (54 percent, 50 percent and 50 percent, respectively). In contrast, among menthol smokers African Americans and Latinos (30 percent and 23 percent, respectively) had lower quit rates compared to whites (43 percent p< 0.001). Logistic regression analyses resulted in a significant two-way interaction between race/ethnicity and menthol (p=0.04) at four weeks. African American and Latino menthol smokers had significantly lower unadjusted (OR: 0.34, 95% CI: 0.17-0.69 and OR: 0.30, 95% CI: 0.14-0.62, respectively) and adjusted odds (OR: 0.32, 95% CI: 0.16-0.62 and OR: 0.43 95% CI: 0.1-0.9, respectively) of quitting than their non- menthol counterparts. For whites this finding was evident only for the unadjusted analysis (OR: 0.75, 95% CI: 0.58-0.97). At six months follow-up, African American menthol smokers had half the odds of being abstinent compared to non-menthol smokers, for unadjusted (OR: 0.40, 95% CI: 0.23-0.07) and adjusted (OR: 0.48, 95% CI: 0.25 0.9) analysis which controlled for specific covariates (e.g., gender, education and employment status). Statistically significant differences were observed in Latinos only for unadjusted analysis (OR: 0.32, 95 percent CI0.13-0.77). The difference between four-week quit rates among menthol and non-menthol cigarette smokers was greater among those who were unemployed vs. employed, especially among African Americans (16 percent vs. 43 percent, p=0.03) whereas no differences were observed among the employed African Americans (42 percent vs. 56 percent, p=0.20).

Two treatment studies were conducted only among African American smokers. Okuyemi et al. (2007) examined 615 menthol and 138 non-menthol light smokers (10 cigarettes a day or less) in a 2 x 2 treatment study (nicotine replacement vs. placebo for eight weeks; motivational interviewing vs. health education for six sessions). Participants self-reported menthol or non-menthol cigarette use. Using logistic regression, no significant differences were observed for seven-day verified abstinence rates at eight weeks for non-menthol vs. menthol (26.8 percent vs. 22.6 percent). However, at 26 weeks post-randomization, seven-day verified abstinence rates were significantly lower for menthol smokers (11.2 percent vs. 18.8 percent, p=0.015). Using logistic regression, at 26 weeks non-menthol cigarette smokers who received nicotine gum had statistically significantly higher abstinence rates than menthol cigarette smokers who had received nicotine gum (p=0.013). There were no statistically significant differences in abstinence rates between menthol vs. non-menthol cigarette smokers who were assigned placebo. Similar findings were observed for those who received Health Education: menthol smokers had lower abstinent rate compared to non-menthol smokers (p=0.037).

In another study, Okuyemi et al. (2003) recruited African American smokers from an inner-city health center for a double-blind, placebo-controlled randomized trial examining bupropion vs. placebo prescribed for seven weeks. Subjects were 471 menthol and 129 non-menthol African American cigarette smokers who smoked at least 10 cigarettes per day. Menthol cigarette use was ascertained by the question, *Do you usually smoke menthol cigarettes?* Outcome variable was seven-day biochemically confirmed abstinence among 535 participants who completed the seven-week medication phase. Logistic regression was used to determine the effects of menthol cigarettes on smoking cessation. Seven-day point prevalence abstinence from smoking at six weeks was statistically significantly lower for menthol vs. non-menthol cigarette smokers (28.3 percent vs. 41.5 percent, p=0.006), but no differences were found at the six-month follow-up (21.4 percent vs. 27.0 percent). When separated by treatment, among those who received bupropion, the seven-day point-prevalence abstinence rate at six weeks was higher for non-menthol compared to menthol cigarette smokers (60.3 percent vs. 36.2 percent, p < 0.01), but no there were no differences within the placebo group (23.3 percent vs.20.5 percent). Statistically significant menthol effects were observed for those under the age of 50 at six-week follow-up, with lower cessation rates among menthol vs. non-menthol smokers (24.9 percent vs. 44.4 percent, p<0.01). No differences were observed among smokers 50 and older. In a stepwise logistic regression

analysis, among smokers < 50 years old, non-menthol cigarette smokers were twice as likely to quit smoking at the end of six weeks compared to menthol smokers (OR: 2.12, 95% CI: 1.32-3.39).

In non-peer-reviewed submission, King et al. (November 2010) conducted a secondary analysis of data collected from a double-blind, randomized placebo-controlled trial of the efficacy of the oral opioid antagonist, naltrexone, in combination with nicotine patch and individual behavioral counseling. Participants were equally randomized to one of two medication groups: patch + counseling (PC) or patch + counseling + naltrexone (PCN). Study participants included 110 African Americans and 181 whites. Among whites, 45 were menthol cigarette users, and 136 were non-menthol cigarette users, but among African Americans, 91 were menthol cigarette users and 19 were non-menthol cigarette users. Subjects were recruited from 2006 to 2009. In a univariate analysis on baseline smoking characteristics, menthol and non-menthol cigarette smokers were comparables in terms of number of prior quit attempts and longest time quit in the past. For week four quitting, the multivariate analysis (controlling for sex, socioeconomic status, and education) indicated a statistically significant three-way interaction [medication x race x menthol, OR(se) = 22.80 (34.47), *p = 0.039*]. Separate analysis indicated a statistically significant interaction between medication and menthol use only in African Americans [OR(se) = 16.19(21.90), p = 0.039]. For week 12 quitting, the multivariate analysis revealed the three-way interaction had a p-value of 0.10 [medication x race x menthol, OR(se) = 16.84 (28.92), *p = 0.10*]. A further examination indicated a statistically significant medication x menthol interaction in African Americans [OR(se) = 31.22(49.16), *p = 0.029*], but not in whites. It appears that naltrexone may mitigate the poorer treatment response among African American menthol cigarette smokers to nicotine replacement treatment. The major weakness of this study is the small sample size, particularly the African American non-menthol group.

In another non-peer-reviewed article, Reitzel (November 2010 c) conducted a secondary analysis of a randomized clinical trial to test the efficacy of motivationally based treatment for smoking relapse prevention among pregnant mothers who were in their $30^{th}$-$33^{rd}$ week of pregnancy at the time of enrollment. Participants (n=251, 32 percent African American, 30 percent Latina, 36 percent white, 2 percent other) who had quit smoking and were interesting in remaining quit postpartum were recruited into the study from 2005–2007. Menthol status was determined by asking participants if their usual brand of cigarettes was menthol or non-menthol. The outcome was continuous abstinence from smoking, defined as self-report of no smoking (not even a puff) since the delivery date and biochemical verification at eight and 26 weeks. Unadjusted continuous abstinence rates by menthol cigarette use status showed that menthol users had lower rates of continuous abstinence than non-menthol users at both follow-up points. However, menthol cigarette use did not significantly predict continuous abstinence from smoking in analyses adjusted for time and treatment group ($p$ = .46; $n$ = 338), or in analyses adjusted for age, race/ethnicity, partner status, income, and educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day ($p$ = .52; $n$ = 304). In a post-hoc racial/ethnic group subgroup analyses, menthol cigarette use predicted continuous smoking abstinence among white women in unadjusted analyses [$p$ = .01; $n$ = 120, OR = .15 (.05 - .40)] and in analyses adjusted for age, partner status, income, and educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day [$p$ = .03; $n$ = 108, OR = .19 (.04 - .89)]. White menthol users were less likely to maintain continuous abstinence through post-quit week 26 than white non-menthol users. In this analysis, the sample size of white menthol cigarette smokers was quite low (n=20).

See Table 6 for summary on population survey studies and Table 7 for summary on longitudinal cohort and treatment studies.

*Summary:* Delnevo et al. (November 2010) astutely points out that many cessation studies rely on convenience samples, secondary analysis of clinical trial data or case control studies. Some study samples are unrepresentative of the general population of smokers who quit. Other studies fail to examine subpopulations of smokers, which is critical in determining the public health effects of menthol. The characterization of cessation outcomes is inconsistent across studies. As a result, TPSAC used specific criteria to select studies that would be considered to be of sufficient quality to make an informative decision on the effects of menthol cigarettes compared to non-menthol cigarettes on cessation.

First, the most weight was placed on population survey studies. Population studies were weighed more heavily because most smokers quit on their own, rather than through cessation programs (Chapman and MacKenzie, 2010), the large sample size and the representativeness of the sample. We also believed that studies that focus on comparing cessation rates between menthol and non-menthol smokers among racial/ethnic groups are important because of potential racial/ethnic differences in response to menthol. Furthermore, the charge for TPSAC was to examine the effects of menthol on specific racial/ethnic groups. We also selected studies that focused on broad age ranges. Limitations of these population surveys include the cross-sectional nature of the study and for some studies, the uncertainty of duration of the quitting attempt.

Using these selection criteria two studies were eliminated because they did not focus on examining cessation rates among racial/ethnic groups (Alexander, et al., 2010; Fagan, et al., 2010). Five of the seven studies that met our criteria for inclusion by specifically examining the effects of menthol status on quit ratios and quit success among different racial/ethnic groups showed lower cessation success among menthol cigarette smokers. Two of these studies used the 2005 NHIS (Gundersen, et al., 2009; Stahre, et al., 2010) and the other three used the 2003/2006-7 TUS-CPS (Delnevo, et al., 2010; Trinidad, Gilpin, Lee, & Pierce, 2004)(Levy et al., in press). The type of analysis differed, but the results were consistent across the studies using similar surveys, that is, less quitting with menthol use in African American populations when analyzing data in the NHIS and less quitting with menthol use among almost all racial/ethnic groups when analyzing data in the TUS-CPS. The Delnevo et al., (2010) study was particularly strong because different subject inclusion criteria were used to examine quitting.

Four national/international surveys (two of which are listed above) found greater quitting success among subgroups of menthol smokers. Two of the studies analyzed the 2005 NHIS (Cubbin, et al., 2010; Gundersen, et al., 2009) in which white smokers were observed to have higher quit rates or duration of quitting. Another study analyzed the ITC-4 (Hyland & Kasza, 2010 a) had found African American women menthol smokers were more likely to succeed in quitting than African American non-menthol smokers. The fourth study (Delnevo, et al., 2010) found that although most other racial/ethnic menthol smokers experienced lower quitting than non-menthol smokers, Mexican American Hispanic menthol smokers as compared to Puerto Rican Hispanic menthol smokers experienced greater success than the respective non-menthol smokers.

To summarize, when focusing on population survey studies that examined difference by menthol status within racial/ethnic groups, in general, most studies support the finding that non-whites, particularly African Americans, who smoke menthol cigarettes have lower quit rates than non-whites who smoke non-menthol cigarettes, but the results for whites is mixed. A few studies showed that white menthol smokers may possibly have higher quit rates compared with non-menthol smokers.

With regards to longitudinal, cohort populations and studies, TPSAC also focused on studies that examined ethnic/racial groups, had sufficient samples sizes at least among whites and blacks (number of subjects that is at least 100 subjects), was broadly representative of a general population of smokers, and had appropriate criteria for cessation (not smoking even a puff on a cigarette). TPSAC also considered studies that focused primarily on African Americans. Of the six longitudinal cohort studies, two studies used the same COMMIT database and found consistent no menthol effect results (Hyland, et al., 2002; Hyland & Rivard, 2010 b). Although the data analyses in both these studies were well-executed, one of the studies examined smokers prior to the 1990s (Hyland, et al., 2002) and the other study had a very small sample size of black smokers who had attempted to quit, which may have reduced the power to detect any differences (Hyland & Rivard, 2010 b). Two other studies also found no effects (Murray, et al., 2007; Muscat, et al., 2002). One of these studies had an unusual definition of cessation (e.g., not smoking each day for the past year), undertook cross-sectional analysis, enrolled a convenience sample, and enrolled an older population of adults, thereby limiting generalizability (Muscat, et al., 2002). The other study did not examine potential racial ethnic differences, had few racial ethnic subjects to see a menthol effect and also enrolled subjects with mild to moderate chronic airflow obstruction (Murray, et al., 2007). The fifth study that found no affect focused on a diverse group of smokers and included a large sample size; however it primarily recruited older adults (Blot, in press). One study found a greater risk of relapse or non-sustained quitting among both African American and European American menthol smokers (Pletcher, et al., 2006). This study had a small sample size of African American non-menthol smokers. The major limitations of all these studies include the secondary analysis of studies not intended to primarily focus on menthol, but more importantly, the limited number of racial/ethnic groups that allow an examination of racial/ethnic effects. Because of their limitations, none of these studies were considered to be sufficiently informative to be considered in TPSAC's evidenence review.

With regards to clinical trials, TPSAC used the criteria that was used to evaluate longitudinal, cohort populations and studies, with the additional requirement that follow-up had to be at least six months. TPSAC also considered studies that focused primarily on African Americans. Five of the eleven clinical trials did not find a menthol effect and three were not considered to meet criteria. Some of these studies tended to have a non-representative population of treatment seekers, were not focused on effects of menthol per se or only observed significant menthol effects in the unadjusted analysis. One of these trials examined female prisoners (Cropsey, et al., 2009), which is a very selective population. Another trial recruited from the VA Medical Center, therefore enrolling smokers who were older, and based on the study by Okuyemi et al. (2003), menthol effects may be found predominantly a younger population of treatment seekers. Harris et al. (2004) analyzed the same sample of African Americans as Okuyemi et al., (2003) and this study was mostly focused on examining ethnic racial differences. It should be noted that univariate analysis of the data did show poorer abstinence among menthol smokers, which is concordant with Okuyemi and associates (2003) findings. Reitzel (November 2010b) examined a more broadly representative ethnic/racial population of smokers (Reitzel, 2010 a) or an African American smokers (Reitzel, 2010 b) that showed no menthol effect . One of these studies conducted by Reitzel (2010a) observed lower cessation rate using unadjusted analysis but not adjusted analysis. Both these studies were considered to be of sufficient quality to be considered as part of TPSAC's evidence review.

With regards to the six clinical trial studies that showed poorer treatment outcomes among menthol smokers, four did not meet criteria. Two studies studies did not meet criteria because they examined pregnant women (Rietzel et. al. 2010c) or had small sample sizes in subgroups of smokers (King et al. 2010). Another study found effects at the end of treatment, but not at sixth-month follow-up (Okuyemi

et al. 2003). Two other studies used a similar population of treatment seekers (Foulds, et al., 2006; Gandhi, et al., 2009). If we eliminate the Foulds et al. (2006) study with a smaller population of treatment seekers, then treatment outcomes is poorer in menthol compared to non-menthol smokers particularly among a non-White population (Gandhi, et al., 2009), which is concordant with the NHIS data results (Gundersen, et al., 2009; Stahre, et al., 2010). The other study that was considered to meet criteria included Okuyemi et al. 2007, where they found African American menthol cigarette smokers experienced a lower cessation rate than non-menthol smokers.

After eliminating clinical studies with low sample sizes, no six month follow-up and no analysis of racial/ethnic minorities, the evidence from clinical trials (Ganhdi et al., 2009; Okuyemi et al., 2007 vs. Rietzel 2101a, b) was mixed.

Studies also show that menthol effects are particularly observed among smokers who are prescribed medications (Okuyemi, et al., 2003). In the Okuyemi et al. (2003; 2007) studies, menthol status is only evident in the active treatment conditions (NRT and bupropion) and not the placebo condition. Similarly, King et al., (November 2010) conducted a study using NRT vs. NRT + Naltrexone. They observed that menthol effects were only found among the NRT only group, leading to the hypothesis that naltrexone, an opioid antagonist, has a mitigating effect. The King et al. (2010) study had very small sample size of African American smokers. Finally, it should be noted that in the Gandhi et al. (2009) and Foulds et al., (2006) study, treatment seekers were recommended to use medications. Thus, the evidence points toward negative effects of menthol cigarettes on the efficacy of medications. It is possible that the lack of response to treatment may be most evident for NRT. In the study that examined bupropion SR (Okuyemi, et al., 2003), menthol effects were only observed at the end of treatment and not at follow-up.

In conclusion, based on the various studies, the evidence is sufficient to indicate that menthol is associated with lower level of cessation among a non-white population, specifically among African Americans, and the evidence in white is mixed. Menthol cigarette smoking may also affect response to medications.

**Adolescents**

No studies have been conducted in adolescent smokers that examine the effects of menthol cigarettes on cessation. Moolchan (2004) examined adolescents living in the Baltimore area who responded via telephone to advertisements or community outreach for an outpatient teenage smoking cessation study. Moolchan (2004) observed that about 90 percent of the 622 adolescents who responded and for whom they had data were smoking menthol cigarettes.

**Mediators of cessation attempts among menthol smokers**

To date, no studies have systematically examined factors that may or may not make it difficult for menthol cigarette smokers to quit smoking. A potentially informative report by Anderson et al. (2010) was commissioned by the FDA. The report examined internal tobacco industry documents to assess menthol's potential role in quit attempts and success in quit attempts. In this qualitative research study of the digitized repository of previously internal tobacco industry documents, a snowball sampling design was used to search the Legacy Tobacco Documents Library. Based on this search and analysis of these documents, Anderson et al. (2010 November submission) came to the following conclusions.

> "Menthol smokers perceive the ….soothing, cooling, anesthetic sensations with menthol cigarettes. These perceptions appear to discourage quitting in menthol smokers (Anderson, November submission, page 9)."
>
> "Two main motivations for smokers to quit are health concerns and the social unacceptability of smoking. Menthol's cooling, soothing, and anesthetic effects mask superficial health effects such as throat irritation and cough in menthol smokers, which lessen their concern about health effects [and provide an alternative to giving up smoking altogether (page 14, Anderson, in press)]. Menthol smokers also believe menthol smoke to smell better and be less offensive to others, which lessens menthol smokers' sense of the social unacceptability of smoking. These aspects of menthol appear to discourage motivation or desire to quit among menthol smokers."
>
> "Menthol appeals to some socio-demographic groups who are also known to have difficulty initiating quitting or staying quit, including women, lower income smokers, and African Americans. Although it is not clear why there is substantial overlap between the overall menthol profile (younger, non-white, female, and low income) and socio-demographic variables that predict difficulty in quitting or staying quit, it appears that tobacco companies took an interest in this overlap (Anderson, November submission, page 10)."
>
> "The evidence demonstrating smokers' switching fro non-menthol to menthol cigarettes when they have a cold or sore throat points to a presumption of therapeutic or health protective effects of menthol, effects that lead smokers to believe it is unnecessary to quit smoking in order to protect one's health. Tobacco industry executives acknowledged the health reassurances such beliefs about menthol imply and have marketed menthol with both explicit and implicit health messages (Anderson in press, page 22)."

Philip Morris observed that African Americans, females and younger smokers were more likely to smoke menthol cigarettes than whites, males and older smokers, according to an analysis of internal company documents by Klausner (2011 in press). A Philip Morris document dated 1978 said: "These differences could have a profound effect on the future growth of the menthol share of the market. We know, for example, that males, whites, and older smokers are more likely to quit smoking than females, blacks and younger smokers."

**EVIDENCE SYNTHESIS**

The goal of chapter 6 was to gather and review evidence on the effects of menthol cigarettes on smoking experimentation and initiation, the transition to regular smoking and addiction, and the success of smoking cessation. The evidence in these areas is summarized below. TPSAC considered this information, along with other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

**Initiation and Experimentation**

*Is there evidence to indicate that the availability of menthol cigarettes increases the likelihood of experimentation and initiation?*

- The evidence is sufficient to conclude that there is a higher prevalence of menthol cigarette use is observed among younger population of smokers compared to an older population (except in African Americans among whom high rates were observed in both adolescents and adults). Within the population of youth, the evidence is sufficient to conclude that the rate of menthol cigarette use is highest among the youngest users then decreases with age.

- The evidence is sufficient to conclude that there is an increasing trend of menthol cigarette smoking and a decreasing trend of non-menthol cigarette smoking among adolescent smokers, including novice smokers (those who have smoked less than 100 cigarettes). Although cigarette smoking is becoming less prevalent, the evidence is sufficient to conclude that menthol cigarette smoking is declining at slower rate than non-menthol cigarette smoking.

- The evidence is sufficient to conclude that less established smokers (less than one year smoking) are more likely to smoke menthol cigarettes than more established smokers (greater than one year smoking).

- Although most studies showed that the age of initiation was similar comparing menthol and non-menthol cigarette smokers, one national survey of adolescents showed that menthol smokers experienced an earlier age of initiation. This finding was observed even after controlling for age, race and gender.

- The evidence shows based on concordant findings of the studies of internal tobacco industry documents, that tobacco companies were aware of the appeal of menthol cigarettes to younger, novice smokers because these cigarettes are easier to smoke. Chapter 3 documents the biological plausibility of an increased appeal of menthol cigarettes because of their pharmacological effects of menthol.

**Addiction**

*Does the availability of menthol cigarettes increase the likelihood of becoming addicted?*

- To date, one unpublished secondary analysis has addressed this issue in sample of adolescent students who were assessed in different regions in the U.S. This study strongly suggests that menthol cigarettes are associated with increased transition to greater or established smoking and dependence.

*Does inclusion of menthol in cigarettes increase the degree of addiction to the smoker compared to non-menthol cigarettes?*

- Among adults there is little evidence to support the conclusion that menthol cigarettes increase addiction to smoking based on the mixed results on differences between menthol and non-menthol for pharmacokinetics of nicotine, cigarettes smoked per day, exposure to nicotine in general and per cigarette (although little is known about differences in those who smoke less than 10 cigarettes per day or those who are in the early stages of smoking acquisition), and subjective measures of dependence.

- Among youth, there is sufficient evidence to indicate that those who smoke menthol tend to be more dependent than those who smoke non-menthol cigarettes as reflected by the number of cigarettes smoked and dependence measures. Thus, this population seems to be particularly vulnerable to the effects of menthol cigarette smoking.

**Cessation**

*Is there evidence to indicate that smokers of menthol cigarettes are less likely to quit successfully than smokers of non-menthol cigarettes?*

- Although the number of studies that are considered to be of sufficient quality is limited, there is sufficient evidence based on national surveys to show that the non-white smokers, particularly African American, of menthol cigarettes compared to non-menthol cigarettes experience more difficulty with cessation. The data in whites is mixed.

- The results also suggest that menthol cigarette smoking leads to less responsiveness to medications. This is an area that requires further exploration.

- No studies have been conducted with adolescent smokers.

- Menthol cigarettes are marketed toward (see Chapter 5) toward African American and the young. These groups are at high risk for poor cessation outcomes.

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# Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Appleyard. Smoking among Asian American and Hawaiian/Pacific Islander youth: data from the 2000 National Youth Tobacco Survey. 2001 American Legacy Foundation and CDC | Cross-sectional survey, secondary analysis of the 2000 National Youth Tobacco Survey | N=35,828 US middle school (MS) and high school (HS) students<br><br>Overall response rate was 84%.<br><br>Number of subjects:<br>Asian-American: 1742<br>Hawaiian/Pacific Islander: 487<br>African-American: 5913<br>Hispanic: 6565<br>White: 19,884<br>American Indian/Alaskan Native: 666 | Independent Variables:<br>MS and HS by Race/ethnicity<br><br>Outcome variable.<br>Menthol smoking initiation—grade smoked first cigarette among ever smokers<br><br>Current smokers defined as reported smoking a cig on ≥1 day of last 30 days<br><br>Menthol use defined as usually smoking menthol brand | Percentage of youth who usually smoke menthol brand of cigarettes by Middle and High School<br><br>Middle School / High School<br>Asian American 50.9% / 59.9%<br>Hawaiian/PI 38.9% / 51.2%<br>African American 70.9% / 75.0%<br>Hispanics 56.9% / 48.7%<br>Whites 42.4% / 29.6% | |
| Barker D. Changes in the Cigarette Brand Preferences of Adolescent Smokers — United States, 1989–1993. 1994. Centers for Disease Control and Prevention | Cross-sectional national survey; secondary analysis 1989 and 1993 Teen Age Attitudes and Practices Survey (TAPS): national household sample of adolescents (aged 12–18 years) | Of the 9135 respondents to the 1989 TAPS, 7960 (87.1%) participated in TAPS-II (age 15-22)<br><br>In addition, 4992 (89.3%) persons from a new probability sample participated in TAPS-II.<br><br>Data for the 12–18-year-olds in each survey were analyzed (n=9135 for TAPS; n=7311 for TAPS-II). | Independent variable:<br>Age group of adolescent<br><br>Outcome Variable:<br>Adolescent current smokers were asked if they usually bought their own cigarettes, and if so, which brand they usually bought.<br><br>Current smoking defined as smoking on 1 or more of the 30 days preceding the survey<br><br>Menthol cigarettes defined as brand usually bought | Younger smokers (aged 12–15 years) were more likely than older smokers (aged 16–18 years) to buy Newport (19.4% vs. 10.6%) and less likely to buy Marlboro (49.5% vs. 63.1%) | • Small number of Black and Hispanic respondents in TAPS II,<br>• Study conducted in early 90s. |
| Caraballo, Asman. Epidemiology of menthol cigarette use in the United States. 2010. | Literature review and data analyses using the National Survey on Drug Use and Health, the National Youth | NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 hs from years '04, '06, '09 who smoked in past 30 days and | Independent Variables:<br>Middle School vs. High School<br><br>Outcome variable:<br>Percent current adolescent | Almost half of smokers age 12-17 reported smoking menthol (~ n=1 million) (NSUDH). | |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 1: Age Gradient for Menthol Cigarette Use

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|---|---|---|---|---|---|
| Funding source not explicitly stated | Tobacco Survey, the Monitoring the Future Survey, and the National Health and Nutrition Examination Survey | have a usual brand. N=2,580 adol. smokers from 35 states | menthol smokers<br><br>Current smoking defined as smoking at least 1 day of past 30 days<br><br>NYTS: Menthol use defined as usually smoking menthol cigarettes | Proportion of menthol use among Middle and High School students (NYTS)<br>Middle School: 49.4%<br>High School: 44.9% | |
| Curtin et al. Descriptive Epidemiological Analysis of Menthol Use from Four National US Surveys: I. Demographics. 2010 (FDA Submission) RJReynolds | Cross-sectional survey; secondary analyses of 2006 NYTS | N=27,038 students enrolled in US public and private schools, grades 6 through12 (aged 9-21 years)<br><br>Response rate information not provided in the article<br><br>N in analysis:<br>Menthol smokers=745<br>Non-menthol smokers =758 | Independent Variables:<br>Age group of smoker<br><br>Outcome variable:<br>Percent current menthol smoker<br><br>Current smokers defined as smoking any cigarettes on 10 or more of the last 30 days<br><br>Menthol use defined by usual cigarettes being menthol | Proportion of menthol use by age group<br>9-13 year olds: 59.3%<br>14-16 years old: 45.8%<br>17-18 years old: 38.3% | |
| Fernander, A., Rayens, M.K., Zhang, M., Adkins, S. Are age of smoking initiation and purchasing patterns associated with menthol smoking? 2010 Funding source not explicitly stated | Cross-sectional survey data; secondary analysis of in 2003 and 2006/2007 TUS-CPS | N=66,145 current smokers<br>Menthol smokers = 16, 294<br>Non-menthol smokers = 46,899<br>[2,952 smokers were unresponsive] | Independent variable<br>Before 18 years old vs. after 18 years old<br><br>Outcome variable:<br>Age at which first started smoking cigarettes fairly regularly<br><br>Current smoking defined as smoking at least 100 cigarettes in life-time and currently smoking every day or some days (including at least once in the last 30 days)<br><br>Menthol smoking status was | Current smokers who were younger were more likely to smoke menthol cigarettes (e.g., OR: 1.66, 95% CI: 1.47-1.88 for 18-24 y/o relative to those aged 65 and above).<br><br>Of the menthol smokers: 53.2% (95% CI +/-.9) started smoking before age 18 and 46.8% (95% CI +/-.9) started smoking at age 18 or older.<br><br>Of non-menthol smokers: 56.2% (95% CI +/-.6) started smoking before age 18 and 43.8% (95% CI +/-.6) started smoking at age 18 or older. | • Reference group was those aged 65 and above |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

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|---|---|---|---|---|---|
| | | | determined with the item: 'Is your usual cigarette band menthol or non-menthol?' with responses of 'menthol', 'nonmenthol' and 'no usual type'. Those who stated that they had no usual type were treated as missing values for the cigarette type variable. | | |
| Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States<br>American Legacy Foundation | Cross-sectional survey; secondary analysis of 2004-2008 NSDUH | 179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >=12 years old to report on patterns of methol use.<br><br>Response rate – 66.2% (2008 survey) | Independent variable:<br>Age<br><br>Outcome variable:<br>Percent menthol use among all smokers<br><br>Current cigarette smoking defined as smoking cigarettes in the past month<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol | Use of mentholated cigarettes by age<br>- 12-17 years old: 49.3%<br>- 18-25 years old: 37.5%<br>- 26-34 years old: 29.9%<br><br>A statistically significant age gradient in these age categories also was observed among males, females, whites, and Hispanics. Among African Americans, a ceiling effect likely occurred, with menthol use rates of at least 91.9% observed in all of the 12-34 year old age categories examined.<br><br>Use of mentholated cigarettes by age and race/ethnicity<br>Total 53.5% 47.0% 40.5% 34.6%<br>White 47.6% 40.1% 32.6% 25.7%<br>Black 95.6% 93.9% 94.1% 92.5%<br>Hispanic 56.2% 50.5% 44.7% 34.9%<br>Asian 70.7% 50.7% 32.8% 39.6% | • Data were weighted to produce estimates that were representative of the population being sampled. |
| Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology of menthol cigarette use. | Cross-section national survey, secondary analysis of 2000 National Household Survey on Drug Abuse (NHSDA) | N in analysis=18,359 current smokers | Independent variable:<br>Age of smoker by race/ethnicity<br><br>Outcome variable:<br>Percent current smoker smoking menthol cigarettes | Percentage of current smokers who most often smoked menthol by age and race/ethnicity: 2000 NHSDA<br><br>12-17 y/o 18-25 y/o 26 + y/o<br>Total 31.6% 25.8% 28.6%<br>White 28.4% 20.1% 22.5%<br>Black 55.7% 68.6% 69.5%<br>Hispanic 35.7% 25.9% 29.7% | • All data were weighted to provide nationally representative estimates, and standard errors for 95% confidence intervals were |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| 2004 National Institute on Drug Abuse | | | Current smoking defined as smoking during the past 30 days<br><br>Menthol status defined as response to: ''During the past 30 days, what brand of cigarettes did you smoke most often?'' and ''During the past 30 days, did you smoke (name of brand) menthol or regular cigarettes most often?'' | Newport cigarettes use by race/ethnicity and age<br><br>12-17 y/o 18-25 y/o 26 + y/o<br>White 18.0% 9.3% 2.9%<br>Black 79.2% 76.7% 31.5%<br>Hispanic 31.4% 16.7% 7.1%<br><br>Marlboro cigarette use by race/ethnicity and age<br><br>12-17 y/o 18-25 y/o 26 + y/o<br>White 58.8% 61.4% 37.9%<br>Black 5.3% 7.3% 6.6%<br>Hispanic 52.5% 67.7% 54.0% | calculated in a way that reflected the complex survey design.<br><br>Potential Weakness:<br>• Misclassification of self reported menthol status in NHSDA |
| Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006 American Legacy Foundation | Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS | 2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002. Response rate: 84% in 2000, 75% in 2002.<br><br>N in analysis=5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS). | Independent variable: School grade by race/ethnicity<br><br>Outcome variable: Prevalence of smoking menthol cigarettes among youth smokers<br><br>Current smoking defined as 'smoking cigarettes on one or more of the past 30 days'<br><br>Menthol use: defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol (''During the past 30 days, what brand of cigarettes did you usually smoke?'' and ''Is the brand of cigarettes that you usually smoked during the past 30 days mentholated?'') | Menthol Use<br><br>Middle School High School<br>Total 59.6% 43.6%<br>White 53.1% 37.4%<br>Black 87.5% 86.8%<br>Hispanic 62.9% 52.4% | • Controlled for demographic background and the length, frequency, and level of smoking;<br>• Takes into account misclassification; standardized scale to measure dependence.<br><br>Weaknesses:<br>• Possible misclassification in the reporting of menthol; |
| Hersey et al., 2010 Menthol cigarettes contribute to the | Cross-sectional survey; secondary analysis of 2006 NYTS | 2006 NYTS: Administered to 27,038 students enrolled in US public and private | Independent variable: School grade by racial/ethnic groups | Percent menthol smokers among past 30 day smokers<br><br>Middle School High School | |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| appeal and addiction potential of smoking for youth, NTR Dec 2010 supplement | | schools, grades 6 through 12 (aged 9-21 years)<br><br>Response rate – 80.2%<br><br>N in analysis=4,738 youth who smoked in the past 30 days, had a regular brand and could identify whether the brand was menthol or non-menthol | Outcome variable: Prevalence of smoking menthol cigarettes among youth smokers<br><br>Current smoking defined as 'smoking cigarettes on one or more of the past 30 days' and smoking 100 plus cigaettes in a lifetime<br><br>Menthol use defined as usual brand of cigarette smoked ("usual brand is menthol or nonmenthol") | White 43.1% 37.6%<br>Black 80.6% 84.8%<br>Hispanic 57.9% 56.4%<br><br>Percent menthol smokers among smokers who smoked 100 plus cigarettes in a lifetime<br><br>High School<br>White 38.1%<br>Black 84.4%<br>Hispanic 66.1% | |
| Hymowitz N, Corle D, Royce J, Hartwell T, Corbett K, Orlandi M, Piland N. Smokers' Baseline Characteristics in the COMMIT Trial 1995. National Cancer Institute | Baseline telephone survey data from 10 of 22 COMMIT sites,<br><br>COMMIT is a collaborative prospective clinical trial of community-based intervention. It is a community-level, multi-channel, 4-year intervention designed to increase quit rates among cigarette smokers. | Smokers ages 25-64 years from intervention and matched comparison communities in CA, NJ, NY, NM, and NC.<br>N=16,857<br><br>White: 11,128<br>Black: 3,322<br>Puerto Rican: 537<br>Mexican: 1,870 | Independent Variables:<br>Age<br><br>Outcome Variables:<br>Menthol cigarette use<br><br>Current smoking defined as smoking cigarettes now<br><br>Menthol use definition not provided in the article | Preference for menthol was greatest among the youngest smokers (OR: 0.71 (0.68-0.74). | • Studies conducted in 90s |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Rock V.J., Davis S.P., Thorne S.L., Asman K.J., Caraballo R.S. Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. 2010 Funding source not explicitly stated | Cross-sectional data: secondary analysis of 2004–2008 NSDUH | 2004-2008 NSDUH: Menthol smokers: 25,579<br>Non-menthol smokers: 46,026<br><br>See Table 1 and 2 (p S119 and S120) for more details. | Independent Variables:<br>Age by race/ethnicity.<br><br>Outcome Variables:<br>Prevalence of menthol use<br><br>A current cigarette smoker defined as anyone who answered "yes" to the question, "During the past 30 days, have you smoked part or all of a cigarette?"<br><br>Menthol use defined by response to "Were the cigarettes you smoked during the past 30 days menthol?" | Higher prevalence of menthol smokers vs. non-menthol smokers among those aged 12-17 years old (5.8% [5.5,6.1] vs. 3.4% [3.3,3.5])<br><br>Proportion of cig smokers smoked menthol among adolescents than young or older adults<br>12-17 y/o: 44.7%<br>18-25 y/o: 36.1%<br>26+: 30.2%<br><br>Prevalence of menthol cigarette use among current smokers aged 12 years or older by race/ethnicity<br><br>12-17 y/o 18-25 y/o 26+ y/o<br>Total 44.7% 36.1% 30.2%<br>White 41.0% 28.8% 21.9%<br>Black 71.9% 85.0% 82.2%<br>Hispanic 47.0% 38.2% 29.5%<br>Asian 51.5% 35.8% 28.6%<br>AI/AN 34.7% 27.4% 23.0%<br><br>. | .<br>• The precision of smoking prevalence estimates for certain racial/ethnic populations was low due to small sample size (i.e., Asians and Native Americans/Alaska Natives), especially when stratified by age. |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Sidney S., Tekawa I., Friedman G. Mentholated cigarette use among multiphasic examinees, 1979–86. 1989 [NCI] | Prospective cohort | Starting in July 1979, patients at Kaiser Permanente Medical Care Program medical centers in Oakland and San Francisco were asked to complete a supplementary questionnaire that explored their smoking habits in detail. Between 1979 – 1986, the questionnaire had been completed by 114,934 examinees (approximately 86 percent of the examinees), of whom 31,428 (27.3 percent) were current smokers.<br><br>Mentholated cigarette use habits were examined in the 29,037 current smokers ages 15-79 years of Black, White, or Asian race. | Independent variable: age<br><br>Outcome variable: percent menthol users<br><br>No definition provided for current smoking or menthol use | There was a marked inverse relationship between age and mentholated cigarette use in Blacks and in Asians, while there was relatively little difference in mentholated cigarette use with age in Whites (see Figure 1, page 1416).. | • |



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# Table 2: Trends in menthol use over time among youth

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Barker D. Changes in the Cigarette Brand Preferences of Adolescent Smokers — United States, 1989–1993. 1994. Centers for Disease Control and Prevention | Cross-sectional national survey; secondary analysis of 1989 and 1993 Teen Age Attitudes and Practices Survey (TAPS): national household sample of adolescents (aged 12–18 years) | Of the 9135 respondents to the 1989 TAPS, 7960 (87.1%) participated in 1993 TAPS-II (age 15-22)<br><br>In addition, 4992 (89.3%) persons from a new probability sample participated in TAPS-II.<br><br>Data for the 12–18-year-olds in each survey were analyzed (n=9135 for TAPS; n=7311 for TAPS-II).<br><br>N for analysis=702 smokers who usually bought their own cigarettes | Independent variable:<br>Brand of cigarettes<br><br>Outcome Variables:<br>Changes in brand preferences of teenage smokers over time<br>Current smoking defined as smoking cigarettes on 1 or more of the past 30 days<br><br>Menthol cigarettes defined as brand usually bought | Between 1989 and 1993, the percentage of adolescents purchasing Newport cigarettes increased 4.5 percentage points (55% increase). Increases for Newport cigarettes were greatest among younger smokers and adolescents residing in the Northeast.<br><br>Change in self-reported cigarette brand preference among adolescents aged 12-18 years<br>TAPS 1989 TAPS 1993 Change<br>Newport 8.2% 12.7% +4.5<br>Marlboro 68.7% 60.0 -8.7<br>Camel 8.1% 13.3% +5.2<br><br>Increase in Newport cigarette preference in youth exceed market share increase of +0.1 | Weaknesses:<br>• Small number of Black and Hispanic respondents in TAPS II,<br>• Study conducted in early 90s, but provide historical perspective |
| Caraballo, Asman. Epidemiology of menthol cigarette use in the United States. 2010. Funding source not explicitly stated | Literature review and data analyses using the National Survey on Drug Use and Health, the National Youth Tobacco Survey, the Monitoring the Future Survey, and the National Health and Nutrition Examination Survey | NSDUH: ages 12-17 who smoked in past month (9,595) and 18+ who smoked in past month (62,010) from surveys conducted 2004-2008<br><br>NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 high school from years '04, '06, '09 who smoked in past 30 days and have a usual brand. Analysis on 2,580 adol. smokers from 35 states | Independent Variables:<br>Menthol status; brand of cigarettes<br><br>Outcome variable:<br>Percent current adolescent menthol smokers over time<br><br>Current smoking defined:<br>smoking at least 1 day of past 30 days | According to NSDUH, menthol cig use increased from 04-08 (see below, Rock et al. 2010)<br><br>According to the MTFS data from 1998 to 2008, no consistent or significant change was observed during the period for Newport among 8th, 10th and 12th graders, however, a significant increase was observed for Kool.<br><br>According to the data from the 2004, 2006, and 2009 NYTS survey, a slight non-significant decrease in smoking Newport was observed among middle school smokers and no change among high school smokers. | |



* Note: Some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 2: Trends in menthol use over time among youth

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| | | MTFS: US Students in 8th (n=20,863), 10th (n=30,722), 12th (n=40,914) grades for years '98-'08 | | | |
| Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology of menthol cigarette use. 2004 National Institute on Drug Abuse | Cross-section national survey, secondary analysis of 1998, 1999, 2000 Monitoring the Future | 136,000 participants surveyed<br>16,313 students analyzed | Independent variable:<br>Brand of cigarettes<br><br>Outcome measure:<br>Percent current smoker who smoked Newport, Kool or Salem between 1998 and 2000 by grade<br><br>Current and menthol status defined as response to what brand usually smoked in the past 30 days. | No significant change was observed in percent smoking menthol cigarettes (Newlport, Kool or Salem) across time within each grade. | Weakness<br>Brands not examined separately. For example, Kool cigarette smoking may have decreased but Newport smoking may have increased. |
| Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States American Legacy Foundation | Cross-sectional survey; analysis of 2004-2008 NSDUH | 2004-2008 NSDUH: 179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >12 years old<br>I<br>Response rate for 2008 survey was 66.2% | Independent variable:<br>Menthol status<br><br>Outcome variable:<br>Prevalence of menthol smokers in all youth over time<br><br>Current smoker defined as smoking cigarettes in the past month<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol | Trends in prevalence of menthol and non-menthol cigarettes among all youth<br>2004 2008<br>12-17 y/o<br>Menthol 5.3% 4.6%<br>Non-menthol 6.0% 3.9%<br><br>Slopes of regression liens are -0.14 for menthol and -0.53 for non-menthol and statistically different (p=0.003).<br><br>18-25 y/o<br>Menthol 14.0% 14.5%<br>Non-menthol 25.7% 20.4%<br><br>Slopes of regression liens are 0.17 for menthol and -1.49 non-menthol and statistically different (p=0.0002). | Strengths:<br>Data were weighted to produce estimates that were representative of the population being sampled. |



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# Table 2: Trends in menthol use over time among youth

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
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| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006 American Legacy Foundation | Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS | 2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002.<br><br>Response rate: 84% in 2000, 75% in 2002.<br><br>Data analyzed on 5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS). | Independent variable: Menthol use<br><br>Outcome variable: Rate of smoking menthol cigarettes among MS and HS by year<br><br>Current smoking defined as smoking cigarettes on one or more of the past 30 days'<br><br>Menthol use defined as the brand of cigarettes usually smoked and if the brand of cigarettes usually smoked during the past 30 days is menthol | Menthol cigarette use among youth between 2000 and 2002<br><br>2000 2002<br>Total * 40.0% 47.4%<br>Middle School* 51.6% 59.6%<br>High School 36.9% 43.6%<br><br>*Significant difference $p < 0.05$ | Strengths:<br>• Controlled for demographic background and the length, frequency, and level of smoking;<br>• Takes into account misclassification; standardized scale to measure dependence.<br><br>Weaknesses:<br>• Possible misclassification in the reporting of menthol; |
| Hersey et al., 2011 Trends in brand and type of cigarette smoking by 12-17 year olds from 2004 to 2008, presentation to TPSAC, February | Cross-sectional survey; secondary analysis of 2004 to 2008 NSDUH | NSDUH samples of 12-17 year olds range from 17,727 to 18,678 for each of the years; number of smokers range from 1,759 to 2,255 | Independent variable: Brand of cigarettes<br><br>Outcome variable: Rate of smoking menthol cigarettes among youth smokers over time | Percentage of brand use among 12-17 year old smokers in the NSDUH: 2004 to 2008<br><br>2004 2008<br>Marlboro Menthol 12.7% 18.2%<br>Marlboro Non-menthol 37.1% 28.5%<br>Camel Menthol 1.7% 6.4% | |



* Note: Some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 2: Trends in menthol use over time among youth

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| 2011 | | | Current cigarette defined as smoking menthol cigarettes in the past month<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol | Camel Non-menthol 7.7% 9.0%<br>Newport 24.2% 23.5% | |
| Kaufman, N.J., Castrucci, B.C., Mowrey, P., Gerlach, K.K., Emont, S., Orlean, T. Changes in Adolescent Cigarette-Brand Preference, 1989 to 1996. 2004<br>Funding source not explicitly stated | Cross-sectional national survey; secondary analysis of The Robert Wood Johnson Foundation 1996 National Survey of Tobacco Price Sensitivity, Behavior, and Attitudes Among Teenagers and Young Adults (RWJF survey) was used to make national estimates of brand preference in 1996. These estimates were compared with similar estimates derived from the Centers for Disease Control and Prevention (CDC) Teenage Attitudes and Practices Surveys (TAPS) conducted in 1989 (TAPS I) and 1993 (TAPS II) surveys | RWJ survey N=17,287<br>TAPS-I N=9,315<br>TAPS-II N=12,952 (7,960 from TAPS-I plus 4,992 new respondents) | Independent variable:<br>Brand preference<br><br>Outcome variable:<br>Trends over time<br><br>Current smoking and menthol use defined as: In TAPS, adolescents who had smoked on at least one day during the past 30 and who usually bought their own cigarettes were asked, "What brand do you usually buy?" RWJF survey respondents who had smoked on at least one day during the past 30 and who had ever bought cigarettes were asked, "When you buy cigarettes, what brand do you usually buy?" The possible cigarette brand choices differed slightly among the 3 surveys. More brands were listed in the RWJF survey than in TAPS. Both the RWJF survey and TAPS-II included "no usual brand" as a | Between 1989 and 1996, Marlboro, Camel, and Newport were the brands respondents most often reported as the "brand usually bought." These 3 brands combined accounted for slightly over 84% in 1989 and 1993 and over 90% in 1996 of all brands respondents reported that they usually bought.<br><br>Of the 3 brands, Newport was the only one to increase significantly in each of 3 age-groups from 1989 to 1996. The percent reporting usually buying Newport increased 347% among 13 to 14 year olds, 189% among 15 year olds, and 69% among 16 to 18 year olds.<br><br>Percentage distribution of cigarette brand usually bought by adolescents by age<br>1989 1996<br>Marlboro<br>13-14 y/o 69.6% 66.9%<br>15 y/o 77.4% 64.1%<br>16-18 66.9% 68.1%<br>Total 68.5% 67.2%<br>Camel<br>13-14 y/o 13.7% 3.3%<br>15 y/o 13.9% 7.6%<br>16-18 3.6% 8.4%<br>Total 8.1% 8.1%<br>Newport<br>13-14 y/o 4.8% 19.2%<br>15 y/o 7.4% 21.4%<br>16-18 8.8% 14.9 % | Weaknesses:<br>• This is not generalizable to children who obtained cigarettes from nonretail sources or who had not smoked during the 30 days prior to survey.<br>• Old data set , but provides historical perspective |



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# Table 2: Trends in menthol use over time among youth

Version Date: 3-12-11

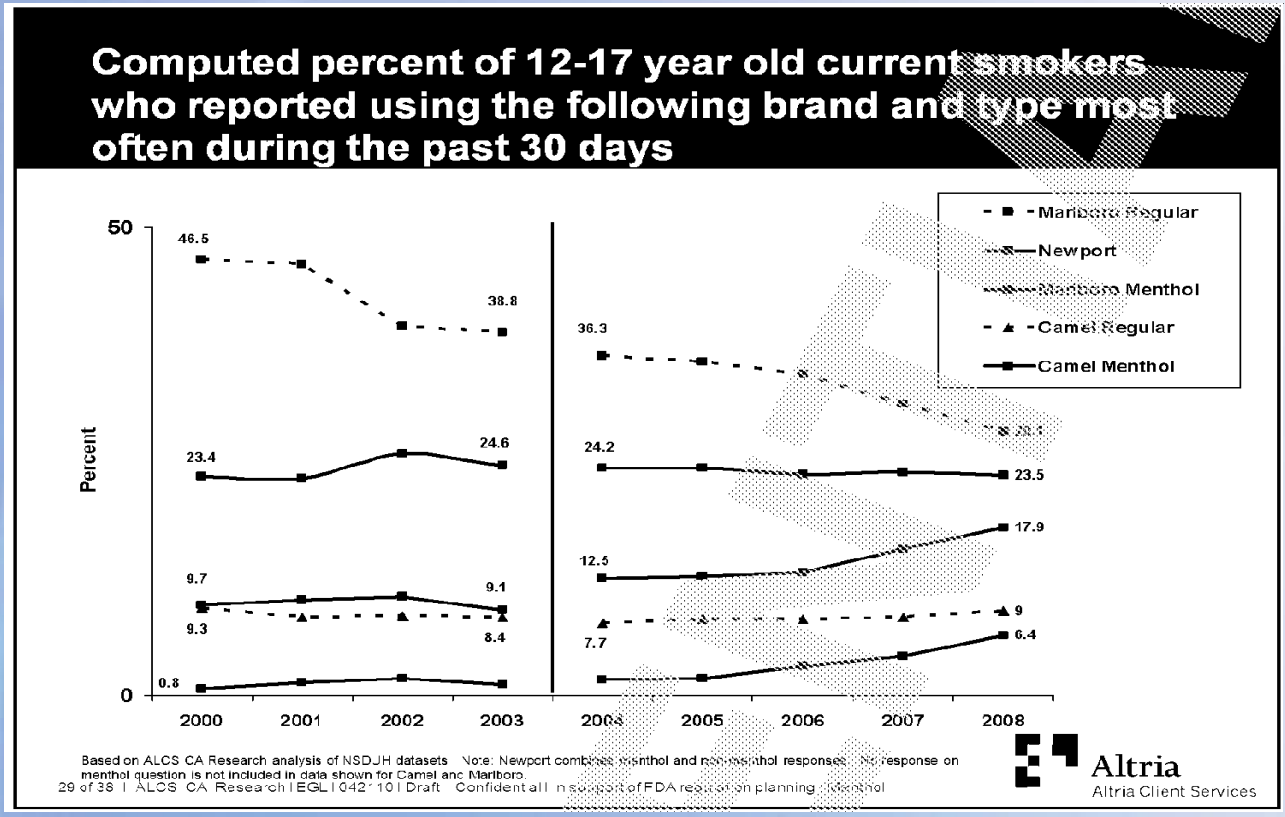
| Author Name(s), Article Title and year | Type of Study and Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| | | | possible response.<br><br>On the RWJF survey, respondents were queried as to the brand they usually smoked. Respondents were asked, "What *one* brand of cigarettes do you *usually* smoke?" | Total 8.3% 16.4%<br><br>When brand preferences by race and ethnicity are examined, only slight fluctuations were found in market share for Marlboro and Camel when comparing 1989 to 1996. However, the percentage of white and Hispanic adolescents who reported Newport as the brand they usually buy doubled (for whites, 5.3% to 10.4%, for Hispanics, 12.8% vs. 25.9%). No significant change was observed in Blacks. Kool also had a significant portion of the African American adolescent market, ranging from 9.4% in 1989 to 7.7% in 1996. Although almost 6% of Hispanic adolescents usually bought Kool in 1989, by 1996 Kool had less than a one-percent preference among any ethnic group or race other than African American. | |
| Rock V.J., Davis S.P., Thorne S.L., Asman K.J., Caraballo R.S. Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. 2010 Funding source not explicitly stated | Cross-sectional data; secondary analysis of 2004–2008 NSDUH | 2004-2008 NSDUH: Menthol smokers: 25,579<br>Non-menthol smokers: 46,026<br><br>See Table 1 and 2 (p S119 and S120) for more details. | Independent variable:<br>Menthol smoking<br><br>Outcome Variables:<br>Prevalence of menthol smoking from 2004 to 2008 by age and race/ethnicity<br><br>A current cigarette smoker was defined as anyone who answered "yes" to the question, "During the past 30 days, have you smoked part or all of a cigarette?"<br><br>To estimate menthol cigarette use, current smokers (*n* = 71,605) were asked, "Were the cigarettes you smoked during the past 30 days menthol?" Anyone who answered "yes" was considered to be a current menthol cigarette smoker. | Trends is prevalence of menthol cigarette use among current smokers of different ages<br><br>2004 2008<br><br>12- 17 y/o<br>--White* 40.3% 46.0%<br>--Black 72.5% 66.6%<br>--Hispanic 40.4% 46.7%<br>18-25 y/o<br>--White* 26.7% 32.5%<br>--Black 86.6% 87.4%<br>--Hispanic* 33.9% 42.4%<br><br>Significant changes from 2004 to 2008 in white 12-17 y/o smokers<br><br>Significant changes from 2004 to 2008 in white and Hispanic 18-25 y/o smokers<br><br>No significant changes from 2004 to 2008 among 26 plus year old among all ethnic/racial groups. | Weakness<br>.<br>• The precision of smoking prevalence estimates for certain racial/ethnic populations was low due to small sample size (i.e., Asians and Native Americans/Alaska Natives), especially when stratified by age. |



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*RTI International*

# Percent of 12–17 Year-Old Smokers Smoking Menthol Cigarettes: 2000–2008 Industry analysis of National Survey on Drug Use and Health (NSDUH)




10

Source: *Industry Document.*



* Note: Some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 3: Rate of menthol smoking in recent vs. established smokers

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study/Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Results/Conclusion(s) related to Menthol* | Comments |
|---|---|---|---|---|---|
| Caraballo, Asman. Epidemiology of menthol cigarette use in the United States. 2010. Funding source not explicitly stated | Literature review and data analyses using the 2004, 2006 and 2009 National Survey on National Youth Tobacco Survey (NYTS) | NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 hs from years '04, '06, '09 who had information on smoking history<br><br>Data analyzed on 2,580 adol. smokers from 35 states | Independent Variables: Amount of cigarette smoking<br><br>Outcome variable: Percent current adolescent menthol smokers in adolescents who started smoking less than 2 years ago<br><br>Current smoking defined as smoking at least 1 day of past 30 days<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol ("During the past 30 days, what brand of cigarettes did you smoke most often?" and "During the past 30 days, did you smoke (name of brand) menthol or regular cigarettes most often?") | # cigarettes by days smoking in the past 30 days / % menthol smoker<br>≤ 1 cigarette on 1-5 days: 39.9%<br>1-5 cigs on 1-5 days: 45.3%<br>1-5 cigs on 6-9 days: 47.5%<br>1-5 cigs on 10-19 days: 44.2%<br>1-5 cigs on 20-29 days: 49.7%<br>1-5 cigs on all 30 days: 46.6% | |
| Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States American Legacy Foundation | Cross-sectional survey; secondary analysis of 2004-2008 NSDUH | 2004-2008 NSDUH: 179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >12 years old<br><br>Response rate for 2008 survey was 66.2% | Independent variable: Amount of cigarette smoking<br><br>Outcome variable: Prevalence of menthol smokers in all youth based on amount of smoking<br><br>Current smoker described as smoking menthol cigarettes in | Percent menthol smoking by number of days per month<br>1-5 days / 6-9 days / ≥10 days<br>>12 y/o: 36.1% / 38.3% / 31.9%<br>12-17 y/o: 52.8% / 54.5% / 46.3% | Strengths:<br>• Data were weighted to produce estimates that were representative of the population being sampled. |



* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 3: Rate of menthol smoking in recent vs. established smokers

Version Date: 3-12-11

| Author Name(s), Article Title and year | Type of Study/Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Results/Conclusion(s) related to Menthol* | Comments |
|---|---|---|---|---|---|
| | | | the past month<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol | | |
| Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006<br>American Legacy Foundation | Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS | 2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002.<br><br>Response rate: 84% in 2000, 75% in 2002.<br><br>Data analyzed on N=5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS). | Independent variable: Duration of smoking<br><br>Outcome variable: Rate of smoking menthol cigarettes among MS and HS smokers<br><br>Current smoking defined as smoking cigarettes on one or more of the past 30 days'<br><br>Menthol use defined as the brand of cigarettes usually smoked and if the brand of cigarettes usually smoked during the past 30 days is menthol | Menthol use and length of smoking by grade level, 2002 NYTS<br><br>Less than year / More than a year<br>Middle school * 62.4% / 53.3%<br>High School 45.9% / 41.9%<br>* $p < 0.002$ | • Takes into account misclassification; standardized scale to measure dependence.<br><br>Weaknesses:<br>• Possible misclassification in the reporting of menthol. |
| Hersey et al., 2010 Menthol cigarettes contribute to the appeal and addiction potential of smoking for youth,<br>NTR Dec 2010 supplement | Cross-sectional survey; secondary analysis of 2006 NYTS | 2006 NYTS: 27,038 students enrolled in US public and private schools, grades 6 through 12<br><br>Response rate: 80.2%<br><br>Data analyzed on 4,738 youth who smoked in the past 30 days, had a regular brand and could identify whether the brand was menthol or non-menthol | Independent variable: Duration of smoking<br><br>Outcome variable: Rate of smoking menthol cigarettes among MS and HS smokers<br><br>Current smoking defined as 'smoking cigarettes on one or more of the past 30 days' and smoking 100 plus cigaettes in a lifetime<br><br>Menthol use defined as | Menthol use and length of smoking by grade level, 2006 NYTS<br><br>Less than year / More than a year<br>Middle school 42.2% / 54.7%<br>High School 42.8%% / 43.1%%<br><br>No significant differences in rate of menthol smoking among less established vs. more established smokers<br><br>No differences were foundi in rate of menthol smoking across different amounts of smoking | |



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| Author Name(s), Article Title and year | Type of Study/Study Design | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Results/Conclusion(s) related to Menthol* | Comments |
|---|---|---|---|---|---|
| | | | usual brand of cigarette smoked ("usual brand is menthol or nonmenthol") | | |
| Footnote<br>Rising & Blader 2010<br><br>RJR June 2010 submission | | | | In a white paper written by the FDA, unpublished data from 2004 to 2008 NSDUH of menthol cigarette use among young smokes (aged 12-21 years) was presented. The data showed that rate of menthol smoking was higher among new smokers (smoking fore less than 1 year) than among experienced smokers (smoking for more than a year). The pattern, however, was reversed in 2008.<br><br>Using the same data, in the June 2010 submission by RJR, an analysis was presented in which menthol smokers were divided into smoking less than 100 cigarettes in a lifetime and smoking 100 cigarettes or more in a lifetime. The results again showed greater menthol cigarette smoking among the initiates as opposed to the more established smokers with the rates converging in 2008. | Data beyond 2008 should be examined to determine whether this data point is unusual. |
| Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *The NSDUH Report: Use of Menthol Cigarettes*. 2009 SAMHSA | Cross-sectional survey; secondary analysis of 2004 to 2008 National Survey on Drug Use and Health (NSDUH) survey includes individuals ages 12 and older. | 2004 to 2008 NSDUH survey of subjects 12 or older | Independent variable: Duration of smoking by age and race/ethnicity<br><br>Outcome Variable: Percent menthol smoker<br><br>Current smoker defined as smoking menthol cigarettes in the past month<br><br>Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol | Past month use of menthol cigarettes among past month cigarette smokers 12 and older, by recency of cigarette initiation and demographic characteristics<br><br>Past year initiate / > 1 year use<br>Age 12 and older: 44.6% / 31.8%<br>12 to 17 y/o: 49.2% / 43.8%<br>18-25 y/o: 40.2% / 36.4%<br><br>Black: 73.9% / 82.8%<br>Hispanic: 42.9% / 32.1%<br>White: 39.9% / 23.6%<br><br>. | |



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**Table 4. Rates of Switching***

| Author | Survey/Study | Menthol to Non-menthol | Non-menthol to menthol |
|---|---|---|---|
| Pletcher 2006 | CARDIA<br>1535 current smokers | Among menthol smokers:12% | Among non-menthol smokers: 11% |
| Hyland 2010 | COMMIT<br>Smokers defined as<br>N=2095 completing 3 waves of surveys | Among all smokers: 6.4% | Among all smokers: 4.2% |
| Hyland & Karza2010 | ITC-4<br>Smokers defined as smoking at least 100 cigarettes in a lifetime and currently smoking monthly<br>N=7532 | Among menthol smokers<br>Total: 8.11%<br>Whites: 7.6%<br>Blacks: 7.8%<br>Hispanics: 17.4% | Among non-menthol smokers<br>Total: 2.2%<br>Whites: 1.74%<br>Blacks: 14.8%<br>Hispanics: 6.7% |
| Switching Book. 1991, Phillip Morris | | Among all past year switchers: 6.9% | Among all past year switchers: 5.7% |

| | | | |
|---|---|---|---|
| Eric Johnson presentation January 10, 2010<br><br>Switching Book | % among 34,117 cigarette smokers 18 year of age and older participating in a national telephone survey (1990-1991). | Among all current smokers:<br><br>0.6%<br><br>Among past year menthol smokers: 26.1% | Among all current smoker's<br><br>0.5%<br><br>Among past year non-menthol smokers: 7.7% |
| Giovino (2010) | 2003 Youth Smoking Cessation Survey<br><br>16-24 y/o<br><br>N=1045 | Among menthol smokers: 15% | Among non-menthol smokers: 6.9% |

## Table 5. Studies of Menthol Smoking and Dependence Among Youth (updated Table from Hersey et al., 2010)

| Study | Population | Operational definition of menthol | Findings |
|---|---|---|---|
| Initial smokers | | | |
| DiFranza et al. (2004) | 267 seventh-grade students in two small Massachusetts cities who had inhaled a cigarette sometime during the study (68% White and 20% Hispanic) followed every 4 months for 30 months | Analysis based on the 50.6% of smokers (n=121) who recalled that their first cigarette was menthol (42%) or nonmenthol | 10-item Hooked on Nicotine Checklist scores not related to reported menthol of first cigarette<br>Menthol / Nonmenthol<br>Median 6.5 / 7.0<br>Mean 6.0 / 6.0<br>*SD* 3.3 / 3.4 |
| Nonemaker et al., 2010 | 1,100 out of 47,237 middle and high school youth in the 2000 through 2003 American Legacy Longitudinal Tobacco Use Reduction Study | First cigarette smoked is reported to be menthol | Menthol initiates higher than nonmenthol initiates on the following:<br>Smoking daily *OR*: 1.99<br>Established (smoking 20 or more days in past 30 days) *OR*: 1.94<br>Lifetime smoking (100+ cigs In lifetime) *OR*: 1.94<br>Nicotine dependence *OR*: 1.04 |
| Earlier smoker | | | |
| Hersey et al. (2006) | 26,149 6th - to 12th-grade students in the 2002 NYTS (for the subset who smoked in last month and had a usual brand of cigarettes) | Youth who identified their usual brand as menthol (excluding nonmenthol brands) | Menthol higher than nonmenthol smokers on a six-item Nicotine Dependence Scale for Adolescents: *OR*: 1.45** (*p*=.006) |
| Hersey et al., (2010) | 3,281 out of 27,038 6th-to-12th grade students in the 2006 NYTS who smoked in the last month and had a usual brand of cigarettes | Youth who identified their usual brand as menthol (excluding nonmenthol brands) | Menthol higher than nonmenthol on reduced time for needing a cigarette among smokers with regular brand: OR: 1.86** |
| Hersey et al., (November 2010 submision) | 5,511 youth in 48 schools around the country in a national biochemical validation survey; 1,215 students smoked in the past 30 days, 441 reported usual brand of cigarettes was menthol, 587 smoked in the prior 3 days and had positive cotinine ($\geq$ 5 ng/ml) | Youth who identified their usual brand as menthol | No main effect for menthol on cotinine levels<br>Menthol higher than nonmenthol on levels of dependence among smokers who smoked less than one year (P< 0.05). No differences in those who smoked 1 year or longer. |

| | | | |
|---|---|---|---|
| Muilenburg and Legge (2008) | 2,061 9th- to 12th-grade students in six southern schools (48% male; 73% Black) | Answered "yes" to usually smoking menthol cigarettes | Menthol higher than nonmenthol smokers on the following:<br>Shorter time since last smoke *OR*: 3.22***<br>Total cigarettes/lifetime *OR*: 4.35***<br>Smoke more days per month *OR*: 5.35**<br>Ever a daily smoker *OR*: 3.41*** |
| Established youth smokers | | | |
| Collins and Moolchan (2006) | 572 adolescent smokers recruited for a cessation study (55% female, 45% Black; mean age: 15.1 years) | Usual brand was menthol | Menthol Nonmenthol<br>Smoke within <5 min after waking 45%* 29% |
| Hersey et al., (2010) | 1,457 out of 27,038 6th-to-12th grade students in the 2006 NYTS who smoked in the last month and had a usual brand of cigarettes and smoked at least a 100 times in their lifetime | Youth who identified their usual brand as menthol (excluding nonmenthol brands) | Menthol higher than nonmenthol on reduced time for needing a cigarette among smokers with regular brand: OR: 2.06** |
| Wackowski and Delnevo (2007) | 1,345 current established smokers (30 days smoking and 100 cigarettes lifetime) in Grades 9 to 12 in the 2004 NYTS | Answered "yes" to usually smoking menthol cigarettes | Menthol vs. nonmenthol smokers more likely to need a cigarette within 1 hr after smoking: 16.3% vs. 7.4%; *AOR*: 2.6*<br>Menthol vs. nonmenthol smokers more likely to experience cravings after not smoking for a few hours: 35.9% vs. 25.4%; *AOR*: 1.6* |

*Note*. *AOR* = adjusted odds ratio; *OR* = odds ratio; NYTS = National Youth Tobacco Survey.
*$p$<.05; **$p$<.01; ***$p$<.001.

# Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| Alexander et al. Occupational status, work-site cessation programs and policies and menthol smoking on quitting behaviors of US smokers. 2010 Funding source not explicitly stated | Cross-sectional study; analysis of 2006/07 TUS CPS | In the 2006/07 TUS CPS data set, there was a total of 172 023 self-respondents. Respondents eligible for inclusion in this analysis were TUS CPS current smokers (every day or some days) aged 18 years or older. There was a total of 31 501 eligible self-respondents. Of these, 1325 were excluded due to missing information on cigarette brand type (non-menthol or menthol).<br><br>Total sample size for current study = 30,176 (Menthol=7718; Non-menthol=22,458)<br><br>Percent in each ethnic group:<br>Menthol smokers--30.2% Black, 69.8% white/other<br>Non-menthol smokers--Black: 4.4%, white/other: 95.6% | Independent variable:<br>Menthol status<br><br>Outcome Variable:<br>Ever stopped smoking for one day or longer because trying to quit smoking | Controlling for occupational status and work-place policies and demographics, there were no differences for menthol versus non-menthol smokers on quitting behaviors OR = 0.98 (95% CI: 0.83-1.15) | Weaknesses:<br>• Menthol use, whether or not survey participants switched brands during or after any quit attempts, and exposure to menthol content in cigs cannot be validated<br>• Measure of quitting (measure is same for quit attempts no matter length of time without smoking) |
| Cubbin C, Mah-Jabeen S, LeClere FB. The intersection of gender and race/ethnicity in smoking behaviors among menthol and non-menthol smokers in the United States. 2010 Funding source not explicitly stated | Cross-sectional survey; analysis of 2005 NHIS and Cancer Control Supplement | Total sample= 31 428; analytical sample = 21,196 (included women and men 25–64); sample analyzed for quitting = 3902 - 3786<br>The final analytical sample size was 21 196, including all current, former and never smokers. Among those, 3902 were current every day smokers and 3786 were former smokers.<br><br>Response rate: 90% of eligible | Independent variable:<br>Menthol status<br><br>Outcome Variables: (i)proportion of quit attempt in the past year (ii) time since quitting<br><br>Current smokers: smoked at least 100 cigs and smoke some or every day<br><br>Former smokers: smoked at least 100 cigs and currently do not smoke | Menthol smokers had higher levels of quit attempts compared with non-menthol smokers; differences were as great as 10–20%<br><br>Among white women menthol smokers had abstained about 2.5 years longer than non-menthol smokers ($p < 0.01$) | • No data if respondents started and remained smoking menthol or non-menthol cigarettes |



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|---|---|---|---|---|---|
| | | households.<br>Percent cigarette type and each racial/ethnic group: See attachment A | | | |
| Delnevo et al. Examining the relationship between menthol smoking and cessation using data from the 2003 and 2006/7 Tobacco Use Supplement 2010 submission. NCI and CDC | Cross-sectional survey; analysis of 2003 and 2006/07 Tobacco Use Supplements to the Current Population Survey: multistage clustered probability sampling | Sample size ranged from 71,193 to 24,465 (depending on criteria used for inclusion)<br><br>Response rate: The individual level self response rates for the 2003 TUSCS were 65.8%, 63.6%, and 61.4% for February, June, and November, respectively, and for the 2006/07 TUS the response rates were 60.7%, 61%, and 64.3% for May, August, and January respectively<br><br>N in each ethnic/racial group: See attachment B | Independent Variables:<br>Menthol status<br><br>Outcome Variables:<br>Cessation operationalized as current and former smokes who quit within the past 5 years who did not report current other tobacco products.<br><br>Former smoker deified as having smoked 100+ cigs in lifetime and now smokes 'not at all.'<br><br>Current smoker defined as having smoked 100+ cigs in lifetime and now smoke 'everyday' or 'some days'<br><br>Menthol use defined as self-report if usual brand in past 12 months (or 12 months prior to quitting) was mentholated | Current smokers who quit in the past 5 years, menthol vs. non-menthol cigarettes<br>AOR (95% CI)<br>Total 0.92 (0.88-0.97)<br>White 0.94 (0.89-0.999)<br>Black 0.78 (0.64-0.95)<br>Hispanics 0.96 (0.81-1.13)<br><br>If Hispanics are divided by country of origin, AORs are 1.34 (1.04- 1.73) for Mexicans and 0.63 (0.40-098) for Puerto Ricans.<br><br>Additional details on the covariates and AORs by the 5 sample restrictions available in Appendix X. | • Replication of Gundersen et al while addressing limitations of that paper. |
| Fagan P, Augustson E, Backinger CL, O'Connell ME, Vollinger RE Jr, Kaufman A, Gibson JT. Quit attempts and intention to quit cigarette smoking among young adults in the United States. 2007 National Cancer Institute | Cross-sectional survey; analysis of 2003 Tobacco Use Special Cessation Supplement (TUSCS) to the Current Population | Total N=33983 smokers and nonsmokers (Table 1 in article).<br><br>Analysis included young adult current smokers aged 18 to 30 years old: N=7912<br><br>Response rate: 82.8%:, 76% were self-respondents and were eligible for the entire TUSCS<br><br>Percent ethnic in each group Hispanic: 19% | Independent variable:<br>Menthol status<br><br>Outcome Variables:<br>Number of quit attempts and a serious intention to quit<br><br>- *Quitting behaviors.* Quit attempts were assessed by asking current smokers, "How many times during the past 12 months have you stopped smoking for 1 day or longer because you were trying to quit smoking?" Responses were | Multivariate logistic regression of 1 or more quit attempts during the past 12 months among menthol vs. non-menthol smokers showed OR (95% CI) was 1.00 (0.89-1.16) for current smokers, 1.00 (0.85-1.18) for daily smokers and 0.99 (0.62-1.41) for nondaily smokers.<br><br>Multivariate logistic regression of 1 or more quit attempts during the past 12 months among smokers who reported serious intention to quit within the next 6 months showed non-significant effects of metnol among current smokers and daily smokers. However among non-daily smokers, the OR (95% CI) was 1.35 (0.60-3.03) | • Small sample sizes for racial/ethnic among nondaily smokers |



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|---|---|---|---|---|---|
| | | 2 or more races: 2%<br>Non-Hispanic White: 61%<br>Non-Hispanic Black: 13%<br>Non-Hispanic Asian/ Pacific Islander: 5%<br>Non-Hispanic American Indian/Alaska Native: 0.7% | categorized into 1 or more quit attempts and zero quit attempts. The intention to quit was assessed by asking smokers, "Are you seriously considering quitting smoking within the next 6 months?" and included the responses yes or no.<br><br>Current smokers defined as smoked every day (daily smokers) or some days (nondaily smokers).<br><br>Menthol status defined as menthol or non-menthol as usual cigarette type or no usual type. | but non-significant.. | |
| Fagan et al. Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns. 2010 National Cancer Institute. | Cross-sectional survey; analysis of 2003 and 2006/07 Tobacco Use Supplements to the Current Population Surveys | Daily current smokers aged 18+ (*n* = 46 273)<br><br>Response rate: 82.9% and 82.6%<br><br>Menthol=11,671; NM=33, 644<br><br>For the number of individuals in each ethnic group by usual cigarette brand smoked, refer to Attachment C. | Independent Variable:<br>Menthol status<br><br>Outcome Variable:<br>--Number of times during the past 12 months quit for one day or longer because trying to quit<br>--Longest period of abstinence in last 12 months because trying to quit smoking<br>--Intention to quit (planning to quit in next 30 days)<br><br>Current daily smoking defined as smoked at least 100 cigarettes and smoking every day<br><br>Menthol status defined as usuabrand of cigarettes as being menthol or non-menthol | Multivariate models did not show sig. associations between usual brand of cigs and quit attempts 1 day or longer in past 12 months: OR (95% CI) ranged from 0.92 (0.83-1.02) to1.10 (0.91-1.34) depending upon cigarettes smoked per day<br><br>Multivariate models did not show sig. associations between usual cig brand duration of smoking abstinence 2 weeks vs. ≤ 2 weeks in the past 12 months: OR (95% CI) ranged from 0.93 (0.79-1.12) to1.05 (0.82-1.36) depending upon cigarettes smoked per day | |
| Gundersen DA, Delnevo CD, | Cross-sectional survey; analysis of 2005 U.S. | N=7815 white, black, and Hispanic current and former | Independent Variable: Menthol status | Menthol smokers were less likely than nonmenthol smokers to be former smokers | • Who quit long ago may be more |



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|---|---|---|---|---|---|
| Wackowski O. Exploring the relationship between race/ethnicity, menthol smoking, and cessation, in a nationally representative sample of adults. 2009 Funding source not explicitly stated | National Health Interview Survey —Cancer Control Supplement (NHIS-CCS). | cigarette smokers who indicated that they do not currently use other tobacco products and have made a quit attempt.<br><br>Response rate: NA<br><br>Menthol smokers : 26.5%<br>Non-menthol smokers: 73.5%<br><br>Percent ethnic in each group<br>White: 82.7%<br>Black: 8.9%<br>Hispanic: 8.4% | Outcome Variable: Cessation operationalized as current vs. former smoker<br><br>Former smoker is defined as having smoked 100 cigarettes in a lifetime and now smoking "not at all."<br><br>Current smoker is defined as having smoked 100 cigarettes in a lifetime and now smoking "everyday" or "some days."<br><br>Menthol use defined as whether or not their usual brand of cigarettes in the past 12 months or in the 12 months prior to quitting was mentholated. | (56.9% vs. 61.5%; p<0.01). This relationship was found among blacks (43.7% vs. 62.1%; p<0.01) and Hispanics (48.5% vs. 61.2%; p<0.001), but was not statistically significant among whites (62.8% vs. 61.6%, p=0.44).<br><br>The odds of being a former smoker does not differ statistically or substantially relative to nonmenthol smokers (AOR=1.05, p=.47; Model 1) after controlling for demographics, smoking behavior, and perceived risk of cancer. White menthol smokers are more likely to be former smokers than their nonmenthol smoking counterparts, while black and Hispanic menthol smokers are less likely to have quit relative to black and Hispanic nonmenthol smokers respectively. Among non-whites (i.e. blacks and Hispanics collapsed) menthol smokers are less likely to have quit relative to nonmenthol smokers (AOR=0.55, p<0.01).<br>AOR (95% CI)<br>White: 1.17 (1.00-1.36)<br>Blacks: 0.78 (0.56-1.09)<br>Hispanic: 0.61 (0.39-0.97)<br>Non-white: 0.55 (0.43-0.71) | subject to recall bias on variables such as number and type of cigarettes smoked compared to more recent quitters or current smokers |
| Hyland & Kasza. A Longitudinal Study of the Association Between Menthol Cigarettes and Indicators of Dependence: Findings from the International Tobacco Control Project 2010. National Cancer Institute<br>Canadian Institutes for Health | Cohort survey; analysis of International Tobacco Control Four Country Survey ITC-4, which is an ongoing prospective cohort survey conducted with nationally representative respondents from four countries, including the United States. | Data were collected from 7532 adult smokers (18 years +) between 2002 and 2008. Random digit dialing was initially used to recruit current smokers within strata defined by geographic region and community size. Respondents who agreed to participate (cooperation rate ~80%) were typically contacted and completed a 35-minute survey designed to evaluate the | Independent variable:<br>Menthol status<br><br>Outcome variables:<br>-Making a quit attempt – respondents were asked: "Have you made any attempts to stop smoking since we last talked with you?"<br>-Successful smoking cessation defined as no longer smoking on at least a monthly basis<br>-Successful cessation among those making a quit attempt | In terms of quit attempts and quit outcomes, white respondents who smoked menthol cigarettes were significantly less likely to report making a quit attempt compared to white respondents who smoked non-menthol brands (0.84). No differences were seen in African Americans and Hispanics.<br><br>No significant differences were observed in successful smoking cessation across all races, except African American women who smoked menthols were more likely to report successful cessation (3.58) and cessation among attempters | • Sample sizes were relatively small among minority racial/ethnic groups. |



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|---|---|---|---|---|---|
| Research, Australian National Health and Medical Research Council, Australian Commonwealth Department of Health and Aging Cancer Research UK, Canadian Tobacco Control Research Initiative, Centre for Behavioural Research and Program Evaluation of the National Cancer Institute of Canada/Canadian Cancer Society | | psychosocial and behavioral impact of various national-level tobacco control policies.<br><br>Menthol smokers: 27%<br>Non-menthol smokers: 73%<br><br>Percent/number in each ethnic group<br>White: 79%<br>African-American: 11%<br>Hispanic 5%<br>Asian: 1%<br>Native American:4% | | at quitting (OR 3.96) than African American non-menthol smokers. | |
| Stahre M., Okuyemi K.S., Joseph A.M., Fu S.S. Racial/ethnic differences in menthol cigarette smoking, population quit ratios and utilization of evidence-based tobacco cessation treatments. 2010 Funding source not explicitly stated | Cross-sectional survey; analysis of 2005 National Health Interview Survey (NHIS). | 6055 current adult smokers. Of these; 3068 male, 4932 White, 861 African American, 54 AI/AN, 119 Asian, average # cpd = 16.8, 1700 menthol smokers, 4355 non-menthol smokers<br><br>5949 former smokers. Of these; 3058 male, 5147 White, 573 African American, 45 AI/AN, 98 Asian, average # cpd = 18.6, 1515 menthol smokers, 4434 non-menthol smokers | Independent variable:<br>Menthol status by racial/ethnic groups<br><br>Outcome Variables:<br>Population quit ratio: dividing the total number of former smokers by the total number of individuals who had reported smoking during their life-time (i.e. both former and current smokers).<br><br>Current smokers not defined<br><br>Former smokers defined as individuals who had reported quitting smoking within the previous 12 months.<br><br>Current smokers were also asked whether they had attempted to quit smoking within the past year.<br><br>Menthol cigarette status defined as | Of current menthol smokers, 49% reported a quit attempt in the past year, while 41% of non-menthol smokers reported a quit attempt. In addition, the quit ratios were significantly higher for non-menthol versus menthol smokers (50% versus 47%, $P = 0.014$).<br><br>No significant difference in the quit ratios for menthol versus non-menthol smokers for whites (52% versus 50%), Asian Americans (38% versus 42%), AI/AN (52% versus 35%) or Hispanics (40% versus 45%). However, significant differences in the quit ratio for menthol versus non-menthol among African American smokers (34% versus 49%, $P < 0.001$). African American menthol smokers were significantly less likely than white nonmenthol smokers to have quit smoking (AOR: 0.72, 95% CI: 0.53, 0.97, $P$-value 0.031) after controlling for age group, sex, region, marital status and average number of cigarettes smoked per day | : |



* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| | | | whether or not respondent's usual brand of cigarettes was mentholated. | | |
| Trinidad D, Perez-Stable EJ, Messer K, White M, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. 2010 Funding source not specified | Cross-sectional survey; analysis of 2003 and 2006-2007 Tobacco Use Supplements to the Current Population Survey (TUS CPS). | Respondents ages 20-65 years at the time of the survey.<br><br>Total N=283,441; 25,758 (Af-Am), 10,853 (Asian), 28,720 (Hispanic), 2,616 (Native American), 212,693 (White)<br><br>Among current smokers – 14,791 were menthol smokers vs 42,352 non-menthol smokers.<br><br>Among former smokers who had quit less than 6 months ago; 2,876 were menthol smokers, 9707 were non-menthol smokers<br><br>Among smokers who had quit smoking for 6+ months prior to the survey; 950 were menthol smokers, 3015 were non-menthol smokers<br><br>Response rate: CPS response rate 92%. Survey includes proxy and self-response data. Response rate for self-response data (only self-response data was used in this article) – 61% | Independent Variables:<br>Menthol status by racial/ethnic group<br><br>Outcome Variables:<br>-Quit attempts: Current smokers were asked if they made an attempt to quit in the past 12 months, and, if so, the length of their longest quit attempt and the length of their last quit attempt.<br>-Quitting intentions: Current smokers were asked if they were seriously considering quitting smoking within the next 6months (yes/ no). Current smokers were also asked to assess how likely they thought they would succeed in quitting smoking altogether in the next 6 months.<br>-Quitting success: Among former smokers, successful smoking cessation/ long-term quitting was defined as being quit for at least 6 months at the time of the survey.<br><br>Menthol status defined as response to question on their brand preferences (menthol, non-menthol or no usual brand). Former smokers were asked to think to the year before they quit and identify their brand preference. Those who reported having no usual brand were excluded from statistical modeling analyses. | African Americans and Hispanics/Latinos who smoked mentholated cigarettes were significantly more likely to be seriously considering quitting in the next 6 months compared to those who smoked nonmentholated cigarettes [African Americans: odds ratio (OR) = 1.62, 95% CI: 1.35–1.95; Hispanics/Latinos: OR = 1.21, 95% CI: 1.00–1.47]. No suggestion of a similar relationship was found among Asian Americans/ Pacific Islanders, Native Americans/Alaska Natives or non-Hispanic whutes,<br><br>African Americans and Hispanics/Latinos who smoked mentholated cigarettes were significantly more likely to have a positive estimation of quitting successfully in the next 6 months compared to those who smoked nonmentholated cigarettes (African Americans: OR = 1.87, 95% CI: 1.60–2.19; Hispanics/Latinos: OR = 1.34, 95% CI: 1.11–1.62). This was not found among Asian Americans/Pacific Islanders, Native Americans/Alaska Natives and non-Hispanic whites.<br><br>Those who smoked mentholated cigarettes were significantly less likely to have quit successfully for at least 6months, for all racial/ethnic groups except Native Americans/Alaska Natives (African Americans: OR = 0.23, 95% CI: 0.17–0.31; Asian Americans/ Pacific Islanders: OR = 0.22, 95% CI: 0.11–0.45; Hispanics/Latinos: OR = 0.48, 95% CI: 0.34–0.69; Native Americans/Alaska Natives: OR = 0.49, 95% CI: 0.14–1.71; non-Hispanic whites: OR = 0.28, 95% CI: 0.25–0.33). | .<br>Pure copy paste from the cited paper |



* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

# Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Independent & Outcome Variables | Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article) | Comments |
|---|---|---|---|---|---|
| | | | Current and former smoker defined as lifetime cigarette use (Have you ever smoked 100 cigarettes?') Current cig use defined as smoking every day or some days; former smoker as not smoking at all. | | |

Note: Please see text for information on embargoed study by Levy et al., in press



* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions. Please read the entire article.

**Table 7** Main Characteristics and Findings of Longitudinal Cohort and Clinical Trial Studies Comparing Smoking Cessation Outcomes in Menthol and Nonmenthol Cigarette Smokers (additional information added to Table in Foulds et al., 2010)

| Author (publication year) / study years | Location | N M / NM | *N*—W / AA / Hisp / Other | Cigarettes / day (M / NM) | Design | Intervention? | Definition (of a quitter) | Evidence of M effect? | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Fu et al. (2008)/2006 | United States—VA pharmacy databases | Total = 1,343<br>M = 342 (25%)/<br>NM = 1,001 (75%)<br>*M* age = 56 (10.3) | All smokers:<br>Caucasian: 76%<br>AA: 14%<br>Other: 10% | Total: 25<br>M: 20<br>NM: 30 | Cross-sectional analysis at end of interventional trial | Intervention aimed to stimulate repeat quit attempts<br>All participants had previously failed using NRT or bupropion | Seven-day point prevalence, self-reported | No overall effect of M on abstinence. Some evidence of increased quitting among menthol smokers, restricted to intervention group, with lower menthol quitting in controls. | Older sample. One significant interaction between menthol status and treatment group only, not significant after Bonferroni correction |
| Cropsey et al. (2009)/ 2004–2006 | Women's prison in Virginia | N=233<br>M=159<br>NM=74<br>*M* age = 34 | W = 109 (49% M)<br>AA = 124 (95% M)<br>(all female) | W = 20<br>AA = 14 | Retrospective analysis of trial cohort. | Randomized trial of NRT plus group, versus wait list control | Seven-day point prevalence by self-report (and exhaled CO < 3 ppm) at 6 weeks and 12 months. | No effect of menthol | Relatively small sample of incarcerated women (only six AA nonmenthol smokers) |
| Gandhi et al. (2009)/ 2001–2005 | Outpatient Smokers' Clinic Central New Jersey | Total = 1688<br>M = 778 (46%)/<br>NM = 910 (54%)<br>*M* age = 42 (13.3) | 1086/374/149/79<br>64%/22%/9%/5% | Total sample: 21<br>M: 19<br>NM: 23 | Clinic cohort, followed up at 4 weeks and 6 months. | Tailored Smoking cessation treatment with meds and counseling | Self-report of not smoking in previous 7 days at 4 weeks and 6 -month follow-up. Biochemical verification in those attending at 4 weeks. | Yes, but restricted to non-whites. Also related to *SES*. For AAs at 6 months, Adj. OR = 0.48 (0.25–0.9) | Cigarettes/day lower in AA and H menthol smokers. Follow-up rate= 74% at 4 weeks and 58% at 6 months. |
| Okuyemi et al. (2007)/ 2003–2004 | Kansas | 755 light smokers (<11 cigarettes/day) *M* age = 45.1 (*SD* = 10.7) | 0/755/0/0 | M: 7.5<br>NM: 7.8 | Clinical trial cohort followed up at 6m. | Nicotine gum × motivational interviewing trial (factorial) | Seven-day point prevalence, verified by CO/salivary cotinine at 6-month follow-up | Yes, unadjusted: 11.2% vs. 18.8% | M not significant in fully adjusted model (overadjusted by using number of appointments attended?) (Nollen et al. 2006); M effect stronger in age < 50 |
| Okuyemi et al. (2003)/ | Kansas | 600 smokers (471/129) | 0/600/0/0 | M: 18<br>NM: 18 | Clinical trial cohort followed up at 6m. | Bupropion versus placebo | Seven-day point | Yes, in subgroup. At 6 weeks in | No significant effect at 6 months or in age |

| Author (publication year) / study years | Location | N M / NM | *N*—W / AA / Hisp / Other | Cigarettes / day (M / NM) | Design | Intervention? | Definition (of a quitter) | Evidence of M effect? | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1999–2000 | | *M* age = 44 | | | | randomized controlled trial | prevalence, verified by CO/salivary cotinine | age < 50: OR (NM) 2.02 (1.03–3.95) | > 50 |
| Murray et al. (2007) / 1986–2001 | United States | Total = 5,883<br>M = 1,216 (21%) /<br>NM = 4,671 (79%)<br>*M* age = 48.4 (*SD* = 6.8) | White:95.2%<br>AA: 3.8%<br>H: 0.6% | Overall average 26 cigarettes/ day<br>Pack-years:<br>M: 38.18<br>NM: 40.1 | Clinical trial cohort followed up 5 and 14 years after enrollment | 12-week group intervention plus nicotine gum (repeatable for 5 years) or usual care | Smoking at all in past 12 months | Three categories: sustained quitter, intermittent smoker, continuing smokers; no menthol effect | Only 114 AA menthol smokers in the study. |
| Pletcher et al. (2006) / 1985–2000 | Birmingham, Chicago, Minneapolis, and Oakland | 1535 smokers (972/563)<br>*M* age= 25.1 (3.6) | 657/878/0/0 | M: 10<br>NM: 15 | Prospective cohort study | No | *Sustained cessation*: not current smoker at last 2 visits<br>*Relapse*: smoker → nonsmoke → smoker at last exam | Yes<br>*Sustained cessation*: Adj. OR = 0.71(0.49-1.02)<br>*Relapse*: Adj. OR = 1.89 (1.17–3.05) | Long-term study, not in context of a quit attempt |
| Muscat et al. (2002) / 1981–1999 | Hospitals in New York, Washington DC, and Pennsylvania | Total = 19545 NM = 16540 (85%)<br>M = 3005 (11%) 56%–72% aged > 54 | W = 17,637 (89%)<br>AA = 1906 (11%) | W:<br>NM = 29<br>M = 28<br>AA<br>NM = 21<br>M = 18 | Cross-sectional case-control study based on convenience sample of cases (lung cancer) and controls (other medical patients) | No intervention | Ever smoked daily for a year and not smoked daily in past year. | No effect on quitting<br>OR = 1.1 | Older and relatively affluent sample, with unusually low menthol rate in AAs (34%).<br>Definition of abstinence relatively lenient.<br>Possible effect of illness on quitting. |

| Author (publication year) / study years | Location | N M / NM | *N*—W / AA / Hisp / Other | Cigarettes / day (M / NM) | Design | Intervention? | Definition (of a quitter) | Evidence of M effect? | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Hyland et al. (2002) / 1988–1993 | 22 communities in North America | *N* = 13,268 (age 25–64) M = 3,184 (24%) / NM = 10,084 (76%) 23% Whites smoke M, 57% AAs smoke M. 51% ages < 45 | All smokers: Caucasian: 10,004 (75%) AA: 878 (7%) Hispanic: 693 (5%) Other: 294 (2%) Canadian: 1,382 (10%) | Total sample: 23.2/day | Prospective population cohort survey, followed up after 5 years. | Randomized community intervention trial | Self-report of no cigarette use in past 6 months at 5-year follow-up. | No. (e.g., adjusted RR for quitting by AA menthol smokers = 1.04.) | M smokers more likely to have 2+ prior quit attempts. No data on whether participants tried to quit. |
| **Unpublished November 2010 submissions to FDA** | | | | | | | | | |
| Hyland, Rivard et al. (2010a) | 22 communities in North America | N=2095 M=400 NM=1464 Other=222 | W=866 AA=91 | | Prospective population cohort survey, assessed in 2005; Menthol status 1988-2001. | Randomized community intervention trial | Self-report of no cigarette use in past 6 months in 2005 | No effect on quitting OR: 0.84 | Sample size too small for AA |
| King et al. | Outpatient smokers clinic Chicago | N=291 M=126 NM=155 | W=181 B=110 | | Clinical trial cohort followed up at 4 and 12 weeks | NRT vs. NRT plus naltrexone | CO verified prolonged abstinence | Significant med x menthol interaction in AA (OR=31.22, p=0.029) | AA menthol vs. nonmenthol smokers who used NRT only did worse |
| Rietzel a | Outpatient clinic Houston TX | N=420 M=175 NM=245 | W=138 B=143 Latino=139 | M=20.7 NM=21.5 | Clinical trial cohort followed up to 26 weeks | NRT plus counseling | CO verified no smoking since quit date | Menthol did not predict abstinence | |
| Rietzel b | Outpatient clinic | N=391 M=321 | B=391 | M=20.6 NM=21.0 | Clinical trial cohort | Treatment with palm pilot | CO verified no | Menthol did not predict | |

| Author (publication year) / study years | Location | N M / NM | *N*—W / AA / Hisp / Other | Cigarettes / day (M / NM) | Design | Intervention? | Definition (of a quitter) | Evidence of M effect? | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | Houston, TX | NM=70 | | | followed up to 26 weeks | computers | smoking since quit date | abstinence | |
| Rietzel c | Outpatient clinic Houston, TX | N=249 M=125 NM=124 | W=88 B=81 Latina=75 Other=5 | M=9.2 NM=11.1 | Clinical trial cohort followed up to 26 weeks | Motivation based treatment for pregnant women | CO verified no smoking since quit date | Menthol did not predict abstinence | Post-hoc analysis showed White menthol vs. non-menthol smokers did worse (small n) |

- *Note.* M = menthol; NM = nonmenthol; OR= odds ratio; RR= relative risk; adj. = adjusted for other baseline variables; CO = exhaled carbon monoxide concentration; AA= African American; W = white (non-Hispanic); H = Hispanic/Latino; *M* age = mean age of sample; SES = Socioeconomic status; NRT = Nicotine Replacement Therapy.
- ***Note:*** **Please see text for embargoed study by Blot et al., in press.**

## CHAPTER 7: EFFECTS OF MENTHOL ON THE DISEASE RISKS OF SMOKING

### INTRODUCTION

This chapter addresses the question: Do smokers of menthol cigarettes have increased risk for diseases caused by smoking in comparison with smokers of non-menthol cigarettes? In the TPSAC conceptual framework, this question is directed at the relative risks for development of the various diseases caused by smoking with the comparison being between users of non-menthol cigarettes as the reference. Risks could be greater or lesser for smokers of menthol cigarettes if the various toxins and carcinogens in smoke differ by type of cigarette; if smoking patterns differ by type of cigarettes in ways that affect the doses of disease causing-agents reaching target sites; if menthol affects the kinetics and metabolism of disease-causing tobacco smoke components; and if menthol itself contributes to disease risk.

Multiple lines of research are relevant to the overall question that is the focus of this chapter. These include: (1) studies directed at the topography of smoking; (2) studies comparing levels of biomarkers of tobacco smoke in smokers of menthol and non-menthol cigarettes; (3) studies on the toxicology of menthol; and (4) epidemiological studies that directly compare disease risks in smokers of menthol compared with non-menthol cigarettes.

### STUDIES OF SMOKING TOPOGRAPHY

An important question in assessing risks of smoking menthol cigarettes is whether menthol cigarette smokers inhale more smoke and are exposed to more tobacco smoke toxins than smokers of non-menthol cigarettes. This question has been examined in two types of studies. The first type involves laboratory studies that compare puffing behaviors (called topography studies) or the increase (boost) of nicotine and/or carbon monoxide levels from smoking a cigarette in individual menthol and non-menthol smokers. This section reviews such studies. The second consists of cross-sectional studies in which tobacco smoke exposure biomarkers are measured in people smoking cigarettes, typically their usual brand of cigarette, and menthol and non-menthol smokers are compared. A subsequent section considers these studies.

Before describing the various studies, it is important to mention important potential confounding factors and other methodologic problems that are relevant to a number of studies. Since most African American smokers smoke menthol cigarettes and most whites smoke non-menthol cigarettes, any comparison of menthol vs. non-menthol without considering race is problematic. African American and white smokers differ in several relevant ways. On average African Americans smoke fewer cigarettes per day, take in more smoke per cigarette and metabolize nicotine and cotinine differently than white smokers (Perez-Stable et al. 1998). Some studies statistically control for race, but "control" may not be possible, given the high proportion of African Americans who smoke menthol cigarettes. The optimal study design compares menthol vs. non-menthol smokers within a racial group, but few studies have adequate numbers to do this. Also, a number of the published studies, particularly the topography studies, are quite small and predominantly include adult heavy smokers recruited by advertisements for

experimental studies. This approach to identifying participants limits the generalizability of findings. Furthermore, topography studies generally measure puffing behavior while smoking one cigarette via a cigarette holder, to which monitoring equipment is attached. Smoking a single cigarette through a cigarette holder is not representative of how a person normally smokes their cigarettes throughout the day. Several studies have involved rapid smoking of cigarettes or smoking with fixed puff sizes or fixed numbers of puffs, also experimental scenarios that are not representative of usual smoking.

Eleven laboratory studies of topography were identified (table 1). These studies varied considerably in design, but included at least some measurement of smoking behavior: number of puffs per cigarette, average puff volume, total puff volume, time to smoke the cigarette and/or biomarker measurements: increase in nicotine and/or carbon monoxide levels before and after smoking a cigarette.

Nine studies reported effects of menthol smoking on number of puffs or puff volume (Nil and Battig 1989; Caskey et al. 1993; Miller et al. 1994; Ahijevych et al. 1996; Jarvik et al. 1994; McCarthy et al. 1995; Ahijevych and Parsley 1999; Pickworth et al. 2002; Strasser et al. 2007). Some studies compared smokers smoking their preferred type of cigarette while some were crossover studies. Some studies reported a decrease, one reported an increase, and others saw no change in puffing behavior comparing menthol to non-menthol cigarette smoking. Jarvik et al. (1994) also compared inhaled volume and lung retention time and found no effect of menthol cigarettes. St Charles et al. (2009) similarly reported no effect of smoking menthol cigarettes on inhalation volume or total lung exposure times, although the inhalational tidal ratio (the inhalation volume as a proportion of resting tidal volume) was borderline lower in menthol (1.52, SD 0.47) compared to non-menthol (1.79, 0.60) smokers ($p = 0.054$).

Six studies reported CO boost in relation to type of cigarette smoked (Nil and Battig, 1989; Miller et al. 1994; McCarthy et al. 1995; Jarvik et al. 1994; Ahijecych et al. 1996; and Pickworth et al. 2002). In general there were small or no differences between the CO boost by type of cigarette. Miller et al. (1994) found that CO boost was higher from smoking cigarettes into which 8 mg menthol had been injected compared to lower levels, despite no change in puff volume. Two other studies also found that the increase in CO in relation to puff volume or number of puffs was higher in smokers of menthol cigarettes compared with non-menthol cigarettes.

Patterson et al. 2003 measured the plasma nicotine boost in treatment-seeking smokers and in a multivariate analysis found no effect of menthol cigarette smoking.

Overall, there is little evidence from laboratory studies that the presence of menthol in a menthol cigarette increases the extent of inhalation of smoke from a cigarette. Some studies suggest that menthol might selectively enhance absorption of CO. However, the generalizability of this finding is uncertain since the subjects in these studies were all experienced adult daily smokers. There are no data on the effect of menthol cigarettes on inhalation parameters in novice smokers, and or in light and intermittent smokers. The latter group is important because there is strong evidence that people who smoke fewer cigarettes per day inhale more smoke per cigarette. Additionally, African Americans are more likely to be light smokers. Since African Americans predominantly smoke menthol cigarettes, it is

important to determine whether menthol facilitates inhalation of large volumes of smoke in those who are smoking few cigarettes per day.

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| 1. Ahijevych, K., Gillespie, J., Demirci, M., Jagadeesh, J., 1996. Menthol and nonmenthol cigarettes and smoke exposure in African American and white women. Pharmacology Biochemistry and Behavior 53, 355–360. | Two-factorial design | N = 37 women stratified by race and menthol or nonmenthol cigarettes<br><br>18 AA/8 menthol<br><br>19 white/10 menthol | Blood nicotine and cotinine and expired air carbon monoxide was measured before and after smoking one of her usual cigarettes. Subjects' smoking and respiratory topography were measured. | Nicotine and expired CO boost; number of puffs, puff volume and total puff duration. | There were significant main and interaction effects of race and menthol/nonmenthol cigarette use on CO boost. African American women had a mean CO boost of 10.1 ppm vs. 7.2 ppm for white women, while women using nonmenthol cigarettes had a higher CO boost (mean = 10.6 ppm) compared to those regularly using menthol cigarettes (mean = 6.5 ppm). African American women had nonsignificantly higher puff volumes compared to white women (mean – 48.4 vs. 43.5 ml), while nonmenthol smokers had nosignificantly higher puff volumes than menthol smokers (mean = 48.5 vs. 42.7 ml). Lower CO boost with mentholated cigarettes suggests factors beyond mentholation may affect elevated smoke constituent exposure among African American women. | Strengths include groups balanced race and mentho<br><br>Weaknesses include small N, research volunte all heavy smoker women only, limi generalizability. |
| 2. Ahijevych, K., Parsley, L.A., 1999. Smoke constituent exposure and stage of change | Two-factorial design | N = 95 women stratified by ethnicity and menthol/nonmenthol preference | Respiratory and puffing topography were measured during the cigarette smoking | Puff volume | Menthol smokers had significantly larger puff volumes compared to nonmenthol smokers | Strengths include groups fairly well balanced by race and menthol. Weaknesses |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| in African American and white women cigarette smokers. Addictive Behaviors 24, 115–120. | | 48 AA/27 menthol<br><br>47 White/22 menthol | bout. | | | include women o |
| 3. Caskey, N.H., Jarvik, M.E., McCarthy, W.J., Rosenblatt, M.R., Gross, T.M., Carpenter, C.L., 1993. Rapid smoking of menthol and non-menthol cigarettes by African American and white smokers. Pharmacology Biochemistry and Behavior 46, 259–263. | Repeated-measures cross-over design | Two independent groups of male cigarettes smokers. One group (N = 12) characterized themselves as predominantly menthol cigarette smokers and other as non-menthol smokers (N = 16).<br><br>25 AA/9 menthol<br><br>11 white/3 menthol | Subjects participated in a modified rapid smoking procedure in two sessions, 1 week apart. In one session, subjects smoked regular cigarettes and in the other, they smoked menthol cigarettes. Subjects puffed cigarettes every 15 seconds until they were unable to continue. | Number of puffs<br><br>Expired CO boost | No difference was observed for the number of puffs taken or CO boost from regular compared to menthol cigarettes. | Weaknesses include small N, imbalance of rac and menthol; rap smoking differs fi usual way of smoking. |
| 4. Clark, P.I., Gautam, S., Gerson, L.W., 1996. Effect of menthol cigarettes on biochemical markers of smoke exposure among African American and white smokers. Chest 110, 1194–1198. | Cross-sectional | N = 65 AA and N = 96 white adult smokers<br><br>65 AA/54 menthol<br><br>96 white/22 menthol | Subjects were asked to smoke one cigarette and carbon monoxide levels were measured. | Expired carbon monoxide | The mean unadjusted expired-air carbon monoxide levels were not significantly higher in menthol smokers (40.3 ppm) compared to nonmenthol smokers (35.8 ppm; p=0.09). However, menthol was a significant contributor to expired-air carbon monoxide levels after adjusting for cigarettes per day and amount of each | Weaknesses include imbalanc or race and ment |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| | | | | | cigarette smoked | |
| 5. Jarvik, M.E., Tashkin, D.P., Caskey, N.H., McCarthy, W.J., Rosenblatt, M.R., 1994. Mentholated cigarettes decrease puff volume of smoke and increase carbon monoxide absorption. Physiology and Behavior 56, 563–570. | Crossover | N = 20 smokers<br><br>10 AA/5 menthol<br><br>10 white/5 menthol | All subjects smoked both types of cigarettes, one on each of two days, through puff monitoring device.. | Carbon monoxide boost<br><br>Number of puffs<br><br>Average puff volume<br><br>Total puff volume<br><br>Mean puff flow | Compared to regular smokers, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide, despite the fact that mentholated cigarettes decreased average and total cumulative puff volumes and increased mean puff flow rates of inhaled smoke. These chemical and topographic differences were independent of race. No significant differences in depth of inhalation of the smoke or the amount of insoluble smoke particulates delivered to or retained in the respiratory tract were noted between the two types of cigarettes. Mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide. | Strengths include balanced race ar menthol.<br><br>Weaknesses include small N a subjects randomized to smoke non-preferred cigaret |
| 6. McCarthy, W.J., Caskey, N.H., Jarvik, M.E., Gross, T.M., Rosenblatt, M.R., Carpenter, C., 1995. Menthol vs. non-menthol | Crossover | N = 29 male smokers<br><br>16 AA/ 8 menthol<br><br>13 white/3 menthol | Smokers smoked either a regular or a mentholated cigarette in two separate sessions 1 week apart. Commercial brands with comparable tar, | Number of puffs<br><br>Puff volume | When smoking the non-mentholated brand of cigarettes, participants smoked 22% more puffs and had 13% higher mean volumes per puff than they did when smoking the mentholated brand of cigarettes. The aggregate | Weaknesses: sm N, race and men imbalance, artific smoking procedu used one brand cigarettes, poor generalizabilty because of samp |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| cigarettes: effects on smoking behavior. American Journal of Public Health 85, 67–72. | | | nicotine, and CO content were used. Smoking behavior was constrained by fixed 15-second interpuff intervals but puff volume and number of puffs were unconstrained. | | 39% excess exposure of cigarette smoke in the regular-cigarette conditions was not accompanied by commensurate excesses in expired carbon monoxide or in physiological measures normally correlated with nicotine exposure. | characteristics |
| 7. Miller, G.E., Jarvik, M.E., Caskey, N.H., Segerstrom, S.C., Rosenblatt, M.R., McCarthy, W.J., 1994. Cigarette mentholation increases smokers' exhaled carbon monoxide levels. Experimental and Clinical Psychopharmacology 2, 154–160. | Crossover | N = 12 male smokers<br><br>Recruited from drug treatment program<br><br>All were AA/6 menthol | 3 smoking sessions spaced 1 week apart. In each session, subjects inhaled cigarette through smoking apparatus, one puff every 30 sec until 1200 cc of cigarette smoke was inhaled. Menthol dosage varied across sessions, such that subjects smoked experimental cigarettes that had been injected with 0 mg, 4 mg, or 8 mg of menthol. | Exhaled carbon monoxide boost<br><br>No puffs, puff volume | No effect of menthol on number or volume of puffs. The CO boost was 5.6, 6.1 and 8.1 ppm for 0, 4 and 8 mg menthol cigarettes (p < 0,004). | Weaknesses include small N, of subjects with drug abuse histo artificial smoking procedure, result in poor generalizability. |
| 8. Nil R, Battig K: Separate effects of cigarette smoke yield and smoke taste on smoking behavior. *Psychopharmacology (Berl)* | Crossover | N = 15; no data on usual brand menthol preference or race | Subjects came to laboratory weekly for 7 weeks. Each week a test cigarette or own brand was smoked. The test cigarettes include 2 menthol brands, | No puffs, average puff volume, puff volume per cigarette, expired CO boost | Significantly fewer puffs and smaller total puff volume in high tar menthol vs other brands during natural smoking; smaller total puff volume for high tar menthol vs other brands for 30 second-puff smoking | Weaknesses include small N, smokers not smoking preferre cigarettes, artifici smoking procedu |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| 1989, 99(1):54–59. | | | one high and one low tar. During each session the first cigarette was smoked naturally through a cigarette holder, the second was puffed every 30 seconds. | | | |
| 9. Patterson, F., Benowitz, N., Shields, P., Kaufmann, V., Jepson, C., Wileyto, P., Kucharski, S., Lerman, C., 2003. Individual differences in nicotine intake per cigarette. Cancer Epidemiology Biomarkers and Prevention 12, 468–471. | Clinical trial of nicotine replacement therapy for smoking cessation | N = 190 treatment-seeking smokers<br><br>120 white, 47 AA and 23 other race<br><br>55 menthol (no data by race) | Plasma nicotine levels measured before and after participants smoked one of their own brand cigarettes *ad libitum*. | Plasma Nicotine boost | Nicotine boost not significantly different in menthol vs nonmenthol cigarettes smokers. | Weaknesses: sample was treatment seeker generalizability, c studied nicotine boost after smok one cigarette in t middle of the day |
| 10. Pickworth, W.B., Moolchan, E.T., Berlin, I., Murty, R., 2002. Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery. Pharmacology, Biochemistry and Behavior 71, | Double blind experimental study | N = 18 menthol smokers (17 AA)<br><br>N = 18 nonmenthol smokers (3 AA) | Menthol and nonmenthol cigarette smokers participated in a single session during which three cigarettes were smoked 45 minutes apart, in random order. Cigarettes were research nicotine low yield (0.2 mg), commercial cigarettes (1.2 | Number of puffs<br><br>CO boost | No differences between menthol and nonmenthol cigarettes on number of puffs or CO boost were observed. | Weaknesses include small number of subjec race by menthol imbalance; smok smoked researcl cigarettes or commercial cigarettes but no their own brand. |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| 55–61. | | | mg) and research high nicotine yield (2.5 mg). Subjects smoked menthol or non-menthol on the basis of their usual brand. | | | |
| 11. St.Charles, F.K., Krautter, G.R., Dixon, M., Mariner, D.C., 2006. A comparison of nicotine dose estimates in smokers between filter analysis, salivary cotinine, and urinary excretion of nicotine metabolites. Psychopharmacology 189, 345–354. | Observational study | N = 74 smokers selected according to machine determined yield of usual cigarettes.<br><br>18 menthol smokers, race not specified. | A 5-day clinical study was conducted.<br><br>Filters were analyzed to estimate the daily mouth exposure of nicotine. Twenty-four-hour urine samples for nicotine equivalents. Saliva samples were collected daily for cotinine analysis. Respiratory pattern recording during smoking of selected cigarettes | Inhalation tidal ratio (ratio of inhalation volume / resting tidal volume) | Inhalation tidal ratio borderline higher in nonmenthol (1.79) compared to menthol (1.52) smokers (p = 0.054) | No Strengths or Weaknesses specifically noted authors. |
| 12. Strasser, A.A., Malaiyandi, V., Hoffmann, E., Tyndale, R.F., Lerman, C., 2007. An association of CYP2A6 genotype and smoking topography. Nicotine and Tobacco | Observational study | N = 119 participants enrolled in smoking cessation clinical | Subjects smoked a cigarette through in a cigarette holder attached to a puffing monitoring device. | Number of puffs<br><br>Mean puff volume<br><br>Total puff volume | Smoking topography variables did not differ significantly by level of nicotine dependence or cigarette mentholation (p values >0.2). | Weaknesses: subjects seeking smoking cessation treatment, smoking a single cigarette through cigarette holder, generalizability |

| Chapter 6 Table 1: Menthol Smoking and Topography | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| Research 9 (4), 511–518. | | | | | | |
| 13. Williams JM, Gandhi KK, Steinberg ML, Foulds J, Ziedonis DM, Benowitz, NL: Higher nicotine and carbon monoxide levels in menthol cigarette smokers with and without schizophrenia. *Nicotine and Tobacco Research* 2007, 9(8):873–881. | Observational study | N = 89 smokers with schizophrenia<br><br>N = 53 control smokers<br><br>Race…<br><br>Menthol…. | All subjects attended on the afternoon of a normal smoking day and provided a measure of exhaled CO and a blood sample approximately 2 min after smoking one of their usual cigarettes. | Expired carbon monoxide<br><br>Serum nicotine<br><br>Serum cotinine | Serum nicotine levels (27 vs. 22 ng/ml, p=.010), serum cotinine levels (294 vs. 240 ng/ml, p=.041), and expired CO (25 vs. 21 ppm, p=.029) were higher in smokers of menthol compared with nonmenthol cigarettes | Weaknesses: mi psychiatric and health study grou race by menthol imbalance,<br><br>generalizability |

**BIOMARKER STUDIES**

This section reviews studies that have compared biomarkers of exposure to tobacco smoke constituents in smokers of menthol and non-menthol cigarettes. Biomarker measurements provide a quantitative assessment of systemic exposure to cigarette constituents. Exposure biomarkers include measurement of nicotine intake (nicotine, cotinine and other nicotine metabolites), gas phase exposure (carbon monoxide and various volatile organic compounds) and particulate phase (the tobacco-specific nitrosamine NNAL and metabolites of polycyclic aromatic hydrocarbons). The biomarkers may be measured in blood, urine or saliva. Carbon monoxide (CO) is measured either as carboxyhemoglobin in blood or as CO in exhaled air. (For details about specific biomarkers of exposure to tobacco smoke, see chapter 3.)

Most biomarker studies are cross-sectional in design, involving comparisons of biomarker levels in menthol vs non-menthol cigarette smokers at a single point in time. Some studies have measured

biomarkers immediately before or after smoking a cigarette in a laboratory. Some additional, general methodologic issues warrant mention. All studies included adult daily smokers and the protocols for most studies required subjects to have smoked five or more cigarettes per day. Some urine samples were collected as spot urine samples and some as 24-hour collections. The latter are more accurate reflectors of daily exposure, but it is difficult to collect a full specimen from people in naturalistic settings. Correction for urine creatinine to deal with dilutional differences is useful. Many researchers do not report time from last cigarette to time of biomarker collection. Information on this interval may be needed as some biomarkers, like nicotine, have relatively short half-lives.

As previously discussed, there is the potential for confounding or modification of results by race in studies of menthol cigarettes. Racial factors are important in relation to interpreting cotinine levels. African Americans on average metabolize cotinine more slowly than whites (Perez-Stable et al 1998). Many studies show that cotinine levels are higher when normalized for cigarettes smoked per day in African Americans vs. whites (for example, Caraballo et al. 1998; Benowitz et al. 2009). Therefore higher cotinine levels in menthol smokers overall could result from a predominance of African Americans among the menthol cigarette smokers. Urine nicotine equivalents is a term used to describe the sum of nicotine and its metabolites, nicotine glucuronide, cotinine, cotinine glucuronide, trans-3' hydroxycotinine and its glucuronide, in urine. The sum of metabolites accounts for 85–90 percent of the nicotine doses and is a useful surrogate for nicotine intake that is not affected by racial differences (Hukkanen et al. 2005).

We have identified thirteen published cross-sectional studies and one unpublished tobacco company analysis of a cross-sectional study that compared biomarker levels in smokers of menthol and non-menthol cigarettes. We also describe one experimental study in which biomarkers of exposure were measured in smokers while smoking menthol or non-menthol cigarettes. Study design and results are summarized in table 2. Brief descriptions of the studies follow.

Wagenknecht et al. (1990) measured serum cotinine in 822 African American and 602 white smokers who were participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. In a multiple linear regression model which included race, age, sex, education, cigarettes per day, inhalation pattern, secondhand smoke exposure and machine-determined nicotine yield, African-American race was associated with substantially and highly statistically significantly greater cotinine levels compared to whites. Higher serum levels in African-Americans compared to whites were seen both in menthol and non-menthol cigarette smokers. The beta coefficient for race in the regression model was higher for menthol smokers (89.0 ng/ml) compared to non-menthol smokers (51.5 ng/ml), but no statistical comparison of these coefficients was presented by the authors.

Ahijevych et al. (1996) measured plasma cotinine in 37 women stratified by race and menthol cigarette smoking. Plasma cotinine tended to be higher in menthol (254 ng/ml) compared to non-menthol (204 ng/ml) smokers, but this difference was not significant. The ratio of plasma cotinine to cigarettes per day was higher in menthol (18.1 ng/ml/cig) compared to non-menthol (15.3 ng/ml/cig) smokers, but this difference also was not statistically significant.

Clark et al. (1996) measured serum cotininine in 65 African American and 96 white smokers who smoked at least five cigarettes per day. Serum cotinine levels overall in menthol (478 ng/ml) vs. non-menthol (349 ng/ml)smokers, and the difference (84 ng/ml) remained statistically significant in a linear regression analysis after controlling for race, cigarettes per day and amount of each cigarette smoked.

Mustonen et al. (2005) measured saliva cotinine in 51 African American and 256 white smokers of at least 10 cigarettes per day. Cotinine levels were higher overall in menthol vs. non-menthol smokers (476 ng/ml vs. 442 ng/ml), but the difference was not statistically significant. The cotinine per cigarette per day ratio was statistically significantly higher in menthol smokers, but this could be due at least in part to racial confounding. Analysis of covariance found several race x sex x menthol subgroup differences, but these cannot be readily interpreted as a general effect of menthol cigarettes.

Williams et al. (2007) measured serum nicotine and cotinine in 155 smokers, of which 89 had schizophrenia or schizoaffective disorder and 53 were healthy controls. Blood samples were collected two minutes after smoking one of their usual cigarettes. After adjustment for psychiatric diagnostic group, race and cigarettes per day, serum nicotine, serum cotinine and expired CO were statistically significantly higher in menthol cigarette smokers.

Signorello et al. (2009) reported serum cotinine levels in 130 African American and 125 white smokers. In a linear regression analysis adjusted for cigarettes per day, age, race and sex no significant effect of menthol brand was observed.

Muscat et al. (2009) measured plasma cotinine, urine cotinine, plasma thiocyanate (a biomarker of cyanide exposure) and urine NNAL (a metabolite of the tobacco-specific nitrosamine and carcinogen NNK) in 237 African American and 288 white smokers of at least 5 cigarettes per day. In a multiple regression analysis adjusted for cigarettes per day, age and sex and performed separately by race, there was no effect of smoking menthol cigarettes on these biomarkers. However, when NNAL was analyzed as the ratio of NNAL glucuronide / NNAL, the ratio was lower in menthol cigarette smokers. This finding was statistically significant, and along with the in vitro data presented in the paper, suggests that menthol may inhibit the glucuronidation of NNAL, which represents a detoxification pathway for this known carcinogen.

In a study conducted by Lorillard Tobacco Company, Heck et al. (2009) measured blood carboxyhemoglobin, urine nicotine and metabolites and urine total NNAL (24-hour urine collection) in 28 African American and 84 white smokers of at least 15 cigarettes per day. The menthol smokers appear to have been switched to a specified menthol brand for 3 weeks prior to sample collection. Statistically significant differences in biomarker levels comparing menthol and non-menthol cigarette smokers were not observed.

Ho et al. (2009) studied 755 African American light smokers (ten or fewer cigarettes per day) who were enrolled in a smoking cessation trial. This group included 569 menthol and 131 nonmenthol cigarette smokers. Menthol smokers smoked fewer cigarettes per day compared to nonmenthol smokers(7.07 vs 7.53, $p = 0.05$). However levels of expired CO and plasma cotinine were quite similar for the groups.

This suggests that the intake of CO and nicotine may be higher per cigarette for menthol compared to nonmenthol cigarettes, although that specific analysis was not presented by the authors.

In the Total Exposure Study supported by Altria Client Services, Wang et al. (2010) reported data from a large multi-center study involving 1,044 menthol cigarette smokers (448 African American and 596 white) and 2,299 non-menthol smokers (161 African American and 2,031 white). All had smoked at least one cigarette per day for a year, with a mean of 15.0 for menthol cigarette smokers and 16.8 for non-menthol smokers. Blood was collected for serum cotinine and blood carboxyhemoglobin and a 24-hour urine for nicotine equivalents was also obtained. In unadjusted analyses, urine nicotine equivalents per 24 hours and carboxyhemoglobin were significantly lower in menthol smokers. As seen in most other studies, African Americans smoked on average fewer cigarettes per day than whites, and the level of nicotine equivalents per cigarette smoked was on average higher in menthol cigarette smokers. Analysis of covariance that adjusted for race found no statistically significant difference. Smoking menthol cigarettes was not associated with serum cotinine level or carboxyhemoglobin level.

Additional unpublished data from the Wang et al. study were provided to the TPSAC by (Altria Client Services 2010). Analyses were presented on particulate phase markers, urine total NNAL and 1-hydroxypyrene, and 4-aminophenol adducts; and gaseous phase markers (metabolites of acrolein and 1,3 butadiene). No statistically significant differences in biomarker levels were found, comparing the two groups of smokers.

Benowitz et al. (2011) examined the menthol cigarette biomarker question from a different perspective. The question was asked: Does smoking menthol cigarettes increase exposure to toxins in tobacco smoke in a dose-related way? As described earlier, different brands of menthol cigarettes contain different amounts of menthol. Benowitz et al. analyzed the relationship between urine menthol concentration (a quantitative indicator of menthol exposure) and various exposure biomarkers. In a group of 60 menthol cigarette smokers (70 percent African American) there were strong positive correlations between urine menthol concentration and plasma nicotine, plasma cotinine, urine nicotine equivalents, urine total NNAL and urine total PAH metabolites. However, in a multiple regression model, when both menthol and a measure of nicotine intake (nicotine equivalents or plasma cotinine) were included, only the nicotine intake effect remained statistically significant. Thus, while urine menthol is highly correlated with biomarkers of exposure, it is not an independent predictor of carcinogen exposure. This study also reported average levels of various biomarkers in menthol vs. regular smokers (not controlled for race) and found no differences in plasma cotinine or urine NNAL. Urine nicotine equivalents and urine PAHs were lower in menthol cigarette smokers, and although this difference was statistically significant, it may be partly due to a longer interval from last cigarette to time of urine collection for the menthol smokers.

Finally, Benowitz et al. (2004) conducted a crossover study involving 14 subjects, half regular menthol and half non-menthol cigarette smokers. All subjects smoked a non-menthol cigarette for the first week, then they were randomized to smoke a menthol or non-menthol for the second week, after which they were switched to other type of cigarette for the third week. From days 3 to 6 subjects were confined to a research ward, where they smoked 20 cigarettes per day and had frequent blood and

urine sampling. Findings with respect to rates and pathways of nicotine metabolism are discussed in chapter 3. While nicotine metabolism was on average slower in menthol cigarette smokers, based on similar levels of plasma nicotine and blood carboxyhemoglobin levels through the day while smoking menthol compared to non-menthol cigarettes, there was no significant effect of menthol on nicotine or CO exposure.

In summary, some cross-sectional studies of biomarkers, particularly smaller studies, have found higher blood nicotine or cotinine levels per cigarette smoked in menthol cigarette smokers, consistent with greater inhalation. This increment persisted after controlling for race in some of the studies. Larger studies have generally not found independent effects of menthol cigarette smoking on exposure biomarkers. However, the findings of the study by Muscat et al. suggest that menthol may impair detoxification of NNAL, which is a pulmonary carcinogen. As mentioned previously, there has been no analysis of menthol effects on biomarkers of exposure at very low levels of cigarette consumption. At such levels of consumption, menthol could have its greatest effects in facilitating greater inhalation and hence exposure to tobacco smoke toxins.

Chapter 6 Table 2: Biomarkers of Exposure

| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description (Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
|---|---|---|---|---|---|---|
| 1. Ahijevych K, Gillespie J, Demirci M, Jagadeesh J. Menthol and nonmenthol cigarettes and smoke exposure in African American and white women. Pharmacol Biochem Behav. 1996 Feb;53(2):355-60. | Laboratory<br><br>Two-factorial design | N = 37 women stratified by race and menthol or nonmenthol cigarettes<br><br>18AA/8menthol<br><br>19 white/10menthol | A blood sample for nicotine and baseline cotinine analysis was obtained before and after smoking a cigarette. | Plasma cotinine | Plasma cotinine was Plasma cotinine was nonsignificantly higher in nonmenthol smokers compared to menthol smokers (254 ng/ml and 204 ng/ml, respectively). Cotinine per cigarette ratios were nonsignificantly higher in nonmenthol smokers as well (18.1 vs. 15.3 ng/ml cotinine/cigarette). | Strengths include groups balanced race and mentho Weaknesses include small N, heavy smokers, women only. |
| 2. Ahijevych K, Parsley LA: Smoke constituent exposure and stage of change in African American and white | Laboratory Two factorial design | N = 95 women stratified by ethnicity and menthol/nonmenthol preference | A blood sample for nicotine and cotinine analysis was obtained 1 min before | Plasma nicotine and cotinine | . Menthol smokers )had significantly, higher cotinine levels compared to nonmenthol smokers | Strengths – race and menthol balanced. Weaknesses include small N, |

| Chapter 6 Table 2: Biomarkers of Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| women cigarette smokers. Addictive Behaviors 1999, 24(1):115–120. | | N = 48 African American/ 27M<br><br>N = 47 White / 22M | smoking. | | | women only |
| 3. Altria Total Exposure Study (Altria 7/15/10; chapter 4) | Cross-sectional multi-center study | Total Exposure Study (TES): 3341 smokers of one or more cpd, recruited from 39 investigative sites from 31 states, selected by 4 categories of machine yields.<br><br>1044 menthol / 448 AA<br><br>2297 non-menthol / 166 AA | Blood and 24-hour urine samples. Smokers were asked to return all cigarette butts smoked over the 24 hour period. | COHb<br><br>Urine 3-HPMA<br><br>MHBMA and DHBMA<br><br>4-aminobiphenyl adducts<br><br>Nicotine<br><br>Cotinine<br><br>Trans-3'-hydroxycotinine<br><br>Total NNAL<br><br>Total 1-hydroxypyrene | No statistically significant differences in biomarkers of exposure were observed between menthol and non-menthol smokers, stratified by race. No statistically significant difference in the nicotine metabolite ratio between menthol and non-menthol smokers. | Strengths include the large study s and the multi-cer recruitment of smokers; weakne if race by mentho imbalance. |
| 4. Benowitz N, Dains K, Dempsey D, et al. Urine menthol as a biomarker of mentholated cigarette smoking. Cancer Epidemiology Biomarkers and Prevention. 2010, 19: 3013-3019. | Cross-sectional study | N = 127 cigarette smokers<br><br>60 menthol / 42 AA<br><br>67 non-menthol / 19 AA | Concentrations of menthol glucuronide, nicotine equivalents, NE), NNAL and polycyclic aromatic hydrocarbon (PAH) metabolites were measured in the urine. | Urine menthol, nicotine equivalents, NNAL, PAH metabolites; plasma cotinine | Urine menthol was measurable in 82% of menthol and 54% in regular cigarette smokers. Among menthol smokers, urine menthol was highly correlated with NE, NNAL, and PAHs. In a multiple regression model NE but not menthol was significantly associated with NNAL and PAHs. Plasma cotinine similar in menthol and non-menthol smokers. | Strengths includ quantification of menthol exposur Weaknesses include race by menthol imbalan |
| 5. Clark PI, GautamS, Gerson LW. Effect of menthol cigarettes on | Laboratory<br><br>cross- | N = 65 African American and N = 96 white smokers | Serum samples for cotinine analyses | Serum Cotinine | After adjusting for race, cigarettes per day, and mean amount of each cigarette smoked, menthol | Weaknesses include race and menthol imbalan |

| Chapter 6 Table 2: Biomarkers of Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| biochemical markers of smoke exposure among African American and white smokers. Chest. 1996 Nov; 110(5):1194-8. | sectional | 65 AA / 54 menthol<br><br>96 W / 22 menthol | | | was associated with higher cotinine levels (p=0.03) and expired carbon monoxide concentrations<br><br>(p=0.02). | |
| 6. Heck JD. Smokers of menthol and nonmenthol cigarettes exhibit similar levels of biomarkers of smoke exposure. Cancer Epidemiol Biomarkers Prev. 2009 Feb; 18(2):622-9. Epub 2009 Feb. 3. Erratum in Cancer Epidemiol Biomarkers Prev. 2009 Jul;18(7):2155. | Parallel arm study | N = 112 male and female heavy smokers<br><br>28 AA / 23 menthol<br><br>84 white / 31 menthol | The study subjects were provided with specified brands of cigarettes according to their menthol or nonmenthol preference for 3 weeks. On the third week two 24-hour urine samples spaced one week apart, were collected. | Blood carboxyhemoglobin<br><br>Urine nicotine equivalents; urine NNAL | There were no significant differences in carboxyhemoglobin, urine nicotine equivalents or total urinary NNAL comparing the menthol and nonmenthol cigarette smokers | Weaknesses include smoking brands other thai usual brand; race menthol imbalan subjects smoked least 15 cigarette per day |
| 7. Ho MK, Mwenifumbo JC, Al Koudsi N, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF: Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. *Clinical Pharmacology and* | Smoking cessation clinical trial | N = 755 African American smokers of 10 or fewer cigarettes per day; 569 smoked menthol cigarettes | Blood and expired CO samples obtained prior to randomization | Plasma cotinine; expired CO | Menthol cigarette smokers tended to smoke fewer cigarettes per day (7.07 vs 7.53, p = 0.05). Expired CO and plasma cotinine were not significantly different in menthol vs nonmenthol smokers (13.49 vs 14.74 ppm; 243 vs 247 ng/ml, respectively). Suggests that CO and/or nicotine intake may be higher per cigarette for menthol smokers. | Strengths include large number of African Americar smokers with considerable numbers of ment and nonmenthol smokers; include light smokers |

| Chapter 6 Table 2: Biomarkers of Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| *Therapeutics* 2009 Jun, 85(6):635-43. | | | | | | |
| 8. Muscat JE, Chen G, Knipe A, Stellman SD, Lazarus P, Richie JP Jr. Effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL glucuronidation. Cancer Epidemiol Biomarkers Prev. 2009 Jan; 18(1):35-41. | Cross-sectional | N = 525 male and female smokers of at least 5 cpd.<br><br>237 AA / 204 menthol<br><br>288 white / 80 menthol | Plasma and urine collection. | Urinary and plasma cotinine<br><br>Plasma thiocyanate<br><br>Urinary NNAL and NNAL-Gluc | In regression models that adjusted for daily cigarette intake, no significant differences were observed in the concentration of these biomarkers by menthol status in both races. The ratio of NNAL-Gluc to NNAL, was significantly lower in menthol versus nonmenthol smokers. The NNAL Gluc/NNAL ratio was 34% lower in Whites (P < 0.01) and 22% lower in African Americans | Strengths include relatively large sample size; Weaknesses include race by menthol imbalan |
| 9. Mustonen TK, Spencer SM, Hoskinson RA, Sachs DP, Garvey AJ. The influence of gender, race, and menthol content on tobacco exposure measures. Nicotine Tob Res. 2005 Aug;7(4):581-90. | Cross-sectional study | N = 307 male and female smokers participating in cessation clinic<br><br>51 AA / 33 menthol<br><br>256 white / 54 menthol | Saliva cotinine obtained prior to cessation treatment | Salivary cotinine<br><br>Expired carbon monoxide | Cotinine and CPD correlations varied by gender and race among menthol cigarette smokers. Significant genderxracexmenthol interaction on salivary cotinine level as well as cotinine/CPD ratio. | Weaknesses included race by menthol imbalan small N for subgroup analys treatment seekin smokers of at lea 10 cigarettes per day |
| 10. Signorello LB, Cai Q, Tarone RE, McLaughlin JK, Blot WJ. Racial differences in serum cotinine levels of smokers. Dis Markers. | Cohort Study; | Southern Community Cohort Study.<br><br>130 AA and 125 white smokers; no data on number of menthol smokers | Blood samples taken at time of baseline evaluation | Serum cotinine measured by radioimmunoassay | After adjustment for race and sex and cigarettes smoked per day, no significant difference in cotinine levels comparing menthol vs non-menthol smokers | Weaknesses include race by menthol imbalan cotinine assay is non-specific with some cross-reactivity with cotinine metaboli |

| Chapter 6 Table 2: Biomarkers of Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| 2009;27(5):187-92. | | | | | | |
| 11. Wagenknecht LE, Cutter GR, Haley NJ, Sidney S, Manolio TA, Hughes GH, Jacobs DR. Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults Study. Am J Public Health. 1990 Sept;80(9):1053-6. | Prospective cohort study | N = 142418-30 year old smokers of at least five cigarettes per week, African American and White, men and women participating in the Coronary Artery Risk Development in (Young) Adults Study<br><br>822 AA/733 menthol<br><br>602 white/ 178 menthol | Blood same at initial examination. | Serum cotinine | . Serum cotinine level was significantly higher in African American than White smokers. The race difference persisted for African Americans who smoked menthol or nonmenthol cigarettes (no details of this analysis were presented) | Strengths include the large study s and the multi-cer recruitment of smokers; weaknesses incl race by menthol imbalance |
| 12. Wang J, Roethig HJ, Appleton S, Werley M, Muhammad-Kah R, Mendes P. The effect of menthol containing cigarettes on adults smokers' exposure to nicotine and carbon monoxide. Regulatory Toxicology and Pharmacology. 2010; 57: 24-30. | Cross sectional multi-center<br><br>study | Total Exposure Study<br><br>N=3341 African-American and White adult cigarette smokers<br><br>1044 menthol / 448 AA<br><br>2297 non-menthol / 166 AA | Blood and 24-hour urine samples.. Smokers were asked to return all cigarette butts smoked over the 24 hour period. | Nicotine equivalents (NE) in 24 hour urine, NE/cigarette, COHb, and serum cotinine | No statistically significant effects of mentholated cigarettes on NE/24 h, COHb, serum cotinine and NE/cigarette. On average menthol users (MS) smoked 15.0 and non-menthol users (NMS) 16.8 cigarettes/day. The unadjusted mean differences were as follows: MS had lower NE/24 h (5.4%) and COHb (3.2%), higher serum cotinine (3.0%) and NE/cigarette (5.7%) than NMS. | |
| 13. Williams JM, Gandhi KK, Steinberg ML, Foulds J, Ziedonis DM, Benowitz, NL: Higher nicotine and carbon monoxide levels in menthol cigarette smokers | Laboratory study | 89 smokers with schizophrenia<br><br>53 control smokers<br><br>Data on number of menthol smokers or | Subjects provided a measure of exhaled CO and a blood sample approximately 2 min after smoking one of their usual cigarettes. | Expired carbon monoxide<br><br>Serum nicotine, cotinine and trans-3' hydroxycotinine | Serum nicotine levels (27<br><br>vs. 22 ng/ml, p=.010), serum cotinine levels (294 vs. 240 ng/ml, p=.041), and expired CO (25 vs. 21 ppm, p5.029)<br><br>were higher in smokers of | Weaknesses include small numbers of subjects, many o whom have psychiatric disea |

| Chapter 6 Table 2: Biomarkers of Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Author Name(s), Article Title and Year | Type of Study | Subject Recruitment, Description<br><br>(Including Special population(s)) and Sample Size | Study Design | Outcome Variables | Results related to Menthol | Strengths / Weaknesses |
| with and without schizophrenia. *Nicotine and Tobacco Research* 2007, 9(8):873–881. | | race not provided | | | menthol compared with nonmenthol cigarette smokers., with no differences in 3 hydroxycotinine/cotinine ratios between cigarette types with adjustment for diagnostic group and race | |

**TOXICOLOGY STUDIES**

Additional understanding of the differential risks posed by menthol versus non-menthol cigarettes comes from toxicological studies. The relevant studies include in vitro and in vivo approaches using menthol or smoke from cigarettes. As for toxicologic studies in general, there are questions about the relevance of animal and cell toxicology studies with respect to the potential toxic effects of menthol in cigarette smokers.

Various studies have addressed the toxicity of menthol using in vitro cellular assays that assess whether menthol damages or kills cells. One general issue in interpreting such studies is the relevance of the concentrations used and the endpoints investigated to toxicity in smokers. Bernson and Pettersson (1983) investigated the toxicity of menthol in four different bioassays. They summarize the findings as suggesting that menthol may lead to "...a deterioration of biological membranes." Other studies have shown that menthol affects cell membrane properties. Azzi et al. (2006) used a system that measures diffusion of carcinogens across porcine esophageal tissue to assess the effect of menthol on permeation and reservoir formation in the tissue for NNK and B[a]P. Menthol slowed the diffusion of these two carcinogens but increased the size of the tissue reservoir for NNK. In another cell system, menthol decreased the transepithelial electrical resistance, but the decrease was not different from that observed with non-menthol cigarettes (Alakayak and Knall 2008).

Several studies have addressed interactions of menthol with membrane receptors. Sidell et al. (1990) used a human neuroblastoma cell line and identified a calcium channel that was blocked by menthol. More recent studies have focused on the TRPM8 $Ca^{2+}$-permeable channel. Results from various cellular systems show that activation of the TRPM8 channel by menthol induces cell death (Yamamura et al. 2008; li et al. 2009), although one study using prostate cancer cells found that TRPM8 activation was not the mechanism of menthol-induced cell death in that system (Kim et al. 2009).




Another inhalation study was reported in the peer-reviewed literature in 1997 (Gaworski et al. 1997). In this study, Fischer 344 rats were exposed to mainstream smoke from a reference cigarette and a similar cigarette containing 5000 ppm synthetic *l*-menthol. The only difference noted between the two exposure groups was a dose-response trend with level of particulate matter for nasal discharge in the reference cigarette group but not in the menthol cigarette group.

R.J. Reynolds Tobacco Co. conducted a 90-day inhalation study comparing menthol vs no menthol in heated tobacco vs. conventional cigarettes (ref 26 cited in Salgado and Glantz 2011 ). Menthol inhalation from heated tobacco produced more severe histopathological changes in the lungs compared to conventional cigarettes.

Several studies have shown that menthol increases the amount of tar and fine particles in cigarette smoke (Carmines 2002, Baker 2004, Rustemeier 2001 as cited in Lee and Glantz 2011). The mechanism of increased particle formation was speculated to be greater transfer of the additive materials to the particle phase of the smoke compared to tobacco constituents (Rustemeier 2001 as cited in Lee and Glantz 2011). Increased particulate matter in smoke is of concern because particulates are associated with greater morbidity and mortality from cardiovascular disease and are suspected to increase the risk

of sudden cardiac death (Brook 2010; Pope 2009; IOM 2010; also see Lee and Glantz 2011). The smoke generated from cigarettes to which menthol was added also delivered higher levels of formaldehyde and lead, both tobacco smoke toxicants, compared to smoke from the control cigarettes (Rustemeier 2001 as cited in Lee and Glantz 2011).

Several short-term human studies also supply relevant information. A group of investigators in Turkey reported findings of a series of studies involving measurements of cardiovascular parameters after smoking menthol cigarettes versus non-menthol cigarettes (Ciftci et al. 2008a, Ciftci et al. 2008b; Ciftci et al. 2009). They describe differing patterns of short-term response using echocardiography and measures of vascular response. The participants were healthy young volunteers. These findings have uncertain implications with regard to the comparative cardiovascular disease risks of smokers of menthol cigarettes versus non-menthol cigarettes. Pritchard et al. (1999) investigated the effects of menthol in cigarettes by having volunteers smoke "denicotinized" cigarettes, with and without menthol. Using electroencephalogram and heart rate as outcome measures, they did not identify differences in response to the menthol-containing and non-menthol-containing cigarettes.

The Altria-supported Total Exposure Study mentioned above also examined biomarkers of potential harm, including markers of oxidative stress (i-epi-prostaglandin-F2 alpha, 8-isoprostaglandin F2 alpha-V1), inflammation (white blood cell count, fibrinogen, C-reactive protein, monocyte chemotactic protein and interleukin-6), endothelial function (von Willebrand factor, microalbumin, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1), coagulation (platelets, fibrinogen, von Willebrand factor, 11-dehydrothroboxane-B2), lipids (triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, oxidized LDL, lipoprotein-associated phospholipase A2) and metabolism (glucose, adiponectin, leptin) (Altria Client Services 2010). No significant effects of menthol smoking on these biomarkers were observed.

**EPIDEMIOLOGICAL STUDIES**

The comparative risks of menthol cigarette smokers versus non-menthol cigarette smokers have been assessed for several cancer sites, and selected cardiovascular and respiratory outcomes. The evidence comes primarily from case-control studies but also from three cohort studies. A variety of indicators were used for classifying the extent of exposure to menthol cigarettes. None of the studies were designed to specifically address risks of menthol cigarettes and consequently the investigators constructed indices that used the available information with acknowledgement of the potential for misclassification. For example, the cohort study of Northern California Kaiser Permanente participants used the type of cigarette smoked on enrollment to classify menthol cigarette status (Sidney et al. 1995). In the four-city case-control study of lung cancer, Kabat and Hebert (1991) determined mentholation for each brand smoked.

For cancer, the evidence is most abundant for lung cancer (table 3). Findings are available from three case-control studies and three cohort studies, the Northern California Kaiser Permanente Study, the Lung Health Study, and the Southern Community Cohort Study. The analyses took account of other smoking-related determinants of lung cancer risk, e.g., amount smoked. Most of the studies found no

significant differences in risk for lung cancer in smokers of menthol compared with non-menthol cigarettes. In fact, most of the point estimates were around unity, indicating no difference in risk, and measures of the extent of menthol smoking were not associated with lung cancer risk. The most recent study, the Southern Community Cohort Study, found a statistically significantly reduced risk of lung cancer in smokers of menthol cigarettes vs. the comparison of non-menthol cigarette smokers (Blot et al., in press). Only one study, the Kaiser Permanente Study, found a statistically significantly increased risk for menthol cigarette smokers. In males, the relative risk for menthol smokers was 1.45 (95 percent confidence interval 1.03–2.02). In females, the relative risk was 0.75 (95 percent confidence interval 0.52–1.11).

More limited findings are available for other cancers, including esophageal and oral cancers and all smoking-related cancers other than lung cancer. For each of these outcomes, findings are available from only a single study (table 3). As for lung cancer, the evidence does not show a difference in risk for menthol smokers compared with non-menthol cigarette smokers.

For cardiovascular disease, two cohort studies provide findings: the Coronary Artery Risk Development in Young Adults (CARDIA) Study (Pletcher et al. 2006) and the Lung Health Study (Murray et al. 2007). In the CARDIA Study, a long-term cohort study, coronary calcification was measured in 2000, 15 years after participants were enrolled (Pletcher et al. 2006). Using the periodically collected smoking information, the numbers of pack-years of smoking menthol and non-menthol cigarettes were estimated. Risk for the prevalence of calcification increased similarly with pack-years of menthol and non-menthol cigarettes. In the Lung Health Study, participants were classified as menthol smokers based on the type of cigarette smoked at enrollment (Murray et al. 2007). Risks of death from coronary heart disease death or cardiovascular disease were not increased for menthol cigarette smokers, nor was all-cause mortality.

The same two cohort studies provide information on several respiratory outcome measures. In the Lung Health Study, the frequencies of participant reports for "...having seen or talked to a physician for the following conditions: any respiratory condition, emphysema, asthma, pneumonia, head cold, chest cold, or sore throat..." were similar in menthol and non-menthol cigarette smokers (Murray et al. 2007). In the CARDIA Study, the 10-year rates of lung function decline (the forced expiratory volume in one second or the $FEV_1$) were similar in the two groups (Pletcher et al. 2006).

Overall, the epidemiological studies indicate comparable risks for a number of cigarette-caused diseases in smokers of menthol compared to non-menthol cigarettes. The point estimates are largely centered around unity. Several limitations of these studies need to be noted in interpreting the findings. The extent of information on smoking of menthol cigarettes was variable and complete across the full smoking history only in one of the case-control studies. Random misclassification of menthol smoking would tend to bias estimates of the comparative risk of smoking menthol cigarettes towards unity, regardless of whether there was a "true" increase or decrease in risk for menthol cigarette smokers. Additionally, many of the studies, particularly those on cancer risk, were carried out several decades previously. Consequently, given historical patterns of menthol cigarette use, there would be few participants in these studies who had smoked menthol cigarettes across their full smoking history.

Finally, the studies generally have relatively small numbers of participants. However, even with the relatively modest sample sizes of some of the studies, the point estimates do not provide any consistent indication of increased risk.

**Table 3: Cancer risk for smokers of menthol versus non-menthol cigarettes**

| Author (Publication year) | Study design, study period, location | Sample size | Menthol exposure | Findings |
|---|---|---|---|---|
| **Lung cancer** | | | | |
| Kabat and Hebert (1991) | Case-control study<br>1985-1990<br>Four U.S. cities | 1044 cases<br>1324 controls | Non-menthol smokers<br>Menthol 1-14 years<br>Menthol ≥15 years | No significant difference in risk overall, or by histological type |
| Sidney et al. (1995) | Cohort study<br>1979-1991<br>Northern California Kaiser enrollees | 9761 participants<br>Current smokers<br>318 cases | Current cigarette brand<br>Menthol or non-menthol | Increased risk for males, but not for females |
| Carpenter et al. (1999) | Case-control study<br>1990-1994<br>Los Angeles county | 337 cases<br>478 controls | Proportion of cigarettes smoked that were menthol | No increase in risk with extent of menthol smoking |
| Brooks et al. (2003) | Case-control study<br>1981-2000<br>Multi-hospital, eastern U.S. | 643 cases<br>4110 controls | Years smoked menthol cigarettes based on current brand and brand smoked the longest | No indication of increased risk for ever smoking menthol or with extent of menthol smoking |
| Murray et al. (2007) | Randomized trial in observational phase<br>1986-2001<br>Multi-site | 5887 participants<br>240 deaths | Baseline cigarette type | No increase in risk for menthol smokers |
| Blot et al. (2011) | Nested case-control study<br>2002-2009<br>Twelve southern U.S. states | 440 cases<br>2213 controls | Menthol or non-menthol, adjusted for pack-years smoked | Significantly lower risk of lung cancer incidence and mortality among menthol compared to non-menthol smokers, with the deficit holding among both African Americans and whites. |
| **Oropharyngeal cancer** | | | | |
| Kabat and Hebert (1994) | Case-control study<br>1985-1990<br>Four U.S. cities | 276 cases<br>1256 controls | Ever menthol use<br>Duration of menthol use | No significant difference in risk overall, or by subsite |
| **Esophageal cancer** | | | | |
| Hebert and Kabat (1989) | Case-control study<br>1969-1984<br>Nine U.S. cities | 312 cases<br>462 controls | Menthol based on brand<br>Ever menthol use<br>Duration of menthol | No clear pattern of significantly different risk |

| | | | | |
|---|---|---|---|---|
| | | | use | |
| **Non-lung smoking-related cancers** | | | | |
| Friedman et al. (1998) | Cohort study<br>1979-1994<br>Northern California Kaiser enrollees | 11760 participants<br>281 cases | Current brand of mentholated cigarettes | No indication of increased risk |

**EVIDENCE SYNTHESIS**

This chapter reviews diverse lines of evidence with regard to potential differential risks to health of smoking menthol versus non-menthol cigarettes. The evidence reviewed includes studies on differences in the ways that menthol cigarettes are smoked versus non-menthol cigarettes; studies on levels of biomarkers of dose of tobacco smoke components in smokers; studies on the toxicity of menthol and smoke from menthol cigarettes; and studies on the comparative risks of smoking menthol and non-menthol cigarettes in human populations. For some of these topics, the number of studies is limited for some of these major lines of evidence. For example, only six epidemiological studies address lung cancer and lesser numbers were identified for other health outcomes.

The in vitro studies show that menthol has activity in various systems. Chapter 3 addresses the pharmacologic actions of menthol which may lead to some of these effects. The very limited bioassay data does not indicate that smoke from menthol cigarettes has greater toxicity than smoke from non-menthol cigarettes. The epidemiological literature, albeit limited in scope, suggests that there is not greater risk for disease development for smokers of menthol versus non-menthol cigarettes. For lung cancer, the studies are consistent in this regard.

TPSAC concludes, based on the evidence reviewed in this chapter, that:

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers inhale more smoke than non-menthol cigarette smokers. Because of methodologic issues in studying smoking topography, the generalizability of these findings to the smoking of menthol cigarettes in daily life is questionable.

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers are exposed to higher levels of nicotine and other tobacco smoke toxins, at least in regular daily smokers of more than 5 or 10 cigarettes per day. There are insufficient data to know if menthol cigarettes result in greater smoke intake and more exposure to tobacco smoke toxins among smokers of relatively few cigarettes per day.

- The evidence is insufficient to conclude that smokers of menthol cigarettes face a different risk of tobacco-caused diseases than smokers of non-menthol cigarettes. Some toxicology studies raise concern, particularly the finding that the addition of menthol is associated with greater fine particles which are suspected to contribute to cardiovascular disease. Available epidemiologic data do not demonstrate increased disease risk in people, but the data are largely limited to lung cancer. The hypothesis that menthol cigarette smoking increases the risk of cardiovascular disease is biologically plausible and needs to be investigated.

# CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

## INTRODUCTION

In this chapter, TPSAC synthesizes the evidence included in chapters 3–6 to address the charge given to it in the Act. Using the methodology described in chapter 2, TPSAC has systematically identified and evaluated relevant studies and other evidence, including papers published in the peer-reviewed literature, documents supplied to the committee by tobacco companies, FDA white papers and unpublished tobacco company documents. Here, TPSAC provides its conclusions to the seven key questions in chapter 1 related to individual smokers and the two key questions related to effects at the population level. These conclusions are expressed in the classification set out in Chapter 2 that is based around the anchoring point of "equipoise" in the strength of evidence for and against a relationship. Answers to these questions underlie TPSAC's qualitative judgment as to whether there is an adverse impact on public health from menthol cigarettes; the results of models are used to provide a quantitative picture of the adverse impact. Because the answers to questions 1 and 2 utilize the same evidence, these closely related questions are answered together. For the same reason, questions 3 and 4, which also are closely related, are answered together. Chapter 8 concludes with recommendations to the FDA and a discussion of contraband, as called for under section 907 (b).

## EVIDENCE SYNTHESIS FOR KEY QUESTIONS

### Related to Individual Smokers

***1. Does availability of menthol cigarettes increase the likelihood of experimentation?***

***2. Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?***

Regular cigarette smoking begins with experimentation, typically during adolescence, as noted in chapter 6. To understand the role of menthol cigarettes in the continuum that ends with regular smoking, TPSAC closely examined data presented in chapters 4 and 6 on the prevalence and patterns of menthol cigarette smoking in youths ages 12 to 17. TPSAC considered studies, summarized in chapters 3 and 6, about the sensory impacts of menthol cigarette smoke and reviewed evidence from internal tobacco company documents and consumer research, presented in chapter 5, on the influences of menthol cigarette advertising and marketing on smoking of menthol cigarettes.

TPSAC's review in these chapters led to key findings related to these two questions. (1) The proportion of youth smokers who smoke menthol cigarettes is higher than the proportion of adult smokers who smoke menthol cigarettes. (2) Younger adolescent smokers have a higher proportion of menthol cigarette smokers than older adolescent smokers. African Americans, who tend to begin smoking later, are an exception. (3) There is some evidence that new smokers—those who have been smoking for less than a year—have a greater prevalence of menthol cigarette use than established smokers. (4) The proportion of menthol cigarette use among youth smokers is trending upward while non-menthol cigarette use is trending downward or is flat. (5) Menthol's cooling and anesthetic properties reduce the harshness of cigarette smoke for new smokers. Menthol cigarettes produce sensory cues, such as a minty taste and odor, a cooling sensation and throat irritation or impact—all of which may provide strong cigarette-associated cues that reinforce smoking behavior. Thus, it is biologically plausible that menthol cigarettes lead to increased experimentation and higher risk for continued regular smoking

among youth. (6) Menthol cigarette marketing influences the anticipated sensory experience of smoking menthol cigarettes, thereby enhancing consumers' subjective sensory experience and liking. (7) Initiating with menthol cigarettes is more likely to lead to established smoking than initiating with non-menthol cigarettes, according to one key cohort study of youth initiators. (8) These findings, coming from multiple lines of investigation, are coherent in supporting a role for menthol cigarettes in increasing experimentation and progression to regular smoking.

TPSAC finds, based on its review, that:

**The evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes increases experimentation and regular smoking. (Above Equipoise)**

***3. Does inclusion of menthol in cigarettes increase the likelihood of the smoker becoming addicted?***

***4. Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?***

TPSAC considered these two questions separately for adults and adolescents. Due to a lack of relevant evidence, TPSAC was unable to reach a conclusion about the relationship between menthol cigarettes and nicotine addiction in adults. Evidence about the severity of addiction in adult menthol cigarette smokers was mixed.

TPSAC found clear evidence of a relationship between menthol cigarettes and nicotine addiction in youth. This evidence, presented in chapters 3 and 6, produced three key findings. (1) Youth who initiated with menthol cigarettes were more likely to become daily, regular, or established smokers than youth who initiated with non-menthol cigarettes. (2) Adolescent menthol cigarette smokers have a higher prevalence of nicotine dependence and degree of addiction than in those who smoke non-menthol cigarettes. (3) Studies of sensory cues and self-administration of addicting drugs in animals show that sensory factors enhance and sustain self-administration of addictive drugs. These animal studies provide biological plausibility for a role of menthol in cigarettes in increasing the likelihood of addiction in youth and increasing the degree of addiction of the young smoker. TPSAC finds, based on its review, that:

**The evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes increases the likelihood of addiction and the degree of addiction in youth smokers. (Above Equipoise)**

**There is insufficient evidence to conclude that menthol cigarettes increase the likelihood of addiction and the severity of addiction in adults. (Below Equipoise)**

***5. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?***

TPSAC examined data from national population surveys and other studies to determine the comparative success of quit attempts among smokers of menthol compared with non-menthol cigarettes. The national surveys provide data on quit ratios (the ratio of former to ever smokers) or rates of quitting among menthol smokers and non-menthol smokers as a measure of the success of quitting. In addition, TPSAC reviewed other types of research, including secondary analyses of data from cohort and treatment studies, both of which have limitations that were discussed in chapter 6. The evidence for whites is mixed. Across the most informative national surveys, the preponderance of evidence for non-

white adults showed lower success rates for quitting among menthol smokers compared to non-menthol smokers, particularly among African Americans. Of the other studies found to be informative and of sufficient quality by TPSAC, the evidence was mixed. Considering all of the evidence, TPSAC concluded that non-white, particularly African American menthol smokers, are less likely to quit successfully than non-menthol smokers.

TPSAC reviewed experimental and pharmacological evidence, presented in chapter 3, that provided a plausible biological explanation for lower cessation success among menthol smokers. Several animal studies showed that once drug self-administration is established, taste and other sensory factors can function as stimuli that substantially enhance the strength and persistence of drug self-administration. Stimuli associated with drug intake can come to evoke craving that promotes resumption of drug self-administration after a period of abstinence. As discussed in chapters 5 and 6, empirical and qualitative research—including consumer research conducted by tobacco companies— showed consumers hold beliefs about the implicit health benefits of menthol cigarettes, which could undermine quitting intentions and attempts. As discussed in chapter 5, these beliefs about the implicit benefits of menthol cigarettes are especially apparent among African Americans.

TPSAC finds, based on evidence reviewed in chapter 6, that:

**The evidence is sufficient to conclude that a relationship 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. (Above Equipoise)**

**The evidence is sufficient to conclude that a relationship is as likely as not that the availability of menthol cigarettes results in lower likelihood of smoking cessation success in other racial/ethnic groups (At Equipoise)**

***6. Do biomarker studies indicate that smokers of menthol cigarettes receive greater doses of harmful agents per cigarette smoked compared with smokers of non-menthol cigarettes?***

To examine the question of whether menthol cigarette smokers are exposed to higher levels of harmful agents, TPSAC reviewed studies directed at the topography of smoking (puffing behavior and exposure to nicotine and carbon monoxide from single cigarettes) and studies comparing levels of biomarkers of tobacco smoke exposure in smokers of menthol and non-menthol cigarettes. This evidence was presented in chapter 7. Because of methodologic issues in studying smoking topography, including small numbers of subjects, imbalance between race and menthol use, smoking through cigarette holders and/or artificial patterns of smoking, the generalizability of the topography findings to the smoking of menthol cigarettes in daily life is questionable. The biomarker studies are more generalizable in that they typically include larger numbers of smokers smoking their own cigarettes in a naturalistic way, and the studies involve larger numbers of smokers than the topography studies. There is some evidence from one large study that while daily exposure is not different, the intake of nicotine per cigarette is higher for menthol compared to non-menthol smokers. There are insufficient data to know if smoking menthol cigarettes is associated with greater smoke intake and more exposure to tobacco smoke toxins among smokers of relatively few cigarettes per day.

TPSAC finds, based on the evidence reviewed, that:

**The evidence is insufficient to conclude that it is more likely than not that menthol smokers inhale more smoke per cigarette or that they are exposed to higher levels of nicotine and other tobacco toxins. (Below Equipoise)**

***7. Do smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes?***

Chapter 7 summarizes the diverse lines of evidence relevant to this question, including the findings of toxicological and epidemiological studies. The findings pertaining to biomarkers and smoking topography, leading to the conclusion for Question 6 related to individual smokers, are also relevant. That conclusion does not give support to increased risk for diseases in smokers of menthol compared to non-menthol cigarettes.

The toxicological studies considered in Chapter 6 use diverse in vivo and in vitro systems. The evidence is mixed. The in vitro studies show that menthol has activity in various systems. Chapter 3 addresses the pharmacologic actions of menthol which may lead to some of these effects. The very limited bioassay data does not indicate that smoke from menthol cigarettes has greater toxicity than smoke from non-menthol cigarettes. The epidemiological literature, albeit limited in scope, suggests that there is not greater risk for disease development for smokers of menthol versus non-menthol cigarettes. For most of the diseases caused by smoking, the evidence is extremely limited. For lung cancer, the most studied disease, there are only six epidemiological studies and lesser numbers were identified for other health outcomes.

TPSAC finds, based on the evidence reviewed in this chapter, that:

> **The evidence is insufficient to conclude that it is more likely than not that smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes. (Below Equipoise)**

**Smoking at the Population Level**

***1. Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?***

The prevalence of adult smoking is substantially driven by the experimentation and subsequent regular smoking by youth and adolescents. As noted in chapter 6, the proportion of menthol cigarette smoking is highest in the 12–15 year age group and decreases progressively within every older age group to age 25. The early use of menthol cigarettes by between one-half to one-third of youth smokers most likely contributes to nicotine dependence in at least the 30 percent of adult smokers who use menthol cigarettes. The evidence for Question 5 above, which indicates that menthol cigarette smokers are less likely to quit smoking than non-menthol cigarette smokers, is also relevant.

In addition, a substantial number of smokers who initiate with menthol cigarettes later switch to non-menthol cigarettes. Thus, menthol initiation also contributes to the prevalence of non-menthol cigarette smoking in the general population. Because of the high prevalence of smoking menthol cigarettes in these early ages and because of the likelihood that smoking menthol cigarettes increases their dependence on smoking and makes quitting less likely, TPSAC concludes that the availability of menthol cigarettes increases the prevalence of smoking in the general population and particularly in African Americans, beyond the anticipated prevalence if such cigarettes were not available.
TPSAC finds, based on the evidence reviewed, that:

**The evidence is sufficient to conclude that it is more likely than not that the availability of menthol cigarettes increases the likelihood of experimentation and regular smoking beyond the anticipated prevalence if such cigarettes were not available, in the general population and particularly in African Americans. The evidence is sufficient to conclude that it is more likely than not there is a causal relationship between the availability of menthol cigarettes and regular smoking among youth. (Above Equipoise)**

***2. Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?***

Chapter 4 provided an introduction to the history of marketing of menthol cigarettes. Chapter 5 summarized strategies for marketing of menthol cigarettes, menthol marketing messages, target groups for menthol marketing and consumer perceptions of menthol cigarettes. The findings pertaining to patterns of menthol smoking for the population overall, and for population subgroups, as reviewed in chapter 4 and 6 are also relevant. In addition, chapter 3 provided information on the sensory properties of menthol cigarettes which are relevant for considering consumer perception issues.

TPSAC found there to be sufficient evidence that marketing messages for menthol cigarettes have been different from those used in non-menthol cigarette marketing. Menthol cigarettes have been and continue to be marketed with a set of associated branding elements and labels that connote health benefits. Early messages featured explicit references to health benefits through medicinal assistance (such as soothing a sore throat or clearing a blocked nose) and later messages emphasized implicit health benefits, through the promotion of the particular features of menthol cigarettes that refer to their 'freshness' and sensory cooling properties. Studies show consumer perceptions of the taste/sensory experience of cigarettes are correlated with perceptions of harm, including for menthol cigarettes. Against a background of consumer research studies demonstrating that taste perception is subjective and highly amenable to suggestion from product advertising, branding and labeling, menthol cigarette marketing influences the anticipated sensory experience of menthol cigarettes, thereby enhancing consumers' subjective sensory experience and liking. There is sufficient evidence from tobacco industry document reviews and empirical studies to conclude that consumers hold beliefs about the implicit health benefits of menthol cigarettes and this is particularly the case among African Americans.

In addition to messages that implied health reassurance, menthol marketing messages promoted a more youthful brand image than for non-menthol cigarettes, and emphasized the role of menthol cigarettes in peer group acceptance. There is substantial evidence that menthol marketing has been especially targeted to youth and African Americans, with youthful imagery, messages promoting an appealing sensory experience, and peer group acceptance. There is also evidence from tobacco industry documents that the tobacco industry designed menthol cigarettes with lower menthol levels, with an awareness that, at these lower levels, the sensory effects of menthol reduce the harshness of cigarettes for new smokers. Menthol smoking is higher in more youthful smoker population groups and among African American smokers.

The evidence is sufficient to conclude that Hispanics have been disproportionately more targeted by menthol than non-menthol marketing. Menthol smoking is also higher among Hispanic smokers. Although menthol smokers comprise a higher proportion of Asian American and Hawaiian/Pacific Islander smokers, there is insufficient evidence to conclude that these population groups have been disproportionately more targeted by menthol than non-menthol marketing. Finally, although female smokers have higher menthol smoking rates than male smokers, there is insufficient evidence to conclude that they have been disproportionately more targeted by menthol than non-menthol marketing.

TPSAC finds, based on the evidence reviewed, that:

**The evidence is sufficient to conclude that it is more likely than not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for the whole population, and for youth and African Americans.(Above Equipoise)**

**The evidence is sufficient to conclude that it is as likely as not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for Hispanics. (At Equipoise)**

**The evidence is insufficient to conclude that it is more likely than not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for Asian Americans, Hawaiians/Pacific Islanders and women. (Below Equipoise)**

**OVERALL CONCLUSIONS**

Based on the conclusions to the nine questions, TPSAC provides the following general conclusions:

- Menthol cigarettes have an adverse impact on public health in the United States.
- There are no public health benefits of menthol compared to non-menthol cigarettes.

**PUBLIC HEALTH IMPACT**

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "the issue of the impact of the use of menthol in cigarettes on the public health including such use among children, African Americans, Hispanics, and other racial and ethnic minorities." The availability of menthol cigarettes in the marketplace could adversely affect public health through two consequences: (1) increasing the risk for the diseases caused by smoking cigarettes; and (2) increasing the number of people who smoke. These two consequences are captured in the population attributable risk statistic, used to calculate the disease burden attributable to a causal factor, such as cigarette smoking.

The committee finds that the evidence does not indicate increased disease risks in smokers of menthol cigarettes compared to non-menthol cigarettes. TPSAC does conclude 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. TPSAC found evidence that the availability of menthol cigarettes increases initiation; of particular concern was the high rate of menthol cigarette smoking among youth and the trend over the last decade of increasing menthol cigarette smoking among 12 to 17 year olds, even as smoking of non-menthol cigarettes declines. TPSAC also concluded that cessation is less likely to be successful among smokers of menthol cigarettes. Thus, the availability of menthol cigarettes increases initiation and reduces cessation, thereby increasing the number of people who are smoking. This increase in the number of smokers represents an adverse impact of the availability of menthol cigarettes on public health.

To gain an understanding of the quantitative impact of menthol cigarettes on public health, TPSAC turned to the results of models of smoking in the United States, one developed for the entire population and the other for the African American population (Appendix A). Details of the models developed by Mendez are provided in Appendix A. Mendez expanded a previously developed compartmental model of smoking in the population of the United States to incorporate smoking of menthol and non-menthol cigarettes (see references in Appendix A for background). Based on the review provided in this report, TPSAC provided specifications for model parameters, including a central or "best" estimate and plausible lower and upper bounds. For parameters not covered in the TPSAC review, parameter values were based on documents available to TPSAC. Table 1 below ( Table 3 in Appendix A) documents these choices.

The model compares two scenarios: a scenario based on the current pattern of smoking of menthol and non-menthol cigarette smoking and a counterfactual or comparison scenario representing smoking in the United States, but without the availability of menthol cigarettes. These two scenarios match at the outset in every way except for the availability of menthol cigarettes. Over time, the patterns of experimentation, initiation, and cessation differ as described in Table 1 of Appendix A and switching occurs between the two types of cigarettes in the menthol cigarette scenario. Models were implemented for the boundary conditions defined by the lower and upper bounds for the model parameters. The results provide insight into the sensitivity of findings to values of model parameters.

## Table 1.Results – General Population

| Scenario | Description | Cumulative Excess Deaths | | | | Cumulative Excess Smoking Initiation | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2020 | 2030 | 2040 | 2050 | 2020 | 2030 | 2040 | 2050 |
| 1 | TPSAC Estimates | 17,182 | 67,817 | 164,590 | 327,565 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 2 | Low Menthol Initiation | 17,181 | 67,812 | 164,555 | 327,396 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 3 | High Menthol Initiation | 17,182 | 67,822 | 164,625 | 327,733 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 4 | Low Menthol Experimentation | 15,411 | 61,041 | 147,794 | 292,601 | 2,019,295 | 3,908,229 | 5,920,677 | 8,051,353 |
| 5 | High Menthol Experimentation | 20,723 | 81,367 | 198,181 | 397,489 | 2,827,013 | 5,471,520 | 8,288,948 | 11,271,894 |
| 6 | Low Yield from Experimenter to Smoker | 2,127 | 10,220 | 21,810 | 30,346 | 0 | 0 | 0 | 0 |
| 7 | High Yield from Experimenter to Smoker | 19,838 | 77,980 | 189,784 | 380,008 | 2,692,393 | 5,210,972 | 7,894,236 | 10,735,137 |
| 8 | Low Menthol Cessation | 18,495 | 74,138 | 178,061 | 346,122 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 9 | High Menthol Cessation | 11,023 | 38,336 | 101,964 | 241,409 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 10 | Low Menthol Mortality Risk | -239,508 | -293,535 | -220,657 | -41,279 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 11 | High Menthol Mortality Risk | 238,551 | 378,451 | 494,892 | 644,022 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 12 | Low Switch Rate Menthol to Non-menthol | 17,227 | 68,265 | 166,070 | 330,538 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 13 | High Switch Rate Menthol to Non-Menthol | 17,138 | 67,397 | 163,252 | 324,972 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 14 | Low Switch Rate Non-menthol to Menthol | 17,139 | 67,399 | 163,249 | 324,993 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 15 | High Switch Rate Non-menthol to Menthol | 17,224 | 68,223 | 165,874 | 329,989 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |

The model results indicate that the availability of menthol cigarettes increases the numbers of people who initiate smoking, as well as leading to premature death from smoking caused diseases. Table 1 provides the numbers of excess initiators and of premature deaths. The first row of the table provides the results based on TPSAC's best estimates of the model parameters. The findings provide an approximate indication of the magnitude of the public health impact of the availability of menthol cigarettes. For example, assuming the best estimates, by 2020 about 17,000 premature deaths will occur and about 2.3 million people will have started smoking, beyond what would have occurred absent availability of menthol cigarettes. The cumulative figures mount over time. The remaining rows of the table provide similar results for the additional scenarios. All show excess mortality and numbers of smoking initiators as associated with the availability of menthol cigarettes.

Mendez also explored the public health impact of the high proportion of menthol cigarette smoking among African American smokers. He compared two scenarios: one reflecting the current proportion of menthol use among experiments and initiators (80% for both) compared with a counterfactual identical to that for the general population (40% of experiments using menthol cigarettes and 45% experimenters). Table 2 below (table 6 in Appendix A) provides the findings for the current situation and for the counterfactual, respectively. The difference between the estimates in any cell of the two tables reflects the difference in menthol cigarette use. For example, in 2020, there are an additional 2,025 (4,716 - 2691) excess deaths because of the higher menthol prevalence in the scenario labeled TPSAC estimates. Similarly, there are about 150,000 additional smokers in 2020 attributable to the higher menthol prevalence.

**Table 2. Results-African American Population**

| Description | Cumulative Excess Deaths | | | | Cumulative Excess Smoking Initiation | | | |
|---|---|---|---|---|---|---|---|---|
| | 2020 | 2030 | 2040 | 2050 | 2020 | 2030 | 2040 | 2050 |
| African American Population – TPSAC Estimates | 4,716 | 16,381 | 35,250 | 66,524 | 461,273 | 859,101 | 1,262,086 | 1,656,005 |
| Low Menthol Prevalence Hypothetical African American Population | 2,691 | 10,244 | 23,218 | 44,771 | 307,515 | 572,734 | 841,391 | 1,104,003 |

The results of all models are subject to uncertainty, reflecting incomplete knowledge about underlying relationships and the values of the parameters in the model. Mendez used previously developed and well-characterized models as the starting point for developing the menthol models. The values for parameters were based on the literature reviews carried out by TPSAC. The consequences of assuming particular values for key parameters were explored through sensitivity analyses. As the parameters used as input of the model are subject to the statistical uncertainty inherent to their individual estimation process, a Monte Carlo analysis would be required to capture the combined effect of such uncertainty or the results of the analysis. This analysis would not likely change the magnitude of the results, as the model is linear, and the simulation settings and parameters chosen were conservative.

TPSAC also considered the findings of modeling carried out by Levy et al. (2011) on the future effects of a menthol cigarette ban in the total US population and among African Americans. While TPSAC is not proposing specific policy actions that should be taken by FDA, the modeling of the consequences of a ban provides further insight into the impact of menthol cigarettes on public health. The scenarios considered involved the consequences of implementing a ban in 2011, using the distribution of smoking in the U.S. population as of 2003. Table 2 provides the principal findings for changes in the numbers of smokers and the avoided premature deaths. The comparison scenarios to the status quo involve changes of 10 percent, 20 percent, and 30 percent in the rates of initiation (reduced) and cessation (increased). The authors do not propose that any of these scenarios is most probable. Regardless of scenario, a ban is associated with avoidance of premature mortality for a substantial number of deaths. The figure for a 10% change is similar to the estimate based on TPSAC's best estimates.

The results from Mendez and Levy et al., while based on different models and assumptions, provide comparable insights into the quantitative magnitude of the public health impact of the availability of menthol cigarettes. The burden is substantial; for example, the cumulative excess deaths estimated by Mendez for the 40-year period, 2010-2050, is about 80% of the number of deaths annually currently attributed to cigarette smoking in the United States (US DHHS 2004). Over that same time period, an estimated 9 million people will initiate smoking because of the availability of menthol cigarettes. The models for African Americans show that the high prevalence of menthol cigarette smoking adds to the burden of premature death experienced by this population.

While subject to uncertainty, the model results confirm TPSAC's qualitative judgment on the adverse impact of menthol cigarettes on public health. They do not capture the considerable excess burden of morbidity, coming from chronic diseases, infectious diseases, and diminished well-being that is attributable to smoking.

**RECOMMENDATIONS**

Mentholation of cigarettes was discovered by accident in the 1920s. Even then, the sensory and medicinal properties of menthol were known and these properties, along with cigarette design and marketing, have made menthol cigarettes a substantial component of the cigarette market in the United States. In the decades since the first menthol cigarettes were made, there have been substantial advances in the understanding of the pharmacology of menthol, of how to use menthol to manipulate flavor and the sensory perception of cigarette smoke, and of the interplay between menthol and

nicotine. Marketing of menthol cigarettes has been successful. Menthol cigarettes are now smoked by most African American smokers and there is a concerning rise of menthol cigarette smoking among youth. Menthol cannot be considered merely a flavoring additive to tobacco. Its pharmacological actions reduce the harshness of smoke and the irritation from nicotine, and may increase the likelihood of nicotine addiction in adolescents and young adults who experiment with smoking. Furthermore, the distinct sensory characteristics of menthol may enhance the addictiveness of menthol cigarettes, which appears to be the case among youth. TPSAC has found that the availability of menthol cigarettes has adverse impact on public health by increasing the numbers of smokers with resulting premature death and avoidable morbidity.

Consequently, TPSAC makes the following overall recommendation to FDA:

**Removal of menthol cigarettes from the marketplace would benefit public health in the United States.**

The Act offers a variety of mechanisms for FDA to consider, if it concludes that it should pursue this recommendation. At this time, TPSAC has no specific suggestions for follow-up by FDA to this recommendation.

**Contraband**

With regard to any proposed standard, the Act states under section 907(b) that: "The Secretary shall consider all other information submitted in connection with a proposed standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or non-tobacco users, such as the creation of a significant demand for contraband or other tobacco products that do not meet the requirements of this chapter and the significance of such demand."

Several presentations in public hearings and written submissions to TPSAC speculated on the potential for contraband as a consequence of a ban on menthol cigarettes. The concerns expressed originated with experience gained from black market activity involving non-menthol cigarettes. The general concern about contraband following a potential ban on menthol cigarettes can be summarized as follows: a black market for menthol cigarettes could be created, criminal activity could ensue, and different methods might be used to supply such a black market. The demand for contraband menthol cigarettes might be met through evasion, illegal production and importation of menthol cigarettes, and after-market mentholation (Public Hearing Date, testimony of from Michael G. Hering, JD deputy chief counsel— Tobacco Master Settlement Agreement, National Association of Attorneys General).

**Evasion**

TPSAC recognizes that the current laws governing the sale and taxation of cigarettes can be evaded. Examples of evasion that might not violate a menthol ban were included in the presentation by Michael G. Hering. One example of such evasion involved the use of menthol cigars, roll your own menthol cigarettes, menthol pipe tobacco, menthol tubes, rolling papers and filters, and the emergence and use of after market mentholation kits. A second example pertained to the FDA tobacco flavoring ban. The flavoring band currently pertains only to cigarettes and not to cigars. Shortly after the FDA flavor ban was implemented, Djarum introduced clove cigars into the market. Other cigars with cherry, peach, strawberry, grape and pina colada and apple tini were also introduced, effectively evading the FDA ban on flavored tobacco.

**Illegal production and importation of menthol cigarettes**

Based on public testimony, TPSAC identified a number of likely sources of menthol cigarettes that would be illegal under a ban. The sources of imported contraband would include foreign manufacturers, domestic manufacturing for foreign markets, and unlicensed domestic manufacturers.

**After Market Mentholation**

If roll your own (RYO) menthol tobacco or menthol pipe tobacco became unavailable, then consumers could purchase their own menthol tubes or rolling paper as well as menthol filter tips. Other forms of aftermarket mentholation were suggested based on current experience with non-menthol cigarettes. Since cigarettes that come off of the manufactures line are mentholated after the fact, it is plausible that after market mentholation kits might become available. After market mentholated kits would allow consumers to create a homegrown menthol cigarette and with the advent of the RYO Filling stations, consumers would not be limited to hand rolling their cigarettes(http://ryofillingstation.com/about.php). Whether such after market mentholation kits could produce levels of mentholation identical to the current branded products or whether 14,000,000 menthol cigarette smokers would make the effort to mentholate their own cigarettes remains unknown.

**Potential Menthol Black Market**

TPSAC recognizes that the potential size of a menthol black market cannot be readily estimated, due to the need to make uncertain assumptions as to the nature and functioning of such a black market. For example, how would distribution of large numbers of contraband menthol cigarettes through illegal channels to the public take place on a daily basis? If the precisely engineered menthol levels in currently available menthol brands cannot be reproduced, is it likely that a substantial black market would develop, particularly since non-menthol cigarettes would be available?
TPSAC did receive industry-supported testimony from Compass Lexecon that attempted to estimate the size of a potential menthol cigarette black market. Based on marketing data provided by Lorillard Inc., Compass Lexecon undertook an analysis that modeled the effect of a menthol cigarette ban. They concluded that a ban would not eliminate menthol cigarette consumption by current menthol smokers in the U.S., and that most current smokers would turn either to a black market for menthol cigarettes or would turn instead to non-menthol cigarettes. Compass Lexecon also speculated on the possible unintended consequences of increased criminal activity as well as concerns about the possibility that youth might have greater access to unregulated cigarettes associated with a black market.

The Compass Lexecon report estimated that a sizable black market would quickly emerge to satisfy the demand for menthol cigarettes. They further estimated that the size of the black market based on the anticipated increased price of black market cigarettes. This report estimated that a 10% increase in the effective price of illegal menthol cigarettes would lead to unit sales of black market menthol cigarettes amounting to about 87% of current legal menthol volumes. Further, the report estimated that a 50% increase in the effective price in black market menthol cigarettes would result in black market menthol sales amounting to about 56% of current legal menthol sales. (Estimating consequences of a Ban on the Legal Sale of Menthol Cigarettes, Compass Lexecon, December 29, 2010). This same analysis predicted that based on the black market price increases noted above, that a 10% price increase would reduce overall smoking rates by 1% and a 50% black market price increase would result in a 3.5% reduction in the overall smoking rates. The authors concluded, based on the above predictions, that less than a 30% reduction in smoking prevalence would be achieved by a ban on menthol cigarettes.

TPSAC noted that this economic analysis did not address the question of a menthol ban's effects on youth smoking initiation or the cumulative effect of a ban after several years. The analysis does not address whether African American smokers who prefer menthol cigarettes and are not yet addicted to nicotine would choose to continue smoking. Because the analysis did not incorporate these possibilities, the results may have underestimated the percentage and number of people who would stop smoking as well as the number of youth who would never begin smoking if menthol cigarettes were not available. Consequently, the model may have overestimated the size of any potential black market.

TPSAC, whose charge is to specifically address issues related to youth smoking, also recognizes that an analysis of the impact of a menthol ban on the overall smoking rates over time should include the effect of price increases on youth. The hypothesis that cigarette smoking by younger persons will be relatively more responsive to price than smoking among older persons is confirmed by studies of cigarette demand based on cross-sectional surveys of youths and young adults. Recent estimates indicate that youths are up to three times more sensitive to price than adults, with a 10- percent price increase estimated to reduce youth smoking prevalence by 5 percent or more and also to reduce cigarette consumption among continuing young smokers (Chaloupka and Grossman, 1996; Evans and Huang, 1998; Lewit et al., 1997,Smoking and Tobacco Control, page 196,NCI Monograph No.14). The greater price sensitivity of youth and young adults, compared to adults 25 years and older, indicates that price increases produced by a black market would reduce initiation and encourage cessation among the youth and young adults.

TPSAC acknowledges that the potential for contraband menthol cigarettes exists, should FDA choose to implement a ban or take some other policy action that restricts availability of menthol cigarettes. Consistent with the requirements of the Act, TPSAC recommends that FDA consult with appropriate experts and carry out relevant analyses depending on the actions taken in response to this report from TPSAC. At present, TPSAC is not constituted to carry out such analyses, and lacking knowledge of FDA's intent on receipt of this report, it concluded that FDA would need to assess the potential for contraband menthol cigarettes as required by the Act.

**Other Considerations**

The removal of menthol cigarettes from the market could result in a substantial reduction in cigarette smoking, according to data from the May 2010 TUS-CPS survey. The survey asked menthol smokers (N=2877)*, "If menthol cigarettes were no longer sold, which of the following would you most likely do?"* According to analysis presented to TPSAC by Anne M. Hartman of the National Cancer Institute (January 2010), 39 percent of menthol smokers would quit, followed by those would switch to non-menthol cigarettes (36.2 percent) or switch to another tobacco product (7.7 percent). Her analysis included a breakdown of potential quitters by race/ethnicity, age and gender: among African American menthol smokers, (47 percent); among non-Hispanic white menthol smokers ( 34 percent) ; among menthol smokers age 18–44 years ( 41 percent) ; among smokers age 45 years and over (37 percent); among female menthol smokers( 42 percent); and among male menthol smokers, (36 percent).

In her presentation, Hartman noted that behavioral intention is associated with actual behavior. She concluded that the results suggest a potential substantial reduction in tobacco use if menthol cigarettes were no longer sold. Should FDA take any action that would remove menthol cigarettes from the marketplace, planning should address the potential demand for cessation services.

**RESEARCH RECOMMENDATIONS**

In the course of reviewing the evidence related to its charge, TPSAC noted gaps in understanding of menthol cigarettes and public health that should be addressed with further research. Here, TPSAC makes brief recommendations with acknowledgement that the priority given to particular recommendations may depend on any policy action taken by the FDA.

- **Subliminal menthol**: TPSAC was given the charge of addressing "menthol in cigarettes", but, as set out in Chapter 1, focused this report on menthol cigarettes. Several studies suggested that menthol may be present in some cigarettes in which it is not a characterizing additive. TPSAC suggests that further research should be carried out to characterize the menthol content of cigarettes in general and to assess whether menthol has pharmacologic effects at these concentrations that might affect initiation, dependence or cessation.
- **Susceptible and vulnerable populations**: TPSAC found little data on use of menthol cigarettes by the severely mentally ill, a population with a high prevalence of cigarette smoking. This gap should be addressed, as should data gaps for other potentially vulnerable populations. There is now substantial research on genetic determinants of addiction to nicotine; studies on this topic should incorporate consideration of menthol cigarette smoking into their protocols. In addition, more research is required to assess whether menthol interacts with genetically determined bitterness taste sensitivity (sensitivity to phenylthiocarbamate (PTC) and 6-n-propylthiouracil (PROP)) to facilitate smoking.

- **Strengthen the evidence foundation on the public health impact of menthol cigarettes:**
    - Cohort studies of adolescents and young adults should be carried out that follow participants from experimentation to initiation to dependence. These studies would provide an improved understanding of the risk for moving across this sequence that is associated with menthol cigarette availability.
    - The consequences of menthol cigarette smoking for likelihood of successful cessation need further investigation in the general population. Additionally, the implications of menthol cigarettes for sustained quitting should be addressed in clinical trials of cessation therapy and other databases.
    - Develop surveillance protocols to track industry marketing practices including price promotions and their impact on smoking patterns with attention to menthol cigarettes. The protocols should be sufficiently fine-grained with regard to populations and places and focus on critical periods of policy implementation.

**APPENDIX A**

# Results from a Population Dynamics Model of the Consequences of Menthol Cigarettes for Smoking Prevalence and Disease Risks[1]

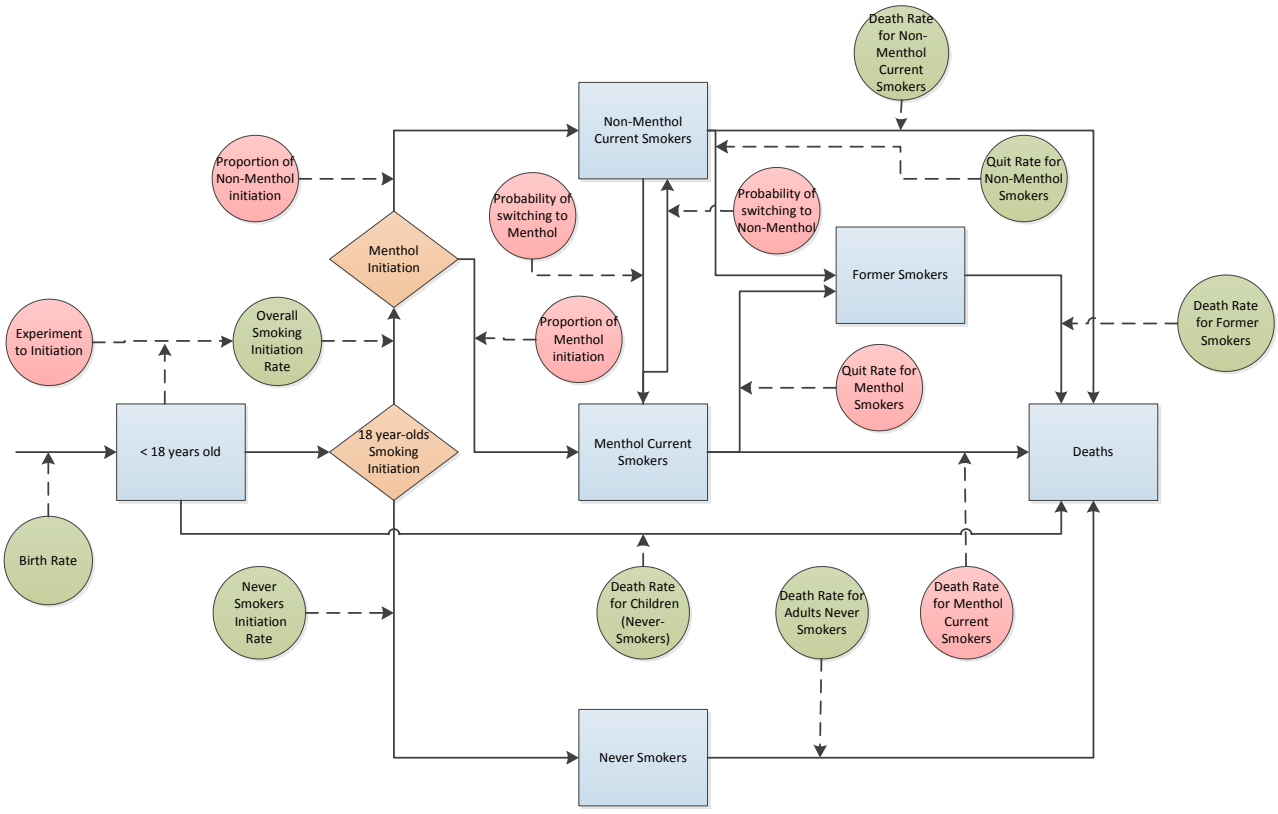
David Méndez, PhD
University of Michigan
March 2011

[1] The work reported was done under contract with the Center for Tobacco Products at FDA. The content and conclusions of this report are solely the author's

**Results from a Population Dynamics Model of the Consequences of Menthol Cigarettes for Smoking Prevalence and Disease Risks**

This document describes the constructs of, and results from, the model commissioned by the Tobacco Products Scientific Advisory Committee (TPSAC) to estimate the consequences of menthol cigarette smoking on the U.S population. The model is an extension and modification of a population dynamics model previously developed to track smoking prevalence and smoking related risks, which has been extensively discussed in the literature.[1-7] The following figure shows the general organization of the model, as modified to address menthol cigarettes:

**Menthol Model Block Simulation Diagram**



The boxes (compartments) represent the stock of individuals in different categories at a given time; the arrows represent the flow between compartments; and the circles represent parameters that modify the flow. Red circles refer to parameters related to menthol smoking while green circles refer to the other parameters. Diamonds represent the event of smoking initiation, concentrated at a single age.

Following is a description of the constructs of the model:

**Definition of dynamic (time-dependent) variables:**

$P(a,t)$ = US population of age $a$ in year $t$

$N(a,t)$ = Population of never – smokers of age $a$ in year $t$

$F(a,t,q)$ = Population of former – smokers of age $a$, in year $t$, that quit $q$ years ago

$C(a,t)$ = Population of current – smokers of age $a$ in year $t$

$C_m(a,t)$ = Population of current menthol – smokers of age $a$ in year $t$

$C_n(a,t)$ = Population of current non – menthol – smokers of age $a$ in year $t$

$\pi_N(a,t)$ = Prevalence of never – smokers of age $a$ in year $t$

$\pi'_N(t)$ = Adult prevalence of never – smokers in year $t$

$\pi_F(a,t)$ = Prevalence of former – smokers of age $a$ in year $t$

$\pi'_F(t)$ = Adult prevalence of former – smokers in year $t$

$\pi_C(a,t)$ = Prevalence of current – smokers of age $a$ in year $t$

$\pi'_C(t)$ = Adult prevalence of curent – smokers in year $t$

$\pi_{C_m}(a,t)$ = Prevalence of current menthol – smokers of age $a$ in year $t$

$\pi'_{C_m}(t)$ = Adult prevalence of current menthol – smokers in year $t$

$\pi_{C_n}(a,t)$ = Prevalence of current non – menthol – smokers of age $a$ in year $t$

$\pi'_{C_n}(t)$ = Adult prevalence of current non menthol smokers in year $t$

$D(t)$ = Total deaths in year $t$

**Definition of Non-dynamic variables and parameters:**

$\mu(a)$ = Overall death rate for individuals of age $a$

$\mu_N(a)$ = Death rate among non − smokers of age $a$

$\mu_F(a,q)$ = Death rate among former − smokers of age $a$ who quit $q$ years ago

$\mu_C(a)$ = Death rate among current − smokers of age $a$

$\mu_{C_m}(a)$ = Death rate among current menthol − smokers of age $a$

$\mu_{C_n}(a)$ = Death rate among current non − menthol − smokers of age $a$

$\rho(a)$ = Overall smoking quit rate for individuals of age $a$

$\rho_{C_m}(a)$ = Smoking quit rate for menthol smokers of age $a$

$\rho_{C_n}(a)$ = Smoking quit rate for non − menthol smokers of age $a$

$S_{mnn}$ = Switching rate from menthol to non − menthol among current menthol smokers

$S_{nnm}$ = Switching rate from non − menthol to menthol among current menthol smokers

$I$ = Smoking initiation age

$\gamma$ = Overall smoking initiation rate

$\gamma_{C_m}$ = Smoking initiation rate for menthol smokers

$\gamma_{C_n}$ = Smoking initiation rate for non − menthol smokers

$RR(a,q)$ = Relative risk of death for a former smoker of age $a$ who quit $q$ years ago − $q = 0$ implie

$K_1$ = Mortality risk ratio $\left(\frac{Menthol}{Non-Menthol}\right)$

$K_2$ = Quit rates ratio $\left(\frac{Menthol}{Non-Menthol}\right)$

$K_3$ = Proportion of Menthol among Initiators

$K_4$ = Proportion of Menthol among Experimenters

$K_E$ = *Ratio of Yields from Experimenter to Established Smoker* $\left(\frac{Menthol}{Non-Menthol}\right)$

**Dynamic (time-dependent) relationships:**

$$N(0,t) = P(0,t)$$

$$N(a,t) = N(a-1,t-1) \times (1 - \mu_N(a)) \quad for\ a \neq 1$$

$$N(a,t) = N(a-1,t-1) \times (1 - \mu_N(a)) \times \left(1 - \gamma_{C_m} - \gamma_{C_n}\right) \quad for\ a = 1$$

$$F(a,t,q) = 0 \quad for\ a - q \leq 1$$

$$F(a,t,1) = C_m(a-1,t-1) \times \left(1 - \mu_{C_m}(a-1)\right) \times \rho_{C_m}(a-1) + C_n(a-1,t-1) \times \left(1 - \mu_{C_n}(a-1)\right) \times \rho_{C_n}(a-1)$$

$$F(a,t,q) = F(a-1,t-1,q-1) \times \left(1 - \mu_{C_F}(a-1,q-1)\right) \quad for\ a - q > 1\ and\ q > 1$$

$$C_m(a,t) = 0\ for\ a < 1$$

$$C_m(a,t) = \gamma_{C_m} \times N(a-1,t-1) \times (1 - \mu_N(a-1)) \quad for\ a = 1$$

$$C_m(a,t) = C_m(a-1,t-1) \times \left(1 \quad \mu_{C_m}(a-1)\right) \times \left(1 \quad \rho_{C_m}(a-1)\right) \times (1 \quad S_{msn}(a-1)) + C_n(a-1,t-1) \times \left(1\right.$$

$$C_n(a,t) = 0\ for\ a < 1$$

$$C_n(a,t) = \gamma_{C_n} \times N(a-1,t-1) \times (1 - \mu_N(a-1)) \quad for\ a = 1$$

$$C_n(a,t) = C_n(a-1,t-1) \times \left(1 - \mu_{C_n}(a-1)\right) \times \left(1 - \rho_{C_n}(a-1)\right) \times (1 - S_{nsm}(a-1)) + C_m(a-1,t-1) \times \left(1 -\right.$$

$$P(a,t) = N(a,t) + \sum_{q=1}^{q=80+} F(a,t,q) + C_m(a,t) + C_n(a,t)$$

$$\pi_N(a,t) = \frac{N(a,t)}{P(a,t)}$$

$$\pi'_N(t) = \frac{\sum_{a=18}^{a=100} N(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_F(a,t) = \frac{\sum_{q=1}^{q=80+} F(a,t,q)}{P(a,t)}$$

$$\pi'_F(t) = \frac{\sum_{a=18}^{a=100} \sum_{q=1}^{q=80+} F(a,t,q)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_{C_m}(a,t) = \frac{C_m(a,t)}{P(a,t)}$$

$$\pi'_{C_m}(t) = \frac{\sum_{a=18}^{a=100} C_m(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_{C_n}(a,t) = \frac{C_n(a,t)}{P(a,t)}$$

$$\pi'_{C_n}(t) = \frac{\sum_{a=18}^{a=100} C_n(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$D(t) = \sum_{a=0}^{a=100} N(a,t) \times \mu_N(a) + \sum_{a=0}^{a=100} \sum_{q=1}^{q=80+} F(a,t,q) \times \mu_F(a,q) + \sum_{a=0}^{a=100} C_m(a,t) \times \mu_{C_m}(a) + \sum_{a=0}^{a=100} C_n(a,t) \times \mu_{C_n}$$

**Non-dynamic relationships:**

- Expressions related to mortality risks and derivation of death rates for current-, former- and never-smokers given overall death rates $\mu(a)$ in 2010.

$$K_1 = \frac{\mu_{C_m}(a)}{\mu_{C_n}(a)}$$

$$\mu_F(a,q) = \mu_N(a) \times RR(a,q)$$

$$\mu_{C_m}(a) = K_1 \times \mu_N(a) \times RR(a,0)$$

$$\mu_{C_n}(a) = \mu_N(a) \times RR(a,0)$$

$$\mu(a) = \mu_N(a) \times \pi_N(a,2010) + \left( \sum_{q=1}^{q=80+} \mu_N(a) \times RR(a,q) \times \pi_F(a,2010,q) \right) + K_1 \times \mu_N(a) \times RR(a,0) \times \pi_{C_m}(a,201$$

$$\mu_N(a) = \frac{\mu(a)}{\pi_N(a,2010) + \sum_{q=1}^{q=80+} (RR(a,q) \times \pi_F(a,2010,q)) + K_1 \times RR(a,0) \times \pi_{C_m}(a,2010) + RR(a,0) \times \pi_{C_n}(a,2010)}$$

Expressions related to quit rates and derivation of quit rates for menthol and non-menthol smokers given overall quit rates $\rho(a)$ in 2010.

$$K_s = \frac{\rho_{C_m}(a)}{\rho_{C_n}(a)}$$

$$\rho_{C_m}(a) = K_s \times \rho_{C_n}(a)$$

$$\rho(a) = K_s \times \rho_{C_n}(a) \times \pi_{C_m}(a, 2010) + \rho_{C_n}(a) \times \pi_{C_n}(a, 2010) \rightarrow$$

$$\rho_{C_n} = \frac{\rho(a)}{K_s \times \pi_{C_m}(a, 2010) + \pi_{C_n}(a, 2010)}$$

- Expressions related to the initiation rate and derivation of initiation rate under the counterfactual scenario (in which menthol cigarettes do not exist) given overall smoking initiation rate $\gamma$ in 2010.

$$\gamma = \gamma_{C_m} + \gamma_{C_n}$$

$$\gamma_{C_m} = K_s \times \gamma$$

$$\gamma_{C_n} = (1 - K_s \times \gamma)$$

*Let $W$ be the size of a cohort of potential experimenters, $E$ the proportion of experimenters in that cohort, $Y_m$ the proportion of menthol experimenters that become established smokers, and $Y_n$ the proportion of non – menthol experimenters that become established smokers; then, $W \times E \times K_s$ is the number of menthol experimenters and $W \times E \times (1 - K_s)$ is the number of non – menthol experimenters. It follows that:*

$$W \times E \times K_s \times Y_m + W \times E \times (1 - K_s) \times Y_n = W \times \gamma$$

*Given that* $\frac{Y_m}{Y_n} = K_s$, *then*

$$W \times E \times K_s \times K_s \times Y_n + W \times E \times (1 - K_s) \times Y_n = W \times \gamma \quad or$$

$$Y_n = \frac{\gamma}{E \times (K_a \times K_s + (1 - K_a))}$$

*Let $\gamma'$ be the initiation rate under the counterfactual, then, assuming the same proportion of experimenters as in the status – quo scenario:*

$$W \times E \times Y_n = W \times \gamma' \text{ or}$$

$$\gamma' = E \times Y_n = \frac{E \times \gamma}{E \times (K_a \times K_s + (1 - K_a))} = \frac{\gamma}{K_a \times K_s + (1 - K_a)}$$

**Description of the Model**

The model projects the US population, distinguished by age (0 to 100) and smoking status, over the period 2010-2050. Smoking status is categorized by current smokers of menthol cigarettes, current smokers of non-menthol cigarettes, never smokers and former smokers. The latter group is further divided by years quit. The model tracks former smokers from 1 to 30 years quit.

Each year, for the next 40 years (2010 to 2050) and for every year of age (from 0 to 100), the model follows the number of individuals in each category. Each simulated year the model introduces a birth cohort obtained from the U.S. Census Bureau projections for the period 2010-2050 and ages the population using age- and smoking status- specific death rates. Individuals younger than 18 are consider non-smokers. At age 18 (age 20 for African Americans) a proportion of individuals become menthol smokers, another fraction become non-menthol smokers and the rest remain non-smokers for their remaining life span. After age 18 smokers are given the chance to quit smoking or switch between menthol and non-menthol cigarettes. Those who quit become former smokers and are tracked not just by age but also by years since quit.

The age-specific background cessation rates used in the simulations are the ones estimated by Mendez and Warner (1998)[1]. Those quit rates have been validated since.[5] The quit rates were adjusted to reflect differences between menthol and non-menthol smoking according to the expressions derived on page 6. Age-specific death rates were computed for current (menthol and non-menthol), never, and former smokers by years quit employing smoking relative risks derived from the Cancer Prevention Study II (CPS II) data[8] and the procedure described on pages 5 and 6. Relative risks for current and former smokers specific to the US African American population were derived from CPS II data and supplied by the American Cancer Society (Michael Thun, American Cancer Society, personal communication, March 2011). Background death rates for the general population were obtained from the US Census Bureau. Initial (2010) estimates for overall smoking prevalence for the general and African American populations were obtained from the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS) respectively. The initiation rate for the general population was taken to be 21.8%, the smoking prevalence among 18 year-olds reported by the NHIS in 2009. For African Americans, the initiation rate was taken to be 19.8%, consistent with the smoking prevalence at age 20 reported by the BRFSS 2005 for African Americans. Initial (2010) estimates of menthol prevalence were obtained from the National Survey on Drug Use and Health (NSDUH). All data used to produce this report are publicly available.

**Simulation Experiments Settings and Results**

The model was used to evaluate the impact of menthol cigarettes on the entire US population and the US African American population. To do this, a simulation covering the period from 2010 to 2050 was performed assuming that current (2010) initiation and cessation

rates will remain constant through that period (status-quo scenario). Then the simulation was repeated, now assuming as the counterfactual that menthol cigarettes have never existed in the U.S. The actual 2010 US smoking prevalence was assumed as the 2010 smoking prevalence under the counterfactual, now produced only by non-menthol smoking. For quit rates under the counterfactual, the same non-menthol age-specific quit rates employed in the comparing status-quo scenario were used; the initiation rate on the counterfactual $(\gamma')$ was computed according to the expression derived on page 6 and 7. The difference in cumulative deaths and cumulative initiation between the status-quo and counterfactual scenarios is reported.

Status quo parameters related to menthol were provided by TPSAC based on literature review findings. An extensive sensitivity analysis of those parameters on the results for the general population was conducted employing parameter ranges also supplied by TPSAC. The results of the analysis for the general population are shown on Tables 1 - 3.

A sensitivity analysis on the African American model was not conducted because of lack of specific data on some parameters and because the rest of the parameters did not show to be sensitive in the general population model. Instead, the results of the African American model were compared to those of a hypothetical population identical to the US African American population in all aspects except menthol prevalence. This hypothetical population was given the same menthol prevalence as the general US population. This comparison highlights the extra burden that menthol imposes on the African American population. The results of the analysis for the African American population are shown on Tables 4 – 6.

**Table 1. Input Parameters – General Population:**

| Parameter | Min | TPSAC Estimate | Max |
|---|---|---|---|
| Proportion of Menthol among Initiators[2] ($K_3$) | 0.35 | 0.40 | 0.45 |
| Proportion of Menthol among Experimenters[2] ($K_14$) | 0.38 | 0.45 | 0.60 |
| Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[2] ($K_15$) | 1.00 | 1.68 | 1.85 |
| Cessation Rates Ratio (Menthol/Non-menthol)[2] ($K_12$) | 0.92 | 0.95 | 1.10 |
| Mortality Risk Ratio (Menthol/Non-menthol)[2] ($K_1$) | 0.80 | 1.00 | 1.20 |
| Switching Rate from Menthol to Non-menthol (among Menthol smokers)[3] ($S_1m2n$) | 0.9% | 1.8% | 2.7% |
| Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[3] ($S_1n2m$) | 0.4% | 0.8% | 1.2% |

[2] Provided by TPSAC
[3] From the switching book adjusted for proper denominator – Range +/- 50%

## Table 2. Scenario Analysis – General Population

| Scenario | Description | Prop of Menthol Initiation | Proportion of Menthol Experimentation | Experimentation to Initiation Yield Ratio Menthol/Non-Menthol | Initiation Rate under Counterfactual | Cessation Ratio Menthol/Non-Menthol | Mortality Ratio Menthol/Non-Menthol | Switching Rate Menthol to Non-Menthol | Switching Rate Non-Menthol to Menthol |
|---|---|---|---|---|---|---|---|---|---|
| 1 | TPSAC Estimates | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 1.8% | 0.8% |
| 2 | Low Menthol Initiation | 0.35 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 1.8% | 0.8% |
| 3 | High Menthol Initiation | 0.45 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 1.8% | 0.8% |
| 4 | Low Menthol Experimentation | 0.40 | 0.38 | 1.68 | 17.3% | 0.95 | 1.00 | 1.8% | 0.8% |
| 5 | High Menthol Experimentation | 0.40 | 0.60 | 1.68 | 15.5% | 0.95 | 1.00 | 1.8% | 0.8% |
| 6 | Low Yield from Experimenter to Smoker | 0.40 | 0.45 | 1.00 | 21.8% | 0.95 | 1.00 | 1.8% | 0.8% |
| 7 | High Yield from Experimenter to Smoker | 0.40 | 0.45 | 1.85 | 15.8% | 0.95 | 1.00 | 1.8% | 0.8% |
| 8 | Low Menthol Cessation | 0.40 | 0.45 | 1.68 | 16.7% | 0.92 | 1.00 | 1.8% | 0.8% |
| 9 | High Menthol Cessation | 0.40 | 0.45 | 1.68 | 16.7% | 1.10 | 1.00 | 1.8% | 0.8% |
| 10 | Low Menthol Mortality Risk | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 0.80 | 1.8% | 0.8% |
| 11 | High Menthol Mortality Risk | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.20 | 1.8% | 0.8% |
| 12 | Low Switch Rate Menthol to Non-menthol | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 0.9% | 0.8% |
| 13 | High Switch Rate Menthol to Non-Menthol | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 2.7% | 0.8% |
| 14 | Low Switch Rate Non-menthol to Menthol | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 1.8% | 0.4% |
| 15 | High Switch Rate Non-menthol to Menthol | 0.40 | 0.45 | 1.68 | 16.7% | 0.95 | 1.00 | 1.8% | 1.2% |

| Scenario | Description | Cumulative Excess Deaths | Cumulative Excess Smoking Initiation |
|---|---|---|---|

**Table 3. Results – General Population**

| | | 2020 | 2030 | 2040 | 2050 | 2020 | 2030 | 2040 | 2050 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | TPSAC Estimates | 17,182 | 67,817 | 164,590 | 327,565 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 2 | Low Menthol Initiation | 17,181 | 67,812 | 164,555 | 327,396 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 3 | High Menthol Initiation | 17,182 | 67,822 | 164,625 | 327,733 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 4 | Low Menthol Experimentation | 15,411 | 61,041 | 147,794 | 292,601 | 2,019,295 | 3,908,229 | 5,920,677 | 8,051,353 |
| 5 | High Menthol Experimentation | 20,723 | 81,367 | 198,181 | 397,489 | 2,827,013 | 5,471,520 | 8,288,948 | 11,271,894 |
| 6 | Low Yield from Experimenter to Smoker | 2,127 | 10,220 | 21,810 | 30,346 | 0 | 0 | 0 | 0 |
| 7 | High Yield from Experimenter to Smoker | 19,838 | 77,980 | 189,784 | 380,008 | 2,692,393 | 5,210,972 | 7,894,236 | 10,735,137 |
| 8 | Low Menthol Cessation | 18,495 | 74,138 | 178,061 | 346,122 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 9 | High Menthol Cessation | 11,023 | 38,336 | 101,964 | 241,409 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 10 | Low Menthol Mortality Risk | -239,508 | -293,535 | -220,657 | -41,279 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 11 | High Menthol Mortality Risk | 238,551 | 378,451 | 494,892 | 644,022 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 12 | Low Switch Rate Menthol to Non-menthol | 17,227 | 68,265 | 166,070 | 330,538 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 13 | High Switch Rate Menthol to Non-Menthol | 17,138 | 67,397 | 163,252 | 324,972 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 14 | Low Switch Rate Non-menthol to Menthol | 17,139 | 67,399 | 163,249 | 324,993 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |
| 15 | High Switch Rate Non-menthol to Menthol | 17,224 | 68,223 | 165,874 | 329,989 | 2,288,534 | 4,429,326 | 6,710,101 | 9,124,867 |

**Table 4. Input Parameters – African American Population:**

| Parameter | TPSAC Estimate |
|---|---|
| Proportion of Menthol among Initiators ($K_3$)[4] | .80 |
| Proportion of Menthol among Experimenters[5] ($K_14$) | .80 |
| Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[6] ($K_15$) | 1.68 |
| Cessation Rates Ratio (Menthol/Non-menthol)[6] ($K_12$) | 0.95 |
| Mortality Risk Ratio (Menthol/Non-menthol)[5] ($K_1$) | 1 |
| Switching Rate from Menthol to Non-menthol (among Menthol smokers)[7] ($S_1m2n$) | 0.9% |
| Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[7] ($S_1n2m$) | 4% |
| Initiation Rate under Counterfactual[8] ($\gamma'$) | 12.7% |

[4] Same values as experimenters
[5] Provided by TPSAC
[6] Same values as those of the general population
[7] From the switching book adjusted for proper denominator
[8] Computed according to expression on page 7

**Table 5. Input Parameters – Hypothetical Low Menthol African American Population:**

| Parameter | Estimate |
|---|---|
| Proportion of Menthol among Initiators ($K_3$)[9] | .40 |
| Proportion of Menthol among Experimenters[9] ($K_14$) | .45 |
| Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[10] ($K_15$) | 1.68 |
| Cessation Rates Ratio (Menthol/Non-menthol)[10] ($K_12$) | 0.95 |
| Mortality Risk Ratio (Menthol/Non-menthol)[10] ($K_1$) | 1 |
| Switching Rate from Menthol to Non-menthol (among Menthol smokers)[10] ($S_1m2n$) | 0.9% |
| Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[10] ($S_1n2m$) | 4% |
| Initiation Rate under Counterfactual[11] ($\gamma'$) | 15.0% |

[9] Same values as in the general population
[10] Same values as in the African American Population
[11] Computed according to expression on page 7

| Description | Cumulative Excess Deaths | | | | Cumulative Excess Smoking Initiation | | | |
|---|---|---|---|---|---|---|---|---|
| | 2020 | 2030 | 2040 | 2050 | 2020 | 2030 | 2040 | 2050 |
| African American Population – TPSAC Estimates | 4,716 | 16,381 | 35,250 | 66,524 | 461,273 | 859,101 | 1,262,086 | 1,656,005 |
| Low Menthol Prevalence Hypothetical African American Population | 2,691 | 10,244 | 23,218 | 44,771 | 307,515 | 572,734 | 841,391 | 1,104,003 |

**Table 6. Results – African American Population**

**References:**


1. Mendez D, Warner KE and Courant PN. "Has Smoking Cessation Ceased? Expected Trends in the Prevalence of Smoking in the United States." *American Journal of Epidemiology*, 1998;148(3):249-58.

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7. Mendez D and Warner KE. "Setting a challenging, yet realistic smoking prevalence target for Healthy People 2020: Learning from the California experience." *American Journal of Public Health*, 2008;98(3):556-9.

8. Mendez D, Warner KE. "The relative risk of death for former smokers: the influence of age and years-quit." *Unpublished research monograph*, 2001. Available at http://www.umich.edu/~dmendez/tobacco/RRiskmonograph.doc. Accessed March 14, 2011.

**APPENDIX B**

**TPSAC Meeting Dates and Topics**

- March 30-31, 2010 – Summary presentation of published literature on menthol
    - Invited Presenters - Lawrence Deyton, M.S.P.H., M.D., Catherine Lorraine, J.D., Corinne Husten, M.D., M.P.H., Ralph Caraballo, Ph.D., M.P.H., Deirdre Lawrence, Ph.D., M.P.H., Joshua Rising, M.D., M.P.H., Allison C. Hoffman, Ph.D.

- July 15-16, 2010 – Industry presentations on menthol in cigarettes as it relates to characterization of menthol, clinical effects of menthol, biomarkers of disease risk, marketing data, and population effects
    - Invited Presenters - Corinne Husten, M.D., M.P.H., James E. Dillard III, Jane Y. Lewis, Ph.D., Michael W. Ogden, Ph.D., William R. True, Ph.D., Mohamadi A. Sarkar, Ph.D., Pascal A. Fernandez, Monica J. Graves, Leonard H. Jones, Geoffrey M. Curtin, Ph.D., Jennifer L. Hunter, William R. True, Ph.D., David L. Ashley, Ph.D.

- September 27, 2010 – Menthol Report Subcommittee met to discuss timelines and the structure of the Menthol Report.
    - Invited Presenters - Corinne Husten, M.D., M.P.H., Karen Templeton-Somers, Ph.D., Jonathan Samet, M.D.

- October 7, 2010 – Presentations on publicly available industry documents from the Legacy Tobacco Documents Library
    - Invited Presenters - Corinne Husten, M.D., M.P.H., Allison C. Hoffman, Ph.D., Jonathan Samet, M.D., Stacey J. Anderson, Ph.D., Valerie B. Yerger, N.D.

- November 18, 2010 – Updates from the Menthol Report Subcommittee and presentation on secondary analysis of the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Presenters - Corinne Husten, M.D., M.P.H., Jonathan Samet, M.D., James C. Hersey, Ph.D., Brett R. Loomis

- January 10-11, 2011 – Updates from the Menthol Report Subcommittee , presentation regarding contraband and menthol, presentation on modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting.
    - Invited Presenters - Jonathan M. Samet, M.D., M.S., Neal L. Benowitz, M.D., Patricia Nez Henderson, M.P.H., M.D.., Dorothy K. Hatsukami, Ph.D., Mark Stuart Clanton, M.D., M.P.H.

- February 10, 2011 – Updates from the Menthol Report Subcommittee, presentation on updated modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Speakers - Corinne Husten, M.D., M.P.H., David Mendez, Ph.D., Brian F. Thomas, Ph.D., Hernán Navarro, Ph.D., Kenneth H. Davis, Jr., James Hersey, Ph.D., Jonathan Samet, M.D.

- February 11, 2011– Menthol Report Subcommittee met to discuss timelines and the structure of the Menthol Report.
    - Invited Speakers - Corinne Husten, M.D., M.P.H., Jonathan M. Samet, M.D., M.S., Neal L. Benowitz, M.D., Patricia Nez Henderson, M.P.H., M.D.., Dorothy K. Hatsukami, Ph.D., Mark Stuart Clanton, M.D., M.P.H.

- March 2, 2011 – Updates from the Menthol Report Subcommittee, presentation on updated modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Speakers - David L. Ashley, Ph.D., David Mendez, Ph.D., Neal Benowitz, M.D., Jonathan Samet, M.D., M.S., Eric O. Johnson, Ph.D., Daniel J. Heck, Ph.D., DABT

- March 17-18, 2011 – Updates from the Menthol Report Subcommittee (including proposed recommendations) and presentation on updated modeling schema

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**Alphabetical list of all invited speakers (consolidated from agendas)**

Stacey J. Anderson, Ph.D.
David L. Ashley, Ph.D.
Neal L. Benowitz, M.D.
Ralph Caraballo, Ph.D., M.P.H.
Mark Stuart Clanton, M.D., M.P.H.
Geoffrey M. Curtin, Ph.D.
Kenneth H. Davis, Jr.
Lawrence Deyton, M.S.P.H., M.D.
James E. Dillard III
Pascal A. Fernandez
Monica J. Graves
Dorothy K. Hatsukami, Ph.D.
Daniel J. Heck, Ph.D., DABT
Patricia Nez Henderson, M.P.H., M.D.
James C. Hersey, Ph.D.
Allison C. Hoffman, Ph.D.
Jennifer L. Hunter
Corinne Husten, M.D., M.P.H.
Eric O. Johnson, Ph.D.
Leonard H. Jones
Deirdre Lawrence, Ph.D., M.P.H.
Jane Y. Lewis, Ph.D.
Brett R. Loomis
Catherine Lorraine, J.D.
David Mendez, Ph.D.
Hernán Navarro, Ph.D.
Michael W. Ogden, Ph.D.
Joshua Rising, M.D., M.P.H.
Jonathan Samet, M.D.
Mohamadi A. Sarkar, Ph.D.
Karen M. Templeton-Somers, Ph.D.
Brian F. Thomas, Ph.D.
William R. True, Ph.D.
Valerie B. Yerger, N.D.
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PROJECT CODE: 1808

# TEST REPORT

# THE DETERMINATION OF SELECTED ANALYTES IN MAINSTREAM SMOKE UNDER FTC CONDITIONS

**Prepared for:**

**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**

**October 31, 2004**

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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APPENDIX L – Metals I

APPENDIX M – Mercury

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## I. STUDY OVERVIEW

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

Test cigarettes for this study consisted of five cigarette types, which are listed in Table I.

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

The laboratory control cigarette for this project was the Kentucky Reference 2R4F cigarette.

A minimum of five observations per brand were determined for mainstream smoke, as specified by the client.

The results were electronically submitted to the client on October 20, 2004.

Analytical Methods and results are included in the attached Appendices.

## II. TESTING FACILITY

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

## III. TEST CIGARETTES

### A. Receipt, storage and conditioning of test cigarettes

- 1400 sticks of each cigarette type were received on August 27, 2004.
- Cigarettes were stored at ambient conditions until required for testing.
- The brand code designations are given in Table I.
- Before smoking, cigarettes were conditioned according to Arista SOP QP-18 Handling of Test Items.

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**Table I: Brand Coding**

| Client Brand Description | Arista Code |
|---|---|
| Camel 100 | 3557 |
| Marlboro Light | 3558 |
| Quest 1 | 3559 |
| Quest 2 | 3560 |
| Quest 3 | 3561 |

**B. Constituent List**

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

**Table II: Constituent List**

| Analyte Group | Arista SOP | Validation Report |
|---|---|---|
| Tar, Nicotine, and CO | T-001 v.2, T-007 v.1 | V-005 and V-005-2 |
| Carbonyls | T-005 v.4 | V-002 |
| Phenolics | T-027 v.4 | V-017 |
| Volatiles | T-015 v.4 | V-007 |
| Semivolatiles | T-006 v.2 | V-004 |
| Ammonia | T-011 v.2 | V-009 |
| Polynuclear Aromatic Hydrocarbons (PAHs) | T-038 v.5 | V-025 |
| Hydrogen Cyanide (HCN) | T-049 v.0 | V-033 |
| Aromatic Amines I | T-030 v.5 | V-016 |
| Nitric Oxide | T-029 v.2 | V-018 |
| Aromatic Amines II | T-091 v. 0 | V-046 |
| Metals | T-021 v.3 | V-014 |
| Mercury | T-036 v.3 | V-021 |
| Tobacco Specific Nitrosamines (TSNAs) | T-020 v.2 | V-013 |

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**C. Sample Generation and Records**

Smoking was performed under FTC conditions (35cc puff volume every 60 seconds). Randomized run orders were generated for each analysis. The project was completed with the electronic submission of the final data.

## IV. QUALITY STATEMENT\SIGNATURES

The results of this study have been 100% independently reviewed by the Quality Assurance Unit.

The analytical results in the attached appendices were tested with the Dixon Q test where deemed necessary. All outliers were noted and repeats were conducted if cause was determined. All control runs passed according to Arista policies and procedures and according to the relevant Arista SOPs.

QA Review: Alex Martin Date Oct. 31/04
A. M. Martin, QA Manager

Management Approval: G. Holloway Date Nov. 1, 2004
G. V. Holloway, Laboratory Director

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# APPENDIX A

## Analysis of Mainstream Cigarette Smoke for Tar, Nicotine and Carbon Monoxide

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# DETERMINATION OF TAR, NICOTINE AND CARBON MONOXIDE IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

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

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

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

**Mainstream TNC Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-001/T-007
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run# | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | CO (mg/cigt) | Water (mg/cigt) | Nicotine (mg/cigt) | Tar (mg/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00420 | E | Camel 100 | 3557 | 11.3 | 24.74 | 16.66 | 3.96 | 1.48 | 19.30 |
| C00420 | J | Camel 100 | 3557 | 11.3 | 23.58 | 16.31 | 2.49 | 1.52 | 19.58 |
| C00420 | Q | Camel 100 | 3557 | 11.6 | 24.66 | 18.05 | 3.56 | 1.53 | 19.57 |
| C00421 | J | Camel 100 | 3557 | 11.2 | 24.14 | 17.36 | 2.79 | 1.49 | 19.86 |
| C00421 | O | Camel 100 | 3557 | 11.5 | 23.66 | 16.82 | 2.74 | 1.49 | 19.43 |
| C00421 | Q | Camel 100 | 3557 | 11.0 | 23.96 | 18.04 | 2.32 | 1.47 | 20.17 |
| | | | **Average** | **11.3** | **24.12** | **17.21** | **2.98** | **1.50** | **19.65** |
| | | | **sd** | **0.2** | **0.49** | **0.73** | **0.64** | **0.02** | **0.32** |
| | | | **%RSD** | **1.9** | **2.0** | **4.3** | **21.7** | **1.4** | **1.6** |
| C00420 | C | Marlboro Light | 3558 | 8.6 | 12.72 | 11.60 | 1.09 | 0.83 | 10.79 |
| C00420 | I | Marlboro Light | 3558 | 8.1 | 12.18 | 12.69 | 0.86 | 0.81 | 10.50 |
| C00420 | K | Marlboro Light | 3558 | 8.1 | 12.56 | 10.90 | 0.99 | 0.81 | 10.76 |
| C00420 | M | Marlboro Light | 3558 | 8.1 | 12.46 | 10.93 | 1.07 | 0.80 | 10.59 |
| C00420 | O | Marlboro Light | 3558 | 8.1 | 12.20 | 10.96 | 0.94 | 0.81 | 10.44 |
| C00421 | R | Marlboro Light | 3558 | 8.6 | 13.50 | 11.70 | 0.95 | 0.86 | 11.70 |
| | | | **Average** | **8.3** | **12.60** | **11.46** | **0.98** | **0.82** | **10.80** |
| | | | **sd** | **0.3** | **0.49** | **0.70** | **0.09** | **0.02** | **0.46** |
| | | | **%RSD** | **3.4** | **3.9** | **6.1** | **8.8** | **2.5** | **4.3** |
| C00421 | A | Quest 1 | 3559 | 7.1 | 11.12 | 11.46 | 1.09 | 0.48 | 9.54 |
| C00421 | D | Quest 1 | 3559 | 6.6 | 11.22 | 11.36 | 0.93 | 0.49 | 9.80 |
| C00421 | F | Quest 1 | 3559 | 6.6 | 10.98 | 10.68 | 1.08 | 0.47 | 9.44 |
| C00421 | H | Quest 1 | 3559 | 6.3 | 10.78 | 10.44 | 1.12 | 0.47 | 9.20 |
| C00421 | K | Quest 1 | 3559 | 6.8 | 11.20 | 11.28 | 1.18 | 0.45 | 9.57 |
| C00421 | M | Quest 1 | 3559 | 6.7 | 11.04 | 11.19 | 0.65 | 0.48 | 9.91 |
| | | | **Average** | **6.7** | **11.06** | **11.07** | **1.01** | **0.47** | **9.58** |
| | | | **sd** | **0.3** | **0.16** | **0.41** | **0.19** | **0.01** | **0.26** |
| | | | **%RSD** | **3.8** | **1.5** | **3.7** | **19.1** | **3.0** | **2.7** |
| C00420 | D | Quest 2 | 3560 | 6.4 | 10.88 | 11.89 | 0.70 | 0.29 | 9.90 |
| C00420 | S | Quest 2 | 3560 | 6.6 | 10.52 | 12.03 | 1.03 | 0.27 | 9.21 |
| C00421 | B | Quest 2 | 3560 | 6.7 | 12.18 | 11.91 | 1.67 | 0.31 | 10.20 |
| C00421 | I | Quest 2 | 3560 | 6.2 | 10.44 | 10.88 | 0.97 | 0.25 | 9.21 |
| C00421 | L | Quest 2 | 3560 | 6.2 | 10.78 | 11.25 | 1.32 | 0.28 | 9.18 |
| | | | **Average** | **6.4** | **10.96** | **11.59** | **1.14** | **0.28** | **9.54** |
| | | | **sd** | **0.2** | **0.71** | **0.50** | **0.37** | **0.02** | **0.48** |
| | | | **%RSD** | **3.9** | **6.4** | **4.3** | **32.7** | **7.0** | **5.0** |

**Mainstream TNC Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-001/T-007
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run# | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | CO (mg/cigt) | Water (mg/cigt) | Nicotine (mg/cigt) | Tar (mg/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00420 | B | Quest 3 | 3561 | 6.1 | 8.72 | 9.79 | 0.79 | 0.049 | 7.89 |
| C00420 | P | Quest 3 | 3561 | 6.1 | 7.94 | 9.76 | 0.44 | 0.047 | 7.46 |
| C00420 | R | Quest 3 | 3561 | 6.3 | 8.58 | 10.39 | 0.58 | 0.052 | 7.95 |
| C00421 | C | Quest 3 | 3561 | 6.2 | 9.22 | 10.30 | 0.89 | 0.045 | 8.28 |
| C00421 | N | Quest 3 | 3561 | 6.2 | 8.62 | 10.38 | 0.95 | 0.047 | 7.62 |
| | | | **Average** | **6.2** | **8.62** | **10.12** | **0.73** | **0.048** | **7.84** |
| | | | **sd** | **0.1** | **0.46** | **0.32** | **0.22** | **0.003** | **0.32** |
| | | | **%RSD** | **1.5** | **5.3** | **3.2** | **29.6** | **5.7** | **4.1** |
| C00420 | N | 2R4F | 912 | 9.0 | 10.80 | 11.50 | 0.62 | 0.79 | 9.39 |
| C00421 | G | 2R4F | 912 | 9.1 | 12.24 | 13.32 | 0.92 | 0.83 | 10.49 |
| C00421 | P | 2R4F | 912 | 9.3 | 11.50 | 12.09 | 0.78 | 0.80 | 9.92 |
| | | | **Average** | **9.1** | **11.51** | **12.30** | **0.77** | **0.81** | **9.93** |
| | | | **sd** | **0.2** | **0.72** | **0.93** | **0.15** | **0.02** | **0.55** |
| | | | **%RSD** | **1.8** | **6.3** | **7.5** | **19.4** | **2.9** | **5.5** |

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PROJECT CODE: 1808

# APPENDIX B

## Analysis of Mainstream Cigarette Smoke for Carbonyls and Aldehydes

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# DETERMINATION OF CARBONYLS AND ALDEHYDES IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-005 Determination of Carbonyls and Aldehydes in Mainstream Smoke.

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

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

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

**Mainstream Carbonyls Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-005
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port Code | Client Code | Arista Code | Puffs (/cigt) | formaldehyde (µg/cigt) | acetaldehyde (µg/cigt) | acetone (µg/cigt) | acrolein (µg/cigt) | propionaldehyde (µg/cigt) | crotonaldehyde (µg/cigt) | methylethylketone (µg/cigt) | butyraldehyde (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 400877 | B | Camel 100 | 3557 | 10 | 32.9 | 811 | 364 | 93.6 | 67.9 | 27.4 | 103 | 42.3 |
| 400878 | A | Camel 100 | 3557 | 9 | 36.5 | 851 | 374 | 97.7 | 71.2 | 24.5 | 110 | 44.2 |
| 400878 | I | Camel 100 | 3557 | 10 | 46.7 | 1015 | 449 | 105 | 86.0 | 34.9 | 137 | 52.0 |
| 400879 | B | Camel 100 | 3557 | 11 | 37.1 | 938 | 410 | 109 | 78.3 | 26.8 | 124 | 47.7 |
| 400879 | H | Camel 100 | 3557 | 11 | 39.0 | 948 | 413 | 101 | 81.2 | 27.8 | 126 | 49.2 |
| 400896 | A | Camel 100 | 3557 | 11 | 45.3 | 925 | 408 | 115 | 75.5 | 30.7 | 122 | 59.5 |
| | | | **Average** | **10.3** | **39.6** | **915** | **403** | **104** | **76.7** | **28.7** | **120** | **49.2** |
| | | | **SD** | **0.8** | **5.4** | **73** | **31** | **8** | **6.6** | **3.6** | **12** | **6.1** |
| | | | **%RSD** | **7.9** | **13.6** | **8.0** | **7.6** | **7.6** | **8.6** | **12.7** | **9.9** | **12.5** |
| 400877 | C | Marlboro Light | 3558 | 8 | 25.7 | 597 | 260 | 70.0 | 50.6 | 20.3 | 77.9 | 30.3 |
| 400877 | E | Marlboro Light | 3558 | 7 | 24.1 | 581 | 251 | 67.8 | 47.8 | 20.1 | 71.7 | 30.2 |
| 400877 | G | Marlboro Light | 3558 | 8 | 27.5 | 715 | 311 | 68.2 | 60.1 | 27.3 | 91.1 | 35.9 |
| 400877 | I | Marlboro Light | 3558 | 7 | 22.0 | 572 | 249 | 53.0 | 48.0 | 19.5 | 65.8 | 28.3 |
| 400878 | C | Marlboro Light | 3558 | 8 | 30.2 | 632 | 275 | 73.6 | 54.6 | 20.1 | 81.9 | 32.8 |
| 400878 | J | Marlboro Light | 3558 | 7 | 24.0 | 618 | 271 | 61.3 | 49.7 | 18.4 | 78.6 | 33.2 |
| | | | **Average** | **7.5** | **25.6** | **619** | **269** | **65.6** | **51.8** | **21.0** | **77.8** | **31.8** |
| | | | **SD** | **0.5** | **2.9** | **52** | **23** | **7.4** | **4.7** | **3.2** | **8.7** | **2.7** |
| | | | **%RSD** | **7.3** | **11.3** | **8.4** | **8.4** | **11.2** | **9.1** | **15.1** | **11.1** | **8.5** |
| 400877 | J | Quest 1 | 3559 | 6 | 21.4 | 399 | 133 | 24.4 | 26.2 | 9.82 | 35.9 | 15.0 |
| 400878 | B | Quest 1 | 3559 | 6 | 31.3 | 558 | 198 | 48.9 | 38.6 | 14.4 | 53.8 | 23.8 |
| 400878 | D | Quest 1 | 3559 | 6 | 19.9 | 352 | 111 | 24.9 | 22.2 | 6.40 | 28.2 | 13.1 |
| 400879 | A | Quest 1 | 3559 | 7 | 19.5 | 360 | 106 | 25.2 | 22.5 | 5.81 | 27.2 | 12.8 |
| 400879 | C | Quest 1 | 3559 | 6 | 24.3 | 447 | 158 | 36.5 | 30.6 | 10.0 | 42.1 | 17.5 |
| 400879 | I | Quest 1 | 3559 | 8 | 23.7 | 498 | 164 | 36.0 | 32.3 | 8.82 | 41.4 | 17.9 |
| | | | **Average** | **6.5** | **23.4** | **436** | **145** | **32.6** | **28.8** | **9.20** | **38.1** | **16.7** |
| | | | **SD** | **0.8** | **4.4** | **81** | **35** | **9.7** | **6.4** | **3.08** | **9.9** | **4.1** |
| | | | **%RSD** | **12.9** | **18.7** | **18.7** | **24.0** | **29.8** | **22.1** | **33.5** | **26.1** | **24.4** |

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**Mainstream Carbonyls Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

| | |
|---|---|
| **Project Code:** | **1808** |
| **Project Start Date:** | **27-Aug-04** |
| **Arista SOP #:** | **T-005** |
| **Smoking Protocol:** | **FTC** |
| **Authorized By:** | **A. Martin** |
| **Title:** | **QA Mgr** |

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

| Run # | Port Code | Client Code | Arista Code | Puffs (/cigt) | formaldehyde (µg/cigt) | acetaldehyde (µg/cigt) | acetone (µg/cigt) | acrolein (µg/cigt) | propionaldehyde (µg/cigt) | crotonaldehyde (µg/cigt) | methylethylketone (µg/cigt) | butyraldehyde (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 400877 | D | Quest 2 | 3560 | 5 | 15.0 | 269 | 75.3 | 17.4 | 15.9 | 4.70 | 19.7 | 9.32 |
| 400879 | D | Quest 2 | 3560 | 6 | 16.4 | 401 | 125 | 25.3 | 24.4 | 6.00 | 31.5 | 14.1 |
| 400879 | G | Quest 2 | 3560 | 7 | 25.9 | 523 | 159 | 35.4 | 33.1 | 8.70 | 39.2 | 18.5 |
| 400896 | B | Quest 2 | 3560 | 6 | 12.4 | 302 | 110 | 22.0 | 19.1 | 4.90 | 27.2 | 13.6 |
| 400896 | E | Quest 2 | 3560 | 6 | 17.0 | 406 | 153 | 29.7 | 26.5 | 8.37 | 40.3 | 19.0 |
| 400896 | H | Quest 2 | 3560 | 7 | 21.9 | 533 | 182 | 39.2 | 33.6 | 10.0 | 45.4 | 23.3 |
| | | | **Average** | **6.2** | **18.1** | **406** | **134** | **28.2** | **25.4** | **7.12** | **33.9** | **16.3** |
| | | | **SD** | **0.8** | **4.9** | **109** | **38** | **8.3** | **7.2** | **2.22** | **9.5** | **4.9** |
| | | | **%RSD** | **12.2** | **27.2** | **26.9** | **28.6** | **29.3** | **28.3** | **31.2** | **28.2** | **30.3** |
| 400877 | A | Quest 3 | 3561 | 6 | 9.12 | 372 | 138 | 25.4 | 22.3 | 7.66 | 34.0 | 15.0 |
| 400878 | E | Quest 3 | 3561 | 6 | 10.6 | 333 | 95.7 | 19.3 | 18.0 | 4.02 | 21.7 | 10.9 |
| 400878 | H | Quest 3 | 3561 | 6 | 9.82 | 312 | 105 | 18.1 | 20.4 | 4.78 | 25.3 | 12.1 |
| 400879 | J | Quest 3 | 3561 | 6 | 10.2 | 342 | 107 | 20.9 | 20.4 | 5.11 | 25.6 | 12.3 |
| 400896 | C | Quest 3 | 3561 | 6 | 8.74 | 375 | 115 | 23.0 | 19.0 | 4.60 | 24.7 | 14.5 |
| 400896 | F | Quest 3 | 3561 | 6 | 8.17 | 338 | 116 | 21.2 | 18.8 | 4.7 | 26.2 | 16.2 |
| | | | **Average** | **6.0** | **9.44** | **345** | **113** | **21.3** | **19.8** | **5.15** | **26.3** | **13.5** |
| | | | **SD** | **0.0** | **0.92** | **24** | **14** | **2.6** | **1.5** | **1.28** | **4.1** | **2.0** |
| | | | **%RSD** | **0.0** | **9.7** | **7.1** | **12.7** | **12.3** | **7.8** | **24.8** | **15.7** | **15.1** |
| 400877 | F | 2R4F | 912 | 8 | 28.6 | 714 | 312 | 71.2 | 57.7 | 21.0 | 96.9 | 36.2 |
| 400878 | G | 2R4F | 912 | 8 | 20.9 | 567 | 256 | 54.2 | 49.1 | 13.4 | 80.2 | 28.1 |
| 400879 | E | 2R4F | 912 | 9 | 27.9 | 706 | 312 | 71.9 | 58.5 | 16.5 | 96.4 | 34.7 |
| 400896 | D | 2R4F | 912 | 9 | 22.2 | 637 | 296 | 67.0 | 51.8 | 15.2 | 91.2 | 39.2 |
| | | | **Average** | **8.5** | **24.9** | **656** | **294** | **66.1** | **54.3** | **16.5** | **91.2** | **34.6** |
| | | | **SD** | **0.6** | **3.9** | **69** | **26** | **8.2** | **4.6** | **3.3** | **7.8** | **4.7** |
| | | | **%RSD** | **6.8** | **15.8** | **10.4** | **8.9** | **12.4** | **8.4** | **19.7** | **8.5** | **13.6** |

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# APPENDIX C

## Analysis of Mainstream Cigarette Smoke for Phenolics

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# DETERMINATION OF PHENOLIC COMPOUNDS IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

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

Phenolics in mainstream tobacco smoke are collected on a 44 mm Cambridge filter pad. The pad is extracted with 20 mL of 1% Acetic Acid/ 5% MeOH in $H_2O$, and the solution is diluted to a known volume. Before analysis by High Performance Liquid Chromatography (HPLC), the solution is filtered. An HPLC equipped with a reversed-phase column and a fluorescence detector is used for the analysis. This system utilizes an increasing methanol fraction in a methanol:water gradient to elute potentially interfering compounds, and the analytes from the column, at different times. All phenolics are well separated except m-cresol and p-cresol, which coelute. Therefore, only one value is reported for m+p-cresol. The eluted compounds are detected with a fluorescence detector. Hydroquinone is detected with an excitation wavelength of 304 nm and emission wavelength of 338 nm. The other compounds are detected with an excitation wavelength of 274 nm and emission wavelength of 298 nm.

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

**Mainstream Phenolics Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-027
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Hydroquinone (µg/cigt) | Resorcinol (µg/cigt) | Catechol (µg/cigt) | Phenol (µg/cigt) | m+p-Cresol (µg/cigt) | o-Cresol (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C00416 | B | Camel 100 | 3557 | 11.2 | 27.0 | 71.6 | 1.55 | 79.6 | 21.0 | 15.1 | 5.44 |
| C00416 | C | Camel 100 | 3557 | 11.3 | 25.1 | 68.8 | 1.46 | 77.7 | 19.7 | 14.0 | 4.98 |
| C00416 | H | Camel 100 | 3557 | 11.5 | 27.3 | 70.5 | 1.52 | 79.4 | 22.5 | 15.2 | 5.49 |
| C00416 | J | Camel 100 | 3557 | 10.8 | 24.3 | 67.4 | 1.47 | 78.8 | 19.2 | 13.9 | 5.05 |
| C00416 | O | Camel 100 | 3557 | 11.0 | 26.1 | 66.6 | 1.47 | 80.1 | 19.8 | 13.5 | 4.79 |
| C00419 | D | Camel 100 | 3557 | 11.9 | 25.1 | 68.2 | 1.40 | 81.7 | 20.8 | 13.8 | 4.98 |
| | | | **Average** | **11.3** | **25.8** | **68.9** | **1.48** | **79.5** | **20.5** | **14.2** | **5.12** |
| | | | **SD** | **0.4** | **1.2** | **1.9** | **0.05** | **1.4** | **1.2** | **0.7** | **0.28** |
| | | | **%RSD** | **3.6** | **4.5** | **2.8** | **3.5** | **1.7** | **5.9** | **5.0** | **5.5** |
| C00416 | T | Marlboro Light | 3558 | 8.7 | 13.7 | 40.4 | 1.10 | 45.9 | 9.45 | 7.38 | 2.42 |
| C00419 | C | Marlboro Light | 3558 | 8.2 | 12.8 | 37.7 | 1.08 | 41.7 | 9.14 | 7.06 | 2.33 |
| C00419 | F | Marlboro Light | 3558 | 8.2 | 13.2 | 38.2 | 1.07 | 43.3 | 8.86 | 6.60 | 2.17 |
| C00419 | H | Marlboro Light | 3558 | 8.2 | 13.0 | 36.8 | 0.99 | 41.5 | 8.06 | 6.15 | 2.02 |
| C00419 | P | Marlboro Light | 3558 | 7.9 | 12.9 | 37.4 | 1.07 | 42.2 | 8.56 | 6.83 | 2.28 |
| C00419 | Q | Marlboro Light | 3558 | 8.0 | 12.3 | 35.6 | 0.99 | 42.1 | 7.20 | 5.86 | 1.93 |
| | | | **Average** | **8.2** | **13.0** | **37.7** | **1.05** | **42.8** | **8.55** | **6.65** | **2.19** |
| | | | **SD** | **0.3** | **0.5** | **1.6** | **0.05** | **1.7** | **0.81** | **0.57** | **0.19** |
| | | | **%RSD** | **3.4** | **3.7** | **4.3** | **4.5** | **3.9** | **9.5** | **8.5** | **8.6** |

**Mainstream Phenolics Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-027
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Hydroquinone (µg/cigt) | Resorcinol (µg/cigt) | Catechol (µg/cigt) | Phenol (µg/cigt) | m+p-Cresol (µg/cigt) | o-Cresol (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C00416 | D | Quest 1 | 3559 | 6.7 | 11.0 | 35.7 | 0.77 | 35.2 | 11.2 | 8.52 | 2.99 |
| C00416 | E | Quest 1 | 3559 | 6.6 | 11.3 | 34.8 | 0.85 | 35.1 | 10.6 | 8.38 | 2.89 |
| C00416 | G | Quest 1 | 3559 | 6.7 | 10.0 | 30.5 | 0.71 | 30.5 | 9.38 | 7.43 | 2.61 |
| C00416 | K | Quest 1 | 3559 | 6.7 | 11.3 | 33.7 | 0.78 | 35.0 | 10.2 | 8.01 | 2.81 |
| C00416 | P | Quest 1 | 3559 | 6.7 | 11.0 | 34.4 | 0.79 | 35.2 | 10.9 | 8.30 | 2.93 |
| C00419 | G | Quest 1 | 3559 | 6.8 | 11.2 | 35.7 | 0.89 | 37.6 | 11.1 | 8.49 | 2.99 |
| | | | **Average** | **6.7** | **11.0** | **34.1** | **0.80** | **34.7** | **10.6** | **8.19** | **2.87** |
| | | | **SD** | **0.1** | **0.5** | **1.9** | **0.06** | **2.3** | **0.7** | **0.42** | **0.14** |
| | | | **%RSD** | **1.0** | **4.5** | **5.7** | **7.83** | **6.6** | **6.4** | **5.1** | **4.9** |
| C00416 | N | Quest 2 | 3560 | 6.3 | 10.9 | 29.9 | 0.63 | 30.9 | 9.67 | 8.06 | 2.79 |
| C00419 | E | Quest 2 | 3560 | 6.2 | 10.1 | 29.2 | 0.57 | 30.2 | 9.43 | 7.49 | 2.67 |
| C00419 | I | Quest 2 | 3560 | 6.4 | 11.1 | 30.5 | 0.65 | 32.1 | 9.77 | 8.31 | 2.92 |
| C00419 | K | Quest 2 | 3560 | 6.4 | 10.8 | 31.5 | 0.69 | 32.7 | 9.32 | 7.99 | 2.79 |
| C00419 | M | Quest 2 | 3560 | 6.0 | 9.68 | 27.7 | 0.57 | 28.7 | 8.89 | 7.43 | 2.61 |
| C00419 | O | Quest 2 | 3560 | 6.3 | 10.9 | 29.1 | 0.59 | 31.0 | 9.76 | 7.82 | 2.69 |
| | | | **Average** | **6.3** | **10.6** | **29.6** | **0.62** | **30.9** | **9.47** | **7.85** | **2.74** |
| | | | **SD** | **0.1** | **0.6** | **1.3** | **0.05** | **1.4** | **0.34** | **0.34** | **0.11** |
| | | | **%RSD** | **2.3** | **5.4** | **4.4** | **7.49** | **4.6** | **3.6** | **4.3** | **4.0** |

**Mainstream Phenolics Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-027
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Hydroquinone (µg/cigt) | Resorcinol (µg/cigt) | Catechol (µg/cigt) | Phenol (µg/cigt) | m+p-Cresol (µg/cigt) | o-Cresol (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C00416 | I | Quest 3 | 3561 | 6.3 | 9.78 | 16.2 | 0.38 | 21.0 | 8.87 | 8.05 | 2.52 |
| C00416 | L | Quest 3 | 3561 | 6.0 | 8.68 | 15.0 | 0.34 | 19.1 | 7.86 | 7.33 | 2.23 |
| C00416 | M | Quest 3 | 3561 | 6.0 | 8.96 | 14.2 | 0.34 | 18.6 | 7.12 | 6.91 | 2.14 |
| C00416 | R | Quest 3 | 3561 | 6.3 | 9.16 | 14.7 | 0.34 | 19.8 | 7.83 | 7.41 | 2.36 |
| C00416 | S | Quest 3 | 3561 | 6.2 | 8.40 | 14.7 | 0.32 | 19.1 | 7.46 | 6.69 | 2.11 |
| C00419 | R | Quest 3 | 3561 | 6.0 | 8.52 | 14.0 | 0.34 | 20.0 | 8.20 | 7.82 | 2.46 |
| | | | **Average** | **6.2** | **8.9** | **14.8** | **0.34** | **19.6** | **7.89** | **7.37** | **2.30** |
| | | | **SD** | **0.1** | **0.5** | **0.8** | **0.02** | **0.8** | **0.61** | **0.52** | **0.17** |
| | | | **%RSD** | **2.2** | **5.7** | **5.2** | **5.62** | **4.3** | **7.7** | **7.0** | **7.3** |
| C00416 | F | 2R4F | 912 | 9.1 | 12.5 | 36.4 | 0.73 | 46.0 | 7.69 | 6.63 | 2.31 |
| C00416 | Q | 2R4F | 912 | 8.9 | 11.4 | 32.3 | 0.67 | 43.8 | 8.57 | 6.96 | 2.48 |
| C00419 | J | 2R4F | 912 | 9.2 | 11.6 | 32.2 | 0.67 | 43.7 | 7.56 | 6.45 | 2.25 |
| C00419 | N | 2R4F | 912 | 9.1 | 12.0 | 30.8 | 0.64 | 41.9 | 6.78 | 5.79 | 1.99 |
| | | | **Average** | **9.1** | **11.9** | **32.9** | **0.68** | **43.8** | **7.65** | **6.46** | **2.26** |
| | | | **SD** | **0.1** | **0.5** | **2.4** | **0.03** | **1.7** | **0.73** | **0.49** | **0.20** |
| | | | **%RSD** | **1.4** | **4.1** | **7.4** | **5.1** | **3.8** | **9.6** | **7.6** | **8.9** |

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# APPENDIX D

## Analysis of Mainstream Cigarette Smoke for Volatiles

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# DETERMINATION OF VOLATILES IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

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

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

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

**Mainstream Volatiles Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-015
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | 1,3-butadiene (µg/cigt) | Isoprene (µg/cigt) | Acrylonitrile (µg/cigt) | Benzene (µg/cigt) | Toluene (µg/cigt) | Styrene (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 400868 | D | Camel 100 | 3557 | 10.6 | 20.9 | 48.1 | 470 | 12.0 | 57.4 | 108 | 10.9 |
| 400868 | G | Camel 100 | 3557 | 10.8 | 23.7 | 59.0 | 560 | 15.0 | 64.4 | 119 | 13.6 |
| 400871 | B | Camel 100 | 3557 | 11.0 | 22.8 | 49.3 | 500 | 16.5 | 66.1 | 122 | 13.3 |
| 400871 | F | Camel 100 | 3557 | 11.0 | 23.8 | 49.0 | 495 | 14.0 | 61.4 | 115 | 12.4 |
| 400871 | H | Camel 100 | 3557 | 11.0 | 22.7 | 57.6 | 556 | 13.9 | 65.3 | 121 | 12.4 |
| 400872 | A | Camel 100 | 3557 | 11.0 | 23.4 | 50.3 | 514 | 13.7 | 61.8 | 116 | 12.5 |
| | | | **Average** | **10.9** | **22.9** | **52.2** | **516** | **14.2** | **62.7** | **117** | **12.5** |
| | | | **sd** | **0.2** | **1.1** | **4.8** | **36** | **1.5** | **3.2** | **5** | **0.9** |
| | | | **%RSD** | **1.5** | **4.7** | **9.1** | **6.9** | **10.6** | **5.1** | **4.5** | **7.4** |
| 400862 | F | Marlboro Light | 3558 | 7.6 | 13.2 | 45.8 | 467 | 10.4 | 45.6 | 83.1 | 8.00 |
| 400868 | E | Marlboro Light | 3558 | 8.0 | 12.6 | 35.3 | 371 | 8.72 | 41.2 | 74.6 | 6.24 |
| 400868 | H | Marlboro Light | 3558 | 7.8 | 12.0 | 43.2 | 417 | 9.04 | 41.8 | 76.2 | 6.76 |
| 400871 | D | Marlboro Light | 3558 | 8.2 | 13.0 | 38.0 | 407 | 9.12 | 42.6 | 80.0 | 6.88 |
| 400872 | E | Marlboro Light | 3558 | 8.0 | 12.8 | 37.7 | 374 | 7.96 | 40.6 | 75.5 | 6.08 |
| 400872 | G | Marlboro Light | 3558 | 8.0 | 13.2 | 38.2 | 377 | 8.28 | 39.6 | 74.2 | 6.36 |
| | | | **Average** | **7.9** | **12.8** | **39.7** | **402** | **8.92** | **41.9** | **77.3** | **6.72** |
| | | | **sd** | **0.2** | **0.4** | **4.0** | **37** | **0.85** | **2.1** | **3.5** | **0.70** |
| | | | **%RSD** | **2.6** | **3.3** | **10.0** | **9.2** | **9.5** | **4.9** | **4.6** | **10.4** |

**Mainstream Volatiles Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-015
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | 1,3-butadiene (µg/cigt) | Isoprene (µg/cigt) | Acrylonitrile (µg/cigt) | Benzene (µg/cigt) | Toluene (µg/cigt) | Styrene (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 400862 | E | Quest 1 | 3559 | 6.6 | 10.1 | 23.0 | 172 | 3.72 | 16.3 | 26.6 | 2.92 |
| 400868 | A | Quest 1 | 3559 | 6.6 | 11.2 | 22.9 | 189 | 5.28 | 17.3 | 28.4 | 2.92 |
| 400868 | C | Quest 1 | 3559 | 6.8 | 11.2 | 23.5 | 184 | 3.92 | 16.3 | 26.4 | 3.00 |
| 400868 | F | Quest 1 | 3559 | 7.0 | 11.8 | 30.0 | 218 | 4.60 | 18.9 | 30.8 | 3.64 |
| 400871 | A | Quest 1 | 3559 | 7.0 | 11.6 | 25.6 | 211 | 4.88 | 20.6 | 33.6 | 3.44 |
| 400871 | J | Quest 1 | 3559 | 6.8 | 13.2 | 27.2 | 213 | 5.08 | 20.8 | 33.5 | 3.84 |
| | | | **Average** | **6.8** | **11.5** | **25.4** | **198** | **4.58** | **18.4** | **29.9** | **3.29** |
| | | | **sd** | **0.2** | **1.0** | **2.8** | **19** | **0.63** | **2.0** | **3.3** | **0.40** |
| | | | **%RSD** | **2.6** | **8.9** | **11.2** | **9.4** | **13.8** | **11.1** | **10.9** | **12.2** |
| 400862 | D | Quest 2 | 3560 | 6.2 | 10.7 | 22.9 | 168 | 5.16 | 19.6 | 32.0 | 3.76 |
| 400862 | H | Quest 2 | 3560 | 6.4 | 10.8 | 26.0 | 182 | 5.16 | 19.6 | 31.6 | 3.88 |
| 400862 | J | Quest 2 | 3560 | 6.2 | 11.4 | 23.4 | 171 | 5.08 | 19.7 | 32.2 | 3.96 |
| 400868 | I | Quest 2 | 3560 | 6.0 | 9.70 | 24.2 | 150 | 4.72 | 16.2 | 26.2 | 3.08 |
| 400871 | C | Quest 2 | 3560 | 6.6 | 11.7 | 22.6 | 164 | 5.12 | 19.5 | 31.8 | 3.72 |
| 400871 | I | Quest 2 | 3560 | 6.0 | 10.1 | 23.3 | 155 | 4.60 | 16.8 | 27.5 | 3.20 |
| | | | **Average** | **6.2** | **10.8** | **23.7** | **165** | **4.97** | **18.6** | **30.2** | **3.60** |
| | | | **sd** | **0.2** | **0.8** | **1.2** | **12** | **0.25** | **1.6** | **2.7** | **0.37** |
| | | | **%RSD** | **3.8** | **7.0** | **5.3** | **7.1** | **5.0** | **8.7** | **8.8** | **10.2** |

**Mainstream Volatiles Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-015
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | 1,3-butadiene (µg/cigt) | Isoprene (µg/cigt) | Acrylonitrile (µg/cigt) | Benzene (µg/cigt) | Toluene (µg/cigt) | Styrene (µg/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 400862 | C | Quest 3 | 3561 | 6.2 | 9.16 | 18.4 | 129 | 4.28 | 13.7 | 22.2 | 2.32 |
| 400862 | G | Quest 3 | 3561 | 6.2 | 10.0 | 18.4 | 128 | 4.60 | 13.8 | 23.3 | 2.64 |
| 400862 | I | Quest 3 | 3561 | 6.2 | 10.2 | 16.6 | 123 | 4.56 | 13.9 | 23.6 | 2.60 |
| 400872 | B | Quest 3 | 3561 | 6.2 | 10.5 | 20.0 | 152 | 5.08 | 16.1 | 26.2 | 3.08 |
| 400872 | D | Quest 3 | 3561 | 6.0 | 10.3 | 21.1 | 149 | 5.04 | 15.2 | 25.6 | 3.04 |
| 400872 | H | Quest 3 | 3561 | 6.0 | 9.34 | 20.5 | 142 | 4.44 | 14.3 | 22.8 | 2.60 |
| | | | **Average** | **6.1** | **9.93** | **19.2** | **137** | **4.67** | **14.5** | **24.0** | **2.71** |
| | | | **sd** | **0.1** | **0.55** | **1.7** | **12** | **0.32** | **1.0** | **1.6** | **0.29** |
| | | | **%RSD** | **1.7** | **5.6** | **8.8** | **8.8** | **7.0** | **6.6** | **6.7** | **10.8** |
| 400862 | A | 2R4F | 912 | 8.8 | 11.9 | 38.8 | 381 | 9.64 | 48.5 | 92.8 | 7.12 |
| 400868 | B | 2R4F | 912 | 8.8 | 12.2 | 40.7 | 399 | 8.76 | 47.7 | 90.7 | 7.36 |
| 400871 | G | 2R4F | 912 | 8.8 | 12.6 | 38.8 | 376 | 8.80 | 47.0 | 87.7 | 7.08 |
| 400872 | C | 2R4F | 912 | 8.8 | 11.5 | 36.7 | 318 | 6.96 | 42.4 | 77.9 | 5.56 |
| | | | **Average** | **8.8** | **12.0** | **38.7** | **369** | **8.54** | **46.4** | 87.3 | **6.78** |
| | | | **sd** | **0.0** | **0.4** | **1.7** | **35** | **1.13** | **2.7** | 6.6 | **0.82** |
| | | | **%RSD** | **0.0** | **3.6** | **4.3** | **9.6** | **13.2** | **5.9** | 7.5 | **12.1** |

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PROJECT CODE: 1808

# APPENDIX E

## Analysis of Mainstream Cigarette Smoke for Pyridine, 3-Vinylpyridine and Quinoline

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-006 Determination of Pyridine, 3-Vinylpyridine and Quinoline in Mainstream Smoke.

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

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

**Mainstream Semivolatiles Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-006
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Pyridine (µg/cigt) | 3-vinylpyridine (µg/cigt) | Quinoline (µg/cigt) |
|---|---|---|---|---|---|---|---|---|
| 400860 | E | Camel 100 | 3557 | 11.0 | 22.9 | 10.5 | 2.72 | 0.438 |
| 400861 | C | Camel 100 | 3557 | 10.8 | 24.0 | 12.7 | 3.36 | 0.503 |
| 400861 | I | Camel 100 | 3557 | 10.6 | 22.1 | 9.88 | 3.23 | 0.483 |
| 400866 | A | Camel 100 | 3557 | 10.6 | 23.4 | 11.7 | 2.97 | 0.458 |
| 400866 | F | Camel 100 | 3557 | 11.0 | 23.6 | 11.2 | 3.00 | 0.426 |
| 400867 | A | Camel 100 | 3557 | 10.8 | 21.0 | 8.52 | 2.37 | 0.333 |
| | | | **Average** | **10.8** | **22.8** | **10.8** | **2.94** | **0.440** |
| | | | **sd** | **0.2** | **1.1** | **1.5** | **0.36** | **0.060** |
| | | | **% RSD** | **1.7** | **4.9** | **13.6** | **12.2** | **13.6** |
| 400860 | C | Marlboro Light | 3558 | 7.6 | 13.0 | 6.15 | 1.59 | 0.241 |
| 400861 | A | Marlboro Light | 3558 | 8.0 | 12.5 | 5.78 | 1.58 | 0.244 |
| 400866 | B | Marlboro Light | 3558 | 7.8 | 11.6 | 5.29 | 1.39 | 0.210 |
| 400866 | E | Marlboro Light | 3558 | 8.0 | 12.1 | 5.96 | 1.43 | 0.218 |
| 400866 | H | Marlboro Light | 3558 | 8.0 | 12.6 | 5.58 | 1.26 | 0.204 |
| 400867 | B | Marlboro Light | 3558 | 8.2 | 14.1 | 7.01 | 1.61 | 0.208 |
| | | | **Average** | **7.9** | **12.6** | **5.96** | **1.47** | **0.221** |
| | | | **sd** | **0.2** | **0.9** | **0.59** | **0.14** | **0.017** |
| | | | **% RSD** | **2.6** | **6.7** | **10.0** | **9.5** | **7.8** |
| 400860 | F | Quest 1 | 3559 | 6.8 | 11.5 | 3.68 | 1.36 | 0.261 |
| 400861 | B | Quest 1 | 3559 | 6.4 | 10.5 | 3.22 | 1.16 | 0.229 |
| 400861 | G | Quest 1 | 3559 | 7.0 | 11.5 | 3.99 | 1.31 | 0.263 |
| 400866 | G | Quest 1 | 3559 | 7.0 | 12.1 | 4.37 | 1.35 | 0.244 |
| 400866 | I | Quest 1 | 3559 | 6.6 | 11.1 | 3.29 | 1.21 | 0.226 |
| 400867 | D | Quest 1 | 3559 | 6.2 | 10.7 | 2.87 | 1.10 | 0.226 |
| | | | **Average** | **6.7** | **11.2** | **3.57** | **1.25** | **0.242** |
| | | | **sd** | **0.3** | **0.6** | **0.55** | **0.11** | **0.017** |
| | | | **% RSD** | **4.9** | **5.4** | **15.4** | **8.5** | **7.2** |
| 400860 | A | Quest 2 | 3560 | 6.0 | 10.7 | 3.11 | 0.749 | 0.213 |
| 400861 | D | Quest 2 | 3560 | 6.2 | 10.9 | 2.99 | 0.721 | 0.211 |
| 400861 | F | Quest 2 | 3560 | 6.4 | 10.4 | 3.17 | 0.781 | 0.211 |
| 400861 | H | Quest 2 | 3560 | 6.2 | 10.4 | 2.76 | 0.697 | 0.204 |
| 400866 | J | Quest 2 | 3560 | 6.8 | 11.2 | 3.58 | 0.873 | 0.231 |
| 400867 | E | Quest 2 | 3560 | 5.8 | 9.16 | 2.20 | 0.557 | 0.174 |
| | | | **Average** | **6.2** | **10.5** | **2.97** | **0.730** | **0.207** |
| | | | **sd** | **0.3** | **0.7** | **0.46** | **0.104** | **0.019** |
| | | | **% RSD** | **5.5** | **6.8** | **15.6** | **14.3** | **9.0** |

**Mainstream Semivolatiles Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-006
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Pyridine (µg/cigt) | 3-vinylpyridine (µg/cigt) | Quinoline (µg/cigt) |
|---|---|---|---|---|---|---|---|---|
| 400860 | B | Quest 3 | 3561 | 6.4 | 11.4 | 4.00 | 0.490 | 0.225 |
| 400860 | D | Quest 3 | 3561 | 6.0 | 9.22 | 2.63 | 0.410 | 0.222 |
| 400860 | G | Quest 3 | 3561 | 6.4 | 11.3 | 4.48 | 0.522 | 0.227 |
| 400860 | J | Quest 3 | 3561 | 6.0 | 8.30 | 2.09 | 0.370 | 0.200 |
| 400867 | C | Quest 3 | 3561 | 6.0 | 10.2 | 3.48 | 0.476 | 0.214 |
| 400867 | F | Quest 3 | 3561 | 6.2 | 9.66 | 3.06 | 0.432 | 0.211 |
| | | | **Average** | **6.2** | **10.0** | **3.29** | **0.450** | **0.216** |
| | | | **sd** | **0.2** | **1.2** | **0.88** | **0.056** | **0.010** |
| | | | **% RSD** | **3.2** | **12.1** | **26.8** | **12.5** | **4.7** |
| 400860 | H | 2R4F | 912 | 9.0 | 11.8 | 4.35 | 1.12 | 0.208 |
| 400861 | E | 2R4F | 912 | 8.8 | 11.4 | 5.26 | 1.12 | 0.225 |
| 400866 | D | 2R4F | 912 | 8.6 | 11.7 | 4.94 | 1.17 | 0.194 |
| 400867 | G | 2R4F | 912 | 9.0 | 11.5 | 5.14 | 1.23 | 0.194 |
| | | | **Average** | **8.9** | **11.6** | **4.92** | **1.16** | **0.205** |
| | | | **sd** | **0.2** | **0.2** | **0.40** | **0.05** | **0.015** |
| | | | **% RSD** | **2.2** | **1.8** | **8.2** | **4.4** | **7.3** |

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# APPENDIX F

## Analysis of Mainstream Cigarette Smoke for Ammonia

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# DETERMINATION OF AMMONIA IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-011 Determination of Ammonia in Mainstream Smoke.

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

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

**Mainstream Ammonia Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-011
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Ammonia (µg/cigt) |
|---|---|---|---|---|---|---|
| 400873 | A | Camel 100 | 3557 | 10.8 | 23.6 | 21.6 |
| 400873 | C | Camel 100 | 3557 | 11.0 | 22.6 | 19.4 |
| 400873 | F | Camel 100 | 3557 | 11.0 | 21.1 | 20.1 |
| 400873 | H | Camel 100 | 3557 | 10.8 | 22.2 | 18.8 |
| 400888 | E | Camel 100 | 3557 | 10.6 | 20.8 | 16.6 |
| 400888 | H | Camel 100 | 3557 | 10.8 | 18.9 | 16.9 |
| | | | **Average** | **10.8** | **21.5** | **18.9** |
| | | | **SD** | **0.2** | **1.6** | **1.9** |
| | | | **%RSD** | **1.4** | **7.7** | **10.2** |
| 400875 | C | Marlboro Light | 3558 | 7.8 | 11.7 | 13.1 |
| 400876 | B | Marlboro Light | 3558 | 7.8 | 12.3 | 13.8 |
| 400876 | H | Marlboro Light | 3558 | 8.0 | 12.9 | 13.3 |
| 400888 | A | Marlboro Light | 3558 | 7.6 | 12.3 | 15.8 |
| 400888 | C | Marlboro Light | 3558 | 7.8 | 11.5 | 13.0 |
| 400888 | G | Marlboro Light | 3558 | 8.4 | 12.6 | 14.7 |
| | | | **Average** | **7.9** | **12.2** | **13.9** |
| | | | **SD** | **0.3** | **0.5** | **1.1** |
| | | | **%RSD** | **3.5** | **4.3** | **8.0** |
| 400873 | D | Quest 1 | 3559 | 6.6 | 10.1 | 11.3 |
| 400873 | I | Quest 1 | 3559 | 6.4 | 10.1 | 11.8 |
| 400875 | B | Quest 1 | 3559 | 6.2 | 10.4 | 10.1 |
| 400875 | E | Quest 1 | 3559 | 6.4 | 9.36 | 9.77 |
| 400875 | H | Quest 1 | 3559 | 6.8 | 12.0 | 11.8 |
| 400875 | J | Quest 1 | 3559 | 6.2 | 10.3 | 10.9 |
| | | | **Average** | **6.4** | **10.4** | **11.0** |
| | | | **SD** | **0.2** | **0.9** | **0.9** |
| | | | **%RSD** | **3.6** | **8.4** | **7.9** |
| 400873 | E | Quest 2 | 3560 | 6.0 | 9.74 | 14.2 |
| 400873 | J | Quest 2 | 3560 | 6.0 | 10.1 | 16.4 |
| 400875 | A | Quest 2 | 3560 | 6.0 | 9.06 | 12.2 |
| 400876 | A | Quest 2 | 3560 | 6.0 | 9.84 | 13.2 |
| 400876 | G | Quest 2 | 3560 | 6.0 | 9.66 | 13.0 |
| 400888 | I | Quest 2 | 3560 | 6.2 | 12.1 | 14.9 |
| | | | **Average** | **6.0** | **10.1** | **14.0** |
| | | | **SD** | **0.1** | **1.0** | **1.5** |
| | | | **%RSD** | **1.4** | **10.2** | **10.7** |

**Mainstream Ammonia Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-011
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Ammonia (µg/cigt) |
|---|---|---|---|---|---|---|
| 400875 | D | Quest 3 | 3561 | 5.8 | 8.58 | 38.6 |
| 400875 | I | Quest 3 | 3561 | 6.0 | 8.94 | 36.4 |
| 400876 | C | Quest 3 | 3561 | 6.2 | 9.96 | 41.8 |
| 400876 | F | Quest 3 | 3561 | 6.4 | 8.70 | 38.7 |
| 400888 | D | Quest 3 | 3561 | 6.2 | 10.3 | 43.1 |
| 400888 | F | Quest 3 | 3561 | 6.4 | 10.1 | 50.0 |
| | | | **Average** | **6.2** | **9.43** | **41.4** |
| | | | **SD** | **0.2** | **0.78** | **4.8** |
| | | | **%RSD** | **3.8** | **8.2** | **11.7** |
| 400873 | B | 2R4F | 912 | 8.8 | 11.4 | 9.76 |
| 400875 | F | 2R4F | 912 | 9.0 | 10.9 | 9.14 |
| 400876 | E | 2R4F | 912 | 8.8 | 10.8 | 9.61 |
| 400888 | J | 2R4F | 912 | 8.6 | 11.1 | 9.69 |
| | | | **Average** | **8.8** | **11.0** | **9.55** |
| | | | **SD** | **0.2** | **0.3** | **0.28** |
| | | | **%RSD** | **1.9** | **2.3** | **3.0** |

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PROJECT CODE: 1808

# APPENDIX G

## Analysis of Mainstream Cigarette Smoke for Select Polynuclear Aromatic Hydrocarbons (PAHs)

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# THE DETERMINATION OF SELECTED POLYNUCLEAR AROMATIC HYDROCARBONS (PAHS) IN MAINSTREAM

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-038 Determination of Selected Polynuclear Aromatic Hydrocarbons (PAHs) in Mainstream Smoke.

Mainstream (MS) smoke from test cigarettes is generated under conditions specified by the study protocol and passed through a 44-mm Cambridge filter and collected in one impinger containing 20 mL of OPTIMA grade MeOH that is immersed in an ice-water bath. After smoking, the MS filter is weighed and transferred to a brown glass bottle. The contents of the impinger and Internal standard are added to the amber bottle and the sample is shaken for 30 min at 200 rpm on an orbital shaker. TYPE-1 water is added and the solution is passed through a C-18 SPE cartridge that has been rinsed with 30% MeOH in Type 1 water using a vacuum manifold. After all of the solution has passed through the SPE cartridge, the eluent is discarded and approximately 1.5 mL of benzene is added to the SPE cartridge for extraction of the PAH fraction. Finally, the extract is passed through a silica SPE cartridge. The sample is then transferred to an autosampler vial for analysis by GC/MSD.

Individual analyte concentrations are determined by the internal standard method using gas-chromatography with a DB-5ms column for chromatographic separation of the analytes and selected ion monitoring (SIM) after electron impact ionization. The concentrations of the analytes, determined by the GC/MSD are reported in units of mass-to-volume (i.e., ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

**Mainstream PAH Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-038
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run# | Port | Client Code | Arista Code | Puffs (/cigt) | MS TPM (mg/cigt) | Naphthalene (ng/cigt) | Fluorene (ng/cigt) | Phenanthrene (ng/cigt) | Anthracene (ng/cigt) | Fluoranthene (ng/cigt) | Pyrene (ng/cigt) | Benz-anthracene (ng/cigt) | Chrysene (ng/cigt) | Benzo(e) pyrene (ng/cigt) | Benzo(a) pyrene (ng/cigt) | Indeno[1,2,3-cd]pyrene (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 400863 | A | Camel 100 | 3557 | 10.6 | 22.2 | 880 | 364 | 285 | 98.9 | 119 | 90.2 | 25.2 | 29.2 | 8.04 | 12.4 | 6.93 |
| 400863 | E | Camel 100 | 3557 | 11.0 | 18.2 | 713 | 325 | 232 | 84.1 | 92.3 | 70.9 | 22.3 | 26.3 | 7.35 | 11.0 | 6.77 |
| 400863 | I | Camel 100 | 3557 | 11.0 | 21.9 | 929 | 373 | 273 | 98.9 | 111 | 84.9 | 26.9 | 31.3 | 8.41 | 12.6 | 7.65 |
| 400864 | A | Camel 100 | 3557 | 11.0 | 22.5 | 940 | 374 | 253 | 94.6 | 105 | 82.6 | 27.9 | 31.7 | 8.58 | 13.2 | 8.09 |
| 400869 | E | Camel 100 | 3557 | 11.0 | 19.8 | 831 | 367 | 257 | 95.8 | 106 | 80.5 | 25.9 | 29.8 | 8.13 | 12.2 | 7.33 |
| 400869 | G | Camel 100 | 3557 | 11.0 | 21.4 | 890 | 375 | 258 | 94.6 | 104 | 80.3 | 25.9 | 30.2 | 8.30 | 12.2 | 8.48 |
| | | | **Average** | **10.9** | **21.0** | **864** | **363** | **260** | **94.5** | **106** | **81.6** | **25.7** | **29.7** | **8.14** | **12.3** | **7.54** |
| | | | **SD** | **0.2** | **1.7** | **83** | **19** | **18** | **5.5** | **9** | **6.4** | **1.9** | **1.9** | **0.43** | **0.7** | **0.66** |
| | | | **%RSD** | **1.5** | **7.9** | **9.7** | **5.3** | **7.0** | **5.8** | **8.3** | **7.8** | **7.4** | **6.5** | **5.3** | **5.9** | **8.8** |
| 400863 | D | Marlboro Light | 3558 | 7.8 | 12.2 | 376 | 175 | 155 | 52.8 | 62.1 | 45.3 | 13.8 | 15.9 | 4.15 | 6.43 | 3.36 |
| 400864 | C | Marlboro Light | 3558 | 8.0 | 13.0 | 456 | 205 | 156 | 55.6 | 58.6 | 45.1 | 14.8 | 17.0 | 4.28 | 7.03 | 3.74 |
| 400864 | E | Marlboro Light | 3558 | 8.0 | 12.2 | 388 | 197 | 160 | 55.0 | 61.8 | 46.9 | 14.9 | 17.2 | 4.49 | 6.98 | 4.10 |
| 400869 | B | Marlboro Light | 3558 | 7.8 | 11.4 | 395 | 182 | 157 | 54.3 | 59.1 | 45.3 | 13.9 | 15.7 | 3.93 | 6.17 | 3.48 |
| 400870 | C | Marlboro Light | 3558 | 8.2 | 11.9 | 377 | 182 | 140 | 51.8 | 53.5 | 41.6 | 14.0 | 16.1 | 4.18 | 6.58 | 3.86 |
| 400870 | F | Marlboro Light | 3558 | 8.0 | 11.8 | 405 | 190 | 146 | 53.5 | 53.2 | 42.0 | 13.9 | 15.6 | 4.03 | 6.63 | 3.57 |
| | | | **Average** | **8.0** | **12.1** | **400** | **188** | **152** | **53.8** | **58.0** | **44.4** | **14.2** | **16.3** | **4.18** | **6.63** | **3.68** |
| | | | **SD** | **0.2** | **0.5** | **30** | **11** | **8** | **1.4** | **3.9** | **2.1** | **0.5** | **0.7** | **0.19** | **0.33** | **0.27** |
| | | | **%RSD** | **1.9** | **4.3** | **7.5** | **6.0** | **5.1** | **2.6** | **6.7** | **4.7** | **3.4** | **4.3** | **4.6** | **4.9** | **7.4** |
| 400863 | C | Quest 1 | 3559 | 6.4 | 10.5 | 343 | 170 | 128 | 43.3 | 50.1 | 33.4 | 9.91 | 11.0 | 3.09 | 4.36 | 2.66 |
| 400864 | J | Quest 1 | 3559 | 6.4 | 10.0 | 347 | 173 | 120 | 41.6 | 43.2 | 30.8 | 10.1 | 11.3 | 3.19 | 4.48 | 2.95 |
| 400869 | C | Quest 1 | 3559 | 6.6 | 11.9 | 400 | 174 | 146 | 47.1 | 57.4 | 39.0 | 11.8 | 12.8 | 3.73 | 5.50 | 3.00 |
| 400869 | I | Quest 1 | 3559 | 6.4 | 9.64 | 340 | 162 | 127 | 41.4 | 47.4 | 31.9 | 9.91 | 11.3 | 3.28 | 4.68 | 3.01 |
| 400870 | A | Quest 1 | 3559 | 6.8 | 10.7 | 420 | 193 | 128 | 46.5 | 47.8 | 32.9 | 11.3 | 12.5 | 3.48 | 5.21 | 3.16 |
| 400870 | E | Quest 1 | 3559 | 6.8 | 10.2 | 348 | 176 | 121 | 42.7 | 46.6 | 33.5 | 10.6 | 11.4 | 3.45 | 4.87 | 2.83 |
| | | | **Average** | **6.6** | **10.5** | **367** | **175** | **128** | **43.8** | **48.8** | **33.6** | **10.6** | **11.7** | **3.37** | **4.85** | **2.94** |
| | | | **SD** | **0.2** | **0.8** | **35** | **10** | **10** | **2.5** | **4.8** | **2.8** | **0.8** | **0.7** | **0.23** | **0.44** | **0.17** |
| | | | **%RSD** | **3.0** | **7.5** | **9.4** | **6.0** | **7.4** | **5.6** | **9.8** | **8.4** | **7.4** | **6.4** | **6.9** | **9.0** | **5.8** |

**Mainstream PAH Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

| | |
|---|---|
| **Project Code:** | **1808** |
| **Project Start Date:** | **27-Aug-04** |
| **Arista SOP #:** | **T-038** |
| **Smoking Protocol:** | **FTC** |
| **Authorized By:** | **A. Martin** |
| **Title:** | **QA Mgr** |

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

| Run# | Port | Client Code | Arista Code | Puffs (/cigt) | MS TPM (mg/cigt) | Naphthalene (ng/cigt) | Fluorene (ng/cigt) | Phenanthrene (ng/cigt) | Anthracene (ng/cigt) | Fluoranthene (ng/cigt) | Pyrene (ng/cigt) | Benz-anthracene (ng/cigt) | Chrysene (ng/cigt) | Benzo(e) pyrene (ng/cigt) | Benzo(a) pyrene (ng/cigt) | Indeno[1,2,3-cd]pyrene (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 400863 | B | Quest 2 | 3560 | 6.2 | 10.2 | 334 | 165 | 133 | 41.8 | 52.7 | 33.5 | 10.3 | 11.4 | 3.54 | 4.49 | 2.44 |
| 400864 | B | Quest 2 | 3560 | 6.0 | 9.74 | 366 | 175 | 113 | 38.2 | 44.5 | 28.5 | 9.49 | 10.3 | 3.23 | 4.37 | 2.36 |
| 400869 | A | Quest 2 | 3560 | 6.2 | 11.1 | 426 | 205 | 162 | 49.7 | 64.6 | 40.0 | 11.7 | 13.1 | 4.07 | 5.46 | 3.40 |
| 400869 | D | Quest 2 | 3560 | 6.2 | 9.98 | 338 | 164 | 129 | 41.7 | 48.8 | 32.0 | 10.3 | 11.1 | 3.28 | 4.55 | 3.01 |
| 400869 | H | Quest 2 | 3560 | 6.2 | 10.6 | 407 | 178 | 136 | 44.0 | 52.1 | 32.9 | 10.5 | 11.2 | 3.68 | 4.90 | 2.88 |
| 400870 | D | Quest 2 | 3560 | 6.0 | 9.40 | 393 | 173 | 116 | 41.5 | 45.6 | 29.9 | 10.2 | 10.8 | 3.47 | 4.72 | 3.22 |
| | | | **Average** | **6.1** | **10.2** | **377** | **177** | **132** | **42.8** | **51.4** | **32.8** | **10.4** | **11.3** | **3.54** | **4.75** | **2.88** |
| | | | **SD** | **0.1** | **0.6** | **38** | **15** | **17** | **3.9** | **7.3** | **4.0** | **0.7** | **0.9** | **0.31** | **0.39** | **0.42** |
| | | | **%RSD** | **1.7** | **5.9** | **10.0** | **8.3** | **13.2** | **9.0** | **14.2** | **12.2** | **6.9** | **8.3** | **8.7** | **8.3** | **14.5** |
| 400863 | F | Quest 3 | 3561 | 6.2 | 8.34 | 326 | 157 | 124 | 38.5 | 48.8 | 28.9 | 8.90 | 9.55 | 3.18 | 4.04 | 2.20 |
| 400863 | H | Quest 3 | 3561 | 6.2 | 9.34 | 337 | 175 | 133 | 41.4 | 53.4 | 31.2 | 9.75 | 10.3 | 3.18 | 4.27 | 2.73 |
| 400864 | D | Quest 3 | 3561 | 6.2 | 9.28 | 374 | 184 | 116 | 38.9 | 46.3 | 27.9 | 9.87 | 9.81 | 3.38 | 4.36 | 2.53 |
| 400864 | F | Quest 3 | 3561 | 6.2 | 9.40 | 357 | 174 | 118 | 39.1 | 44.3 | 27.5 | 9.54 | 9.51 | 3.18 | 4.06 | 2.53 |
| 400864 | I | Quest 3 | 3561 | 6.2 | 8.60 | 369 | 176 | 119 | 38.4 | 44.7 | 27.4 | 9.30 | 9.77 | 3.32 | 4.38 | 2.50 |
| 400870 | B | Quest 3 | 3561 | 6.0 | 9.36 | 330 | 172 | 119 | 38.9 | 44.4 | 27.3 | 9.99 | 10.1 | 3.17 | 4.23 | 2.68 |
| | | | **Average** | **6.2** | **9.05** | **349** | **173** | **122** | **39.2** | **47.0** | **28.4** | **9.56** | **9.84** | **3.23** | **4.22** | **2.53** |
| | | | **SD** | **0.1** | **0.46** | **21** | **9** | **6** | **1.1** | **3.6** | **1.5** | **0.41** | **0.31** | **0.09** | **0.15** | **0.19** |
| | | | **%RSD** | **1.3** | **5.1** | **5.9** | **5.1** | **5.2** | **2.9** | **7.7** | **5.4** | **4.3** | **3.2** | **2.8** | **3.4** | **7.3** |
| 400863 | G | 2R4F | 912 | 8.6 | 10.6 | 380 | 198 | 162 | 54.8 | 56.7 | 41.0 | 13.0 | 14.8 | 3.98 | 5.80 | 2.74 |
| 400864 | H | 2R4F | 912 | 9.0 | 11.0 | 409 | 217 | 171 | 56.6 | 60.6 | 44.8 | 14.5 | 16.8 | 4.21 | 6.29 | 3.35 |
| 400869 | J | 2R4F | 912 | 9.0 | 12.5 | 426 | 217 | 168 | 60.5 | 61.0 | 45.6 | 15.0 | 16.7 | 4.34 | 6.58 | 3.56 |
| 400870 | G | 2R4F | 912 | 9.0 | 10.8 | 350 | 206 | 144 | 54.5 | 52.9 | 41.4 | 13.9 | 15.2 | 3.75 | 6.03 | 3.32 |
| | | | Average | **8.9** | **11.2** | **391** | **210** | **161** | **56.6** | **57.8** | **43.2** | **14.1** | **15.9** | **4.07** | **6.17** | **3.24** |
| | | | **SD** | **0.2** | **0.9** | **33** | **9** | **12** | **2.8** | **3.8** | **2.3** | **0.9** | **1.0** | **0.26** | **0.33** | **0.35** |
| | | | **%RSD** | **2.2** | **7.9** | **8.5** | **4.4** | **7.5** | **4.9** | **6.6** | **5.4** | **6.0** | **6.3** | **6.3** | **5.4** | **10.9** |

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PROJECT CODE: 1808

# APPENDIX H

## Analysis of Mainstream Cigarette Smoke for Hydrogen Cyanide (HCN)

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# DETERMINATION OF HYDROGEN CYANIDE IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-049 Determination of Hydrogen Cyanide (HCN) in Mainstream Smoke.

HCN is determined from mainstream smoke collected on a Cambridge filter followed by one non-fritted impinger containing 0.1N sodium hydroxide as the collection media. An automated spectrophotometer is used to analyze the pad extract and the impinger trapping solutions where each sample undergoes quantitative addition of reagents. Hydrogen cyanide in the sample is converted to cyanogen chloride by the addition of an aqueous solution of chloramine-T. The cyanogen chloride then reacts with pyridine and barbituic acid to produce a reddish-violet color complex that is measured photometrically at 575nm. The Beer-Lambert Law linearly relates formation of the colored complex to concentration.

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

**Mainstream HCN Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-049
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Impinger HCN (µg/cigt) | Pad HCN (µg/cigt) | Total HCN (µg/cigt) |
|---|---|---|---|---|---|---|---|---|
| 400881 | C | Camel 100 | 3557 | 11.0 | 23.7 | 101.2 | 91.8 | 193.1 |
| 400881 | H | Camel 100 | 3557 | 10.3 | 22.7 | 98.6 | 87.4 | 186.0 |
| 400882 | B | Camel 100 | 3557 | 11.0 | 20.9 | 85.3 | 79.3 | 164.6 |
| 400882 | H | Camel 100 | 3557 | 10.3 | 22.5 | 95.8 | 96.5 | 192.2 |
| 400883 | H | Camel 100 | 3557 | 11.0 | 22.9 | 98.5 | 95.0 | 193.5 |
| 400883 | J | Camel 100 | 3557 | 11.0 | 24.1 | 101.8 | 83.8 | 185.7 |
| | | | **Average** | **10.8** | **22.8** | **96.9** | **89.0** | **185.8** |
| | | | **sd** | **0.3** | **1.1** | **6.1** | **6.7** | **11.0** |
| | | | **%RSD** | **3.2** | **4.8** | **6.3** | **7.5** | **5.9** |
| 400881 | F | Marlboro Light | 3558 | 8.0 | 11.8 | 68.6 | 49.5 | 118.1 |
| 400881 | J | Marlboro Light | 3558 | 7.0 | 11.8 | 75.6 | 49.8 | 125.3 |
| 400882 | I | Marlboro Light | 3558 | 7.7 | 12.8 | 86.0 | 55.7 | 141.7 |
| 400883 | B | Marlboro Light | 3558 | 7.7 | 12.2 | 76.0 | 53.9 | 129.9 |
| 400883 | D | Marlboro Light | 3558 | 8.0 | 12.2 | 68.1 | 53.6 | 121.7 |
| 400883 | F | Marlboro Light | 3558 | 8.0 | 12.5 | 69.6 | 57.8 | 127.4 |
| | | | **Average** | **7.7** | **12.2** | **74.0** | **53.4** | **127.4** |
| | | | **sd** | **0.4** | **0.4** | **6.8** | **3.3** | **8.2** |
| | | | **%RSD** | **5.0** | **3.1** | **9.2** | **6.1** | **6.4** |
| 400881 | B | Quest 1 | 3559 | 6.3 | 12.6 | 56.6 | 33.4 | 89.9 |
| 400882 | C | Quest 1 | 3559 | 6.7 | 10.6 | 47.8 | 29.2 | 77.0 |
| 400882 | G | Quest 1 | 3559 | 7.0 | 11.7 | 55.5 | 32.2 | 87.7 |
| 400883 | C | Quest 1 | 3559 | 6.3 | 10.1 | 45.3 | 34.1 | 79.4 |
| 400884 | C | Quest 1 | 3559 | 6.3 | 11.2 | 52.2 | 27.1 | 79.4 |
| 400884 | I | Quest 1 | 3559 | 6.0 | 9.63 | 49.9 | 23.0 | 73.0 |
| | | | **Average** | **6.4** | **11.0** | **51.2** | **29.8** | **81.1** |
| | | | **sd** | **0.3** | **1.1** | **4.4** | **4.3** | **6.5** |
| | | | **%RSD** | **5.3** | **9.9** | **8.6** | **14.3** | **8.0** |
| 400881 | A | Quest 2 | 3560 | 7.0 | 12.2 | 54.3 | 28.0 | 82.3 |
| 400881 | G | Quest 2 | 3560 | 6.7 | 11.9 | 62.4 | 32.0 | 94.4 |
| 400882 | J | Quest 2 | 3560 | 6.0 | 9.13 | 52.7 | 28.4 | 81.1 |
| 400883 | G | Quest 2 | 3560 | 6.3 | 9.40 | 54.0 | 25.8 | 79.8 |
| 400884 | H | Quest 2 | 3560 | 6.0 | 11.0 | 55.9 | 28.7 | 84.6 |
| | | | **Average** | **6.4** | **10.7** | **55.9** | **28.6** | **84.4** |
| | | | **sd** | **0.4** | **1.4** | **3.8** | **2.2** | **5.8** |
| | | | **%RSD** | **6.8** | **13.2** | **6.8** | **7.8** | **6.9** |

**Mainstream HCN Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-049
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Impinger HCN (µg/cigt) | Pad HCN (µg/cigt) | Total HCN (µg/cigt) |
|---|---|---|---|---|---|---|---|---|
| 400881 | I | Quest 3 | 3561 | 6.0 | 9.47 | 53.5 | 22.2 | 75.7 |
| 400882 | A | Quest 3 | 3561 | 6.3 | 11.6 | 42.9 | 34.2 | 77.1 |
| 400883 | A | Quest 3 | 3561 | 6.0 | 8.70 | 53.6 | 22.1 | 75.7 |
| 400884 | B | Quest 3 | 3561 | 6.3 | 10.3 | 51.2 | 22.9 | 74.1 |
| 400884 | D | Quest 3 | 3561 | 6.0 | 9.07 | 56.4 | 21.9 | 78.3 |
| 400884 | G | Quest 3 | 3561 | 6.0 | 9.77 | 58.9 | 23.6 | 82.5 |
| | | | **Average** | **6.1** | **9.82** | **52.8** | **24.5** | **77.2** |
| | | | **sd** | **0.2** | **1.04** | **5.5** | **4.8** | **3.0** |
| | | | **%RSD** | **2.8** | **10.6** | **10.4** | **19.6** | **3.8** |
| 400881 | D | 2r4f | 912 | 8.3 | 11.2 | 68.1 | 46.5 | 114.6 |
| 400882 | F | 2r4f | 912 | 9.0 | 11.1 | 60.1 | 45.8 | 105.9 |
| 400883 | I | 2r4f | 912 | 8.7 | 11.9 | 59.3 | 44.9 | 104.1 |
| 400884 | F | 2r4f | 912 | 8.3 | 12.0 | 68.2 | 50.7 | 118.9 |
| | | | **Average** | **8.6** | **11.6** | **63.9** | **47.0** | **110.9** |
| | | | **sd** | **0.3** | **0.5** | **4.9** | **2.6** | **7.0** |
| | | | **%RSD** | **3.7** | **4.0** | **7.7** | **5.5** | **6.3** |

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# APPENDIX I

## Analysis of Mainstream Cigarette Smoke for Polycyclic Aromatic Amines I (PAA I)

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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

## I. PRINCIPLE OF METHOD

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

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

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

**Mainstream Aromatic Amines Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-030
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | 1-Naphthyl Amine (ng/cigt) | 2-Naphthyl Amine (ng/cigt) | 3-Amino Biphenyl (ng/cigt) | 4-Amino Biphenyl (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00414 | G | Camel 100 | 3557 | 11.7 | 24.7 | 12.3 | 6.78 | 3.15 | 1.97 |
| C00414 | I | Camel 100 | 3557 | 11.4 | 23.0 | 10.2 | 6.15 | 2.71 | 1.68 |
| C00414 | K | Camel 100 | 3557 | 11.3 | 24.2 | 10.9 | 6.04 | 2.74 | 1.67 |
| C00414 | O | Camel 100 | 3557 | 11.6 | 24.5 | 12.7 | 6.91 | 3.17 | 2.12 |
| C00417 | I | Camel 100 | 3557 | 11.4 | 24.3 | 13.6 | 7.69 | 3.50 | 2.13 |
| C00417 | P | Camel 100 | 3557 | 12.1 | 24.7 | 12.8 | 7.15 | 3.22 | 2.02 |
| | | | **Average** | **11.6** | **24.2** | **12.1** | **6.79** | **3.08** | **1.93** |
| | | | **sd** | **0.3** | **0.6** | **1.3** | **0.62** | **0.30** | **0.21** |
| | | | **% RSD** | **2.4** | **2.6** | **10.4** | **9.2** | **9.8** | **10.7** |
| C00414 | C | Marlboro Light | 3558 | 8.0 | 13.1 | 7.67 | 4.68 | 1.99 | 1.36 |
| C00414 | E | Marlboro Light | 3558 | 8.1 | 12.7 | 7.91 | 4.95 | 2.11 | 1.46 |
| C00414 | N | Marlboro Light | 3558 | 8.1 | 12.7 | 8.67 | 5.16 | 2.25 | 1.58 |
| C00414 | T | Marlboro Light | 3558 | 8.1 | 13.5 | 8.20 | 5.01 | 2.11 | 1.40 |
| C00417 | H | Marlboro Light | 3558 | 8.7 | 12.7 | 8.55 | 5.45 | 2.32 | 1.62 |
| C00417 | M | Marlboro Light | 3558 | 8.3 | 13.3 | 7.97 | 5.07 | 2.16 | 1.35 |
| | | | **Average** | **8.2** | **13.0** | **8.16** | **5.05** | **2.16** | **1.46** |
| | | | **sd** | **0.3** | **0.3** | **0.39** | **0.25** | **0.12** | **0.11** |
| | | | **% RSD** | **3.1** | **2.6** | **4.7** | **5.0** | **5.3** | **7.9** |
| C00414 | B | Quest 1 | 3559 | 6.7 | 11.6 | 8.21 | 4.92 | 2.13 | 1.58 |
| C00414 | F | Quest 1 | 3559 | 6.7 | 12.6 | 7.89 | 4.39 | 2.13 | 1.50 |
| C00414 | L | Quest 1 | 3559 | 6.5 | 11.1 | 6.51 | 3.75 | 1.86 | 1.30 |
| C00414 | S | Quest 1 | 3559 | 6.7 | 12.4 | 7.66 | 4.25 | 2.20 | 1.44 |
| C00417 | N | Quest 1 | 3559 | 6.7 | 11.1 | 6.38 | 3.81 | 1.87 | 1.17 |
| C00417 | Q | Quest 1 | 3559 | 7.0 | 12.0 | 6.35 | 3.94 | 1.96 | 1.20 |
| | | | **Average** | **6.7** | **11.8** | **7.17** | **4.18** | **2.03** | **1.37** |
| | | | **sd** | **0.2** | **0.6** | **0.85** | **0.44** | **0.15** | **0.17** |
| | | | **% RSD** | **2.4** | **5.4** | **11.8** | **10.6** | **7.2** | **12.1** |

**Mainstream Aromatic Amines Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-030
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | 1-Naphthyl Amine (ng/cigt) | 2-Naphthyl Amine (ng/cigt) | 3-Amino Biphenyl (ng/cigt) | 4-Amino Biphenyl (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00414 | M | Quest 2 | 3560 | 6.3 | 9.90 | 6.89 | 3.92 | 2.16 | 1.49 |
| C00414 | P | Quest 2 | 3560 | 6.1 | 10.7 | 7.24 | 4.05 | 2.25 | 1.54 |
| C00414 | R | Quest 2 | 3560 | 6.1 | 11.3 | 6.76 | 3.90 | 2.28 | 1.37 |
| C00417 | C | Quest 2 | 3560 | 6.4 | 10.4 | 7.58 | 4.12 | 2.33 | 1.65 |
| C00417 | E | Quest 2 | 3560 | 6.5 | 10.9 | 7.61 | 4.45 | 2.43 | 1.71 |
| C00417 | G | Quest 2 | 3560 | 6.5 | 9.76 | 7.40 | 4.35 | 2.36 | 1.65 |
| | | | **Average** | **6.3** | **10.5** | **7.25** | **4.13** | **2.30** | **1.57** |
| | | | **sd** | **0.2** | **0.6** | **0.36** | **0.22** | **0.09** | **0.13** |
| | | | **% RSD** | **2.6** | **5.6** | **4.9** | **5.4** | **4.1** | **8.2** |
| C00414 | A | Quest 3 | 3561 | 6.2 | 8.76 | 8.65 | 5.11 | 3.03 | 2.26 |
| C00414 | Q | Quest 3 | 3561 | 6.4 | 9.96 | 8.44 | 4.76 | 3.06 | 2.16 |
| C00417 | D | Quest 3 | 3561 | 6.0 | 8.72 | 8.23 | 4.60 | 2.93 | 2.06 |
| C00417 | J | Quest 3 | 3561 | 6.0 | 9.00 | 8.45 | 4.74 | 3.00 | 2.08 |
| C00417 | L | Quest 3 | 3561 | 6.1 | 8.96 | 7.52 | 4.25 | 2.62 | 1.84 |
| C00417 | O | Quest 3 | 3561 | 6.0 | 8.84 | 7.05 | 4.32 | 2.71 | 1.82 |
| | | | **Average** | **6.1** | **9.04** | **8.06** | **4.63** | **2.89** | **2.04** |
| | | | **sd** | **0.2** | **0.46** | **0.63** | **0.32** | **0.18** | **0.18** |
| | | | **% RSD** | **2.5** | **5.1** | **7.8** | **6.8** | **6.3** | **8.7** |
| C00414 | D | 2R4F | 912 | 8.9 | 11.5 | 7.36 | 4.60 | 1.96 | 1.34 |
| C00414 | J | 2R4F | 912 | 9.1 | 11.5 | 6.57 | 4.40 | 1.90 | 1.21 |
| C00417 | F | 2R4F | 912 | 8.8 | 10.8 | 7.70 | 4.83 | 2.06 | 1.47 |
| C00417 | K | 2R4F | 912 | 9.0 | 11.1 | 7.06 | 4.59 | 1.96 | 1.20 |
| | | | **Average** | **9.0** | **11.2** | **7.17** | **4.60** | **1.97** | **1.30** |
| | | | **sd** | **0.1** | **0.4** | **0.48** | **0.17** | **0.06** | **0.13** |
| | | | **% RSD** | **1.0** | **3.2** | **6.7** | **3.8** | **3.2** | **9.9** |

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# APPENDIX J

## Analysis of Mainstream Cigarette Smoke for Nitric Oxide (NO)

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# THE DETERMINATION OF NITRIC OXIDE IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-029 - The Determination of Nitric Oxide in Mainstream Cigarette Smoke.

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

**Mainstream Nitric Oxide Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-029
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Day | Run # | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | NO (µg/cigt) |
|---|---|---|---|---|---|---|
| 500759 | 5 | Camel 100 | 3557 | 11.0 | 24.0 | 231 |
| 500759 | 6 | Camel 100 | 3557 | 11.0 | 21.6 | 213 |
| 500760 | 7 | Camel 100 | 3557 | 10.0 | 21.4 | 215 |
| 500760 | 10 | Camel 100 | 3557 | 11.0 | 19.0 | 234 |
| 500760 | 11 | Camel 100 | 3557 | 11.0 | 18.8 | 224 |
| | | | **Average** | **10.8** | **21.0** | **223** |
| | | | **SD** | **0.4** | **2.1** | **9** |
| | | | **%RSD** | **4.1** | **10.2** | **4.2** |
| 500759 | 3 | Marlboro Light | 3558 | 8.0 | 11.8 | 171 |
| 500759 | 4 | Marlboro Light | 3558 | 8.0 | 12.5 | 178 |
| 500759 | 7 | Marlboro Light | 3558 | 8.0 | 14.2 | 198 |
| 500759 | 14 | Marlboro Light | 3558 | 7.0 | 11.3 | 163 |
| 500759 | 19 | Marlboro Light | 3558 | 8.0 | 10.8 | 167 |
| | | | **Average** | **7.8** | **12.1** | **175** |
| | | | **SD** | **0.4** | **1.3** | **14** |
| | | | **%RSD** | **5.7** | **10.9** | **8.0** |
| 500759 | 9 | Quest 1 | 3559 | 7.0 | 11.1 | 166 |
| 500759 | 13 | Quest 1 | 3559 | 6.0 | 9.6 | 139 |
| 500760 | 4 | Quest 1 | 3559 | 7.0 | 13.2 | 166 |
| 500760 | 6 | Quest 1 | 3559 | 7.0 | 14.6 | 173 |
| 500760 | 8 | Quest 1 | 3559 | 7.0 | 11.6 | 163 |
| | | | **Average** | **6.8** | **12.0** | **161** |
| | | | **SD** | **0.4** | **1.9** | **13** |
| | | | **%RSD** | **6.6** | **16.1** | **8.1** |
| 500759 | 10 | Quest 2 | 3560 | 6.0 | 9.2 | 154 |
| 500759 | 15 | Quest 2 | 3560 | 6.0 | 10.7 | 176 |
| 500759 | 16 | Quest 2 | 3560 | 6.0 | 8.7 | 151 |
| 500760 | 3 | Quest 2 | 3560 | 6.0 | 11.0 | 165 |
| 500760 | 5 | Quest 2 | 3560 | 7.0 | 10.4 | 193 |
| | | | **Average** | **6.2** | **10.0** | **168** |
| | | | **SD** | **0.4** | **1.0** | **17** |
| | | | **%RSD** | **7.2** | **10.0** | **10.2** |

**Mainstream Nitric Oxide Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-029
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Day | Run # | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | NO (µg/cigt) |
|---|---|---|---|---|---|---|
| 500759 | 8 | Quest 3 | 3561 | 6.0 | 10.1 | 229 |
| 500759 | 12 | Quest 3 | 3561 | 6.0 | 9.5 | 255 |
| 500759 | 17 | Quest 3 | 3561 | 6.0 | 9.6 | 253 |
| 500759 | 18 | Quest 3 | 3561 | 6.0 | 9.1 | 206 |
| 500760 | 9 | Quest 3 | 3561 | 6.0 | 7.8 | 178 |
| | | | **Average** | **6.0** | **9.2** | **224** |
| | | | **SD** | **0.0** | **0.9** | **33** |
| | | | **%RSD** | **0.0** | **9.4** | **14.6** |
| 500759 | 2 | 2R4F | 912 | 9.0 | 12.9 | 207 |
| 500759 | 11 | 2R4F | 912 | 9.0 | 11.1 | 184 |
| 500759 | 20 | 2R4F | 912 | 9.0 | 11.7 | 197 |
| 500760 | 2 | 2R4F | 912 | 10.0 | 12.3 | 191 |
| 500760 | 12 | 2R4F | 912 | 9.0 | 11.7 | 203 |
| | | | **Average** | **9.2** | **11.9** | **196** |
| | | | **SD** | **0.4** | **0.7** | **9** |
| | | | **%RSD** | **4.9** | **5.7** | **4.8** |

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PROJECT CODE: 1808

# APPENDIX K

## Analysis of Mainstream Cigarette Smoke for Polycyclic Aromatic Amines II (PAA II)

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# THE DETERMINATION OF ANILINE, ORTHO-TOLUIDINE, META-TOLUIDINE, AND ORTHO-ANISIDINE (PAA II) IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-091, The Determination Of Aniline, ortho-Toluidine, meta-Toluidine, and ortho-Anisidine (PAAs) in Mainstream Smoke.

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

Individual analyte concentrations are determined by the internal standard method using gas-chromatography mass spectrometry. The GC/MSD is equipped with a DB-5MS column for chromatographic separation of the analytes and selected ion monitoring (SIM) detection after negative chemical ionization. The concentrations of the analytes determined, are reported in units of mass-to-volume (i.e., ng/mL). The measured concentration, the number of cigarettes smoked, and the sample solution volume(s) are used to calculate the total analyte mass on a per cigarette basis.

**Mainstream Aromatic Amines II Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-091
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Aniline (ng/cigt) | o-Toluidine (ng/cigt) | m-Toluidine (ng/cigt) | o-Anisidine (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00414 | G | Camel 100 | 3557 | 11.7 | 24.7 | 284 | 63.8 | 57.3 | 4.39 |
| C00414 | I | Camel 100 | 3557 | 11.4 | 23.0 | 282 | 60.5 | 63.2 | 5.27 |
| C00414 | K | Camel 100 | 3557 | 11.3 | 24.2 | 251 | 57.0 | 50.4 | 4.04 |
| C00414 | O | Camel 100 | 3557 | 11.6 | 24.5 | 283 | 64.5 | 57.7 | 4.19 |
| C00417 | I | Camel 100 | 3557 | 11.4 | 24.3 | 285 | 63.2 | 56.4 | 4.60 |
| C00417 | P | Camel 100 | 3557 | 12.1 | 24.7 | 282 | 62.6 | 56.0 | 4.69 |
| | | | **Average** | **11.6** | **24.2** | **278** | **61.9** | **56.8** | **4.53** |
| | | | **sd** | **0.3** | **0.6** | **13** | **2.8** | **4.1** | **0.44** |
| | | | **% RSD** | **2.4** | **2.6** | **4.8** | **4.4** | **7.2** | **9.6** |
| C00414 | C | Marlboro Light | 3558 | 8.0 | 13.1 | 171 | 35.7 | 33.9 | 2.74 |
| C00414 | E | Marlboro Light | 3558 | 8.1 | 12.7 | 188 | 38.4 | 37.3 | 2.87 |
| C00414 | N | Marlboro Light | 3558 | 8.1 | 12.7 | 193 | 40.1 | 38.9 | 2.86 |
| C00414 | T | Marlboro Light | 3558 | 8.1 | 13.5 | 206 | 42.5 | 42.8 | 3.22 |
| C00417 | H | Marlboro Light | 3558 | 8.7 | 12.7 | 201 | 40.3 | 40.8 | 3.25 |
| C00417 | M | Marlboro Light | 3558 | 8.3 | 13.3 | 176 | 36.1 | 36.1 | 2.85 |
| | | | **Average** | **8.2** | **13.0** | **189** | **38.9** | **38.3** | **2.97** |
| | | | **sd** | **0.3** | **0.3** | **14** | **2.7** | **3.2** | **0.21** |
| | | | **% RSD** | **3.1** | **2.6** | **7.3** | **6.8** | **8.5** | **7.2** |
| C00414 | B | Quest 1 | 3559 | 6.7 | 11.6 | 186 | 40.2 | 35.9 | 2.55 |
| C00414 | F | Quest 1 | 3559 | 6.7 | 12.6 | 194 | 43.1 | 36.9 | 2.71 |
| C00414 | L | Quest 1 | 3559 | 6.5 | 11.1 | 162 | 35.8 | 31.7 | 2.32 |
| C00414 | S | Quest 1 | 3559 | 6.7 | 12.4 | 199 | 43.0 | 39.8 | 2.98 |
| C00417 | N | Quest 1 | 3559 | 6.7 | 11.1 | 179 | 38.2 | 38.2 | 2.91 |
| C00417 | Q | Quest 1 | 3559 | 7.0 | 12.0 | 192 | 41.7 | 42.2 | 3.28 |
| | | | **Average** | **6.7** | **11.8** | **185** | **40.3** | **37.5** | **2.79** |
| | | | **sd** | **0.2** | **0.6** | **13** | **2.9** | **3.6** | **0.34** |
| | | | **% RSD** | **2.4** | **5.4** | **7.2** | **7.2** | **9.6** | **12.2** |
| C00414 | M | Quest 2 | 3560 | 6.3 | 9.90 | 180 | 40.2 | 36.0 | 2.06 |
| C00414 | P | Quest 2 | 3560 | 6.1 | 10.7 | 197 | 42.8 | 39.2 | 2.67 |
| C00414 | R | Quest 2 | 3560 | 6.1 | 11.3 | 167 | 36.9 | 33.7 | 2.19 |
| C00417 | C | Quest 2 | 3560 | 6.4 | 10.4 | 195 | 43.1 | 38.3 | 2.18 |
| C00417 | E | Quest 2 | 3560 | 6.5 | 10.9 | 201 | 43.5 | 39.9 | 2.34 |
| C00417 | G | Quest 2 | 3560 | 6.5 | 9.76 | 192 | 41.5 | 38.3 | 2.37 |
| | | | **Average** | **6.3** | **10.5** | **189** | **41.3** | **37.6** | **2.30** |
| | | | **sd** | **0.2** | **0.6** | **13** | **2.5** | **2.3** | **0.21** |
| | | | **% RSD** | **2.6** | **5.6** | **6.7** | **6.0** | **6.1** | **9.3** |

**Mainstream Aromatic Amines II Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-091
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run # | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Aniline (ng/cigt) | o-Toluidine (ng/cigt) | m-Toluidine (ng/cigt) | o-Anisidine (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00414 | A | Quest 3 | 3561 | 6.2 | 8.76 | 215 | 39.5 | 41.7 | 1.95 |
| C00414 | Q | Quest 3 | 3561 | 6.4 | 9.96 | 217 | 41.0 | 42.6 | 2.01 |
| C00417 | D | Quest 3 | 3561 | 6.0 | 8.72 | 210 | 37.9 | 39.5 | 1.99 |
| C00417 | J | Quest 3 | 3561 | 6.0 | 9.00 | 222 | 40.4 | 42.3 | 2.05 |
| C00417 | L | Quest 3 | 3561 | 6.1 | 8.96 | 183 | 34.0 | 35.6 | 1.79 |
| C00417 | O | Quest 3 | 3561 | 6.0 | 8.84 | 198 | 35.7 | 38.9 | 2.24 |
| | | | **Average** | **6.1** | **9.04** | **208** | **38.1** | **40.1** | **2.00** |
| | | | **sd** | **0.2** | **0.46** | **15** | **2.8** | **2.7** | **0.15** |
| | | | **% RSD** | **2.5** | **5.1** | **7.0** | **7.2** | **6.6** | **7.4** |
| C00414 | D | 2R4F | 912 | 8.9 | 11.5 | 173 | 38.5 | 36.8 | 2.86 |
| C00414 | J | 2R4F | 912 | 9.1 | 11.5 | 191 | 40.4 | 46.5 | 3.27 |
| C00417 | F | 2R4F | 912 | 8.8 | 10.8 | 167 | 36.9 | 35.1 | 2.63 |
| C00417 | K | 2R4F | 912 | 9.0 | 11.1 | 159 | 34.8 | 34.1 | 2.70 |
| | | | **Average** | **9.0** | **11.2** | **173** | **37.6** | **38.1** | **2.86** |
| | | | **sd** | **0.1** | **0.4** | **14** | **2.4** | **5.7** | **0.29** |
| | | | **% RSD** | **1.0** | **3.2** | **8.0** | **6.3** | **14.9** | **10.0** |

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PROJECT CODE: 1808

# APPENDIX L

## Analysis of Mainstream Cigarette Smoke for Selected Trace Elements

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

Arista LABORATORIES

*ISO 17025 Accredited*
*Certificate No. 1873.01*

# THE DETERMINATION OF SELECTED METALS IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-021 - The Determination of Selected Metals in Mainstream Cigarette Smoke. Note that the term metals, in this SOP, refers to the following: Arsenic, Cadmium, Chromium, Lead, Nickel and Selenium.

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

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

**Mainstream Metals Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-021
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Set # | Run# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Chromium (ng/cigt) | Selenium (ng/cigt) | Arsenic (ng/cigt) | Nickel (ng/cigt) | Lead (ng/cigt) | Cadmium (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 800157 | 3 | Camel 100 | 3557 | 11.3 | 21.1 | <LOD | [redacted] | 8.89 | <LOD | 28.7 | 75.5 |
| 800157 | 16 | Camel 100 | 3557 | 11.3 | 21.3 | <LOD | [redacted] | 8.76 | <LOD | 28.5 | 74.4 |
| 800158 | 6 | Camel 100 | 3557 | 11.5 | 19.7 | <LOD | [redacted] | 7.02 | <LOD | 23.8 | 63.5 |
| 800158 | 11 | Camel 100 | 3557 | 11.0 | 20.3 | <LOD | [redacted] | 7.20 | <LOD | 24.2 | 64.5 |
| 800158 | 12 | Camel 100 | 3557 | 11.5 | 22.6 | <LOD | [redacted] | 8.47 | <LOD | 27.2 | 73.0 |
| 800158 | 16 | Camel 100 | 3557 | 11.2 | 21.1 | <LOD | [redacted] | 7.57 | <LOD | 25.1 | 65.4 |
| | | | **Average** | **11.3** | **21.0** | **<LOD** | [redacted] | **7.99** | **<LOD** | **26.2** | **69.4** |
| | | | **SD** | **0.2** | **1.0** | **na** | **0.2** | **0.82** | **na** | **2.2** | **5.5** |
| | | | **%RSD** | **1.7** | **4.6** | **na** | **8.3** | **10.3** | **na** | **8.2** | **7.9** |
| 800157 | 4 | Marlboro Light | 3558 | 8.0 | 11.5 | <LOD | [redacted] | 4.70 | <LOD | 15.8 | 48.4 |
| 800157 | 18 | Marlboro Light | 3558 | 8.4 | 12.1 | <LOD | [redacted] | 4.55 | <LOD | 14.0 | 49.1 |
| 800157 | 21 | Marlboro Light | 3558 | 8.2 | 11.6 | <LOD | [redacted] | 3.97 | <LOD | 13.4 | 46.6 |
| 800157 | 22 | Marlboro Light | 3558 | 8.1 | 11.4 | <LOD | [redacted] | 4.42 | <LOD | 14.4 | 46.8 |
| 800158 | 4 | Marlboro Light | 3558 | 8.0 | 11.5 | <LOD | [redacted] | 4.43 | <LOD | 13.9 | 45.3 |
| 800158 | 14 | Marlboro Light | 3558 | 8.3 | 11.5 | <LOD | [redacted] | 3.95 | <LOD | 14.1 | 45.4 |
| | | | **Average** | **8.2** | **11.6** | **<LOD** | [redacted] | **4.34** | **<LOD** | **14.3** | **46.9** |
| | | | **SD** | **0.2** | **0.3** | **na** | **0.1** | **0.31** | **na** | **0.8** | **1.5** |
| | | | **%RSD** | **1.9** | **2.4** | **na** | **4.7** | **7.1** | **na** | **5.6** | **3.3** |

**Mainstream Metals Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-021
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Set # | Run# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Chromium (ng/cigt) | Selenium (ng/cigt) | Arsenic (ng/cigt) | Nickel (ng/cigt) | Lead (ng/cigt) | Cadmium (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 800157 | 13 | Quest 1 | 3559 | 6.6 | 9.63 | <LOD | [illegible] | [illegible] | <LOD | 12.4 | 15.3 |
| 800157 | 15 | Quest 1 | 3559 | 6.6 | 9.45 | <LOD | <LOD | [illegible] | <LOD | 11.6 | 15.1 |
| 800158 | 5 | Quest 1 | 3559 | 6.1 | 7.90 | <LOD | <LOD | [illegible] | <LOD | 9.90 | 12.1 |
| 800158 | 7 | Quest 1 | 3559 | 6.5 | 9.30 | <LOD | <LOD | [illegible] | <LOD | 11.7 | 13.4 |
| 800158 | 8 | Quest 1 | 3559 | 6.6 | 9.33 | <LOD | <LOD | [illegible] | <LOD | 11.5 | 14.8 |
| 800158 | 15 | Quest 1 | 3559 | 6.8 | 9.96 | <LOD | [illegible] | [illegible] | <LOD | 12.7 | 15.1 |
| | | | **Average** | **6.5** | **9.26** | **<LOD** | **<LOD** | [illegible] | **<LOD** | **11.6** | **14.3** |
| | | | **SD** | **0.2** | **0.71** | **na** | **na** | **0.28** | **na** | **1.0** | **1.3** |
| | | | **%RSD** | **3.8** | **7.7** | **na** | **na** | **11.6** | **na** | **8.3** | **8.9** |
| 800157 | 5 | Quest 2 | 3560 | 6.2 | 8.83 | <LOD | [illegible] | 2.82 | <LOD | 14.3 | 16.4 |
| 800157 | 6 | Quest 2 | 3560 | 6.2 | 8.99 | <LOD | [illegible] | 3.15 | <LOD | 15.6 | 16.9 |
| 800157 | 7 | Quest 2 | 3560 | 6.3 | 8.62 | <LOD | [illegible] | 3.56 | <LOD | 17.5 | 18.8 |
| 800157 | 11 | Quest 2 | 3560 | 6.0 | 8.76 | <LOD | [illegible] | 2.89 | <LOD | 14.4 | 15.1 |
| 800157 | 12 | Quest 2 | 3560 | 6.1 | 8.84 | <LOD | [illegible] | 3.11 | <LOD | 15.4 | 15.5 |
| 800157 | 20 | Quest 2 | 3560 | 6.4 | 9.45 | <LOD | [illegible] | 2.88 | <LOD | 14.3 | 15.4 |
| | | | **Average** | **6.2** | **8.92** | **<LOD** | [illegible] | **3.07** | **<LOD** | **15.2** | **16.3** |
| | | | **SD** | **0.1** | **0.29** | **na** | **0.1** | **0.28** | **na** | **1.2** | **1.4** |
| | | | **%RSD** | **2.3** | **3.2** | **na** | **10.5** | **9.0** | **na** | **8.1** | **8.4** |

**Mainstream Metals Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-021
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Set # | Run# | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | Chromium (ng/cigt) | Selenium (ng/cigt) | Arsenic (ng/cigt) | Nickel (ng/cigt) | Lead (ng/cigt) | Cadmium (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 800157 | 8 | Quest 3 | 3561 | 6.3 | 9.65 | <LOD | 1.1 | 2.82 | <LOD | 14.4 | 23.9 |
| 800157 | 14 | Quest 3 | 3561 | 6.1 | 7.84 | <LOD | 1.1 | 2.80 | <LOD | 13.3 | 22.6 |
| 800157 | 19 | Quest 3 | 3561 | 6.1 | 7.45 | <LOD | 1.1 | 2.86 | <LOD | 14.0 | 20.5 |
| 800158 | 3 | Quest 3 | 3561 | 6.1 | 7.69 | <LOD | 1.1 | 2.77 | <LOD | 12.6 | 21.4 |
| 800158 | 13 | Quest 3 | 3561 | 6.2 | 8.08 | <LOD | 1.1 | 2.78 | <LOD | 12.3 | 22.9 |
| | | | **Average** | **6.2** | **8.14** | **<LOD** | **1.1** | **2.73** | **<LOD** | **13.3** | **22.3** |
| | | | **SD** | **0.1** | **0.87** | **na** | **0.1** | **0.20** | **na** | **0.9** | **1.3** |
| | | | **%RSD** | **1.6** | **10.7** | **na** | **8.3** | **7.4** | **na** | **6.5** | **6.1** |
| 800157 | 2 | 2R4F | 912 | 9.0 | 10.3 | <LOD | 1.0 | 3.37 | <LOD | 12.6 | 45.9 |
| 800157 | 10 | 2R4F | 912 | 9.1 | 10.1 | <LOD | 1.0 | 3.17 | <LOD | 12.7 | 50.5 |
| 800157 | 23 | 2R4F | 912 | 9.1 | 10.6 | <LOD | 1.0 | 3.47 | <LOD | 12.7 | 53.2 |
| 800158 | 2 | 2R4F | 912 | 9.3 | 10.6 | <LOD | 1.0 | 3.59 | <LOD | 12.6 | 50.5 |
| | | | **Average** | **9.1** | **10.4** | **<LOD** | **1.0** | **3.40** | **<LOD** | **12.7** | **50.0** |
| | | | **SD** | **0.1** | **0.2** | **na** | **0.0** | **0.18** | **na** | **0.0** | **3.0** |
| | | | **%RSD** | **1.5** | **2.1** | **na** | **3.0** | **5.3** | **na** | **0.3** | **6.0** |
| | | | | | ***LOD*** | ***1.8*** | ***0.9*** | ***1.0*** | ***1.8*** | ***0.8*** | ***0.5*** |
| | | | | | ***LOQ*** | ***4.3*** | ***2.3*** | ***2.8*** | ***4.8*** | ***2.0*** | ***1.3*** |

Note: Shaded cells contain values between the Limit of Detection (LOD) and Limit of Quantitation (LOQ) for the method.





Arista Laboratories, Inc.
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PROJECT CODE: 1808

# APPENDIX M

## Analysis of Mainstream Cigarette Smoke For Mercury (Hg)

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

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# ANALYSIS OF MAINSTREAM CIGARETTE SMOKE FOR MERCURY (Hg)

## I. PRINCIPLE OF METHOD

The analytical method used for this study is detailed in Arista SOP T-036 - The Determination of Mercury in Mainstream Cigarette Smoke.

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

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

**Mainstream Mercury Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-036
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Set # | Run # | Client Code | Arista Code | Puffs/Cigt | Mercury (ng/cigt) |
|---|---|---|---|---|---|
| 800157 | 3 | Camel 100 | 3557 | 11.3 | 2.59 |
| 800157 | 16 | Camel 100 | 3557 | 11.3 | 2.69 |
| 800158 | 6 | Camel 100 | 3557 | 11.5 | 2.73 |
| 800158 | 11 | Camel 100 | 3557 | 11.0 | 2.44 |
| 800158 | 12 | Camel 100 | 3557 | 11.5 | 2.58 |
| 800158 | 16 | Camel 100 | 3557 | 11.2 | 2.44 |
| | | | **Average** | **11.3** | **2.58** |
| | | | **SD** | **0.2** | **0.12** |
| | | | **%RSD** | **1.7** | **4.8** |
| 800157 | 4 | Marlboro Light | 3558 | 8.0 | 1.82 |
| 800157 | 18 | Marlboro Light | 3558 | 8.4 | 1.96 |
| 800157 | 21 | Marlboro Light | 3558 | 8.2 | 1.95 |
| 800157 | 22 | Marlboro Light | 3558 | 8.1 | 1.95 |
| 800158 | 4 | Marlboro Light | 3558 | 8.0 | 1.90 |
| 800158 | 14 | Marlboro Light | 3558 | 8.3 | 1.82 |
| | | | **Average** | **8.2** | **1.90** |
| | | | **SD** | **0.2** | **0.07** |
| | | | **%RSD** | **1.9** | **3.5** |
| 800157 | 13 | Quest 1 | 3559 | 6.6 | 1.26 |
| 800157 | 15 | Quest 1 | 3559 | 6.6 | 1.19 |
| 800158 | 5 | Quest 1 | 3559 | 6.1 | 1.08 |
| 800158 | 7 | Quest 1 | 3559 | 6.5 | 1.26 |
| 800158 | 8 | Quest 1 | 3559 | 6.6 | 1.31 |
| 800158 | 15 | Quest 1 | 3559 | 6.8 | 1.25 |
| | | | **Average** | **6.5** | **1.23** |
| | | | **SD** | **0.3** | **0.08** |
| | | | **%RSD** | **3.9** | **6.5** |
| 800157 | 5 | Quest 2 | 3560 | 6.2 | 1.16 |
| 800157 | 6 | Quest 2 | 3560 | 6.2 | 1.14 |
| 800157 | 11 | Quest 2 | 3560 | 6.0 | 1.15 |
| 800157 | 12 | Quest 2 | 3560 | 6.1 | 1.17 |
| 800157 | 20 | Quest 2 | 3560 | 6.4 | 1.22 |
| | | | **Average** | **6.2** | **1.17** |
| | | | **SD** | **0.2** | **0.03** |
| | | | **%RSD** | **2.5** | **2.7** |

**Mainstream Mercury Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-036
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Set # | Run # | Client Code | Arista Code | Puffs/Cigt | Mercury, (ng/cigt) |
|---|---|---|---|---|---|
| 800157 | 8 | Quest 3 | 3561 | 6.3 | 1.37 |
| 800157 | 14 | Quest 3 | 3561 | 6.1 | 1.34 |
| 800157 | 19 | Quest 3 | 3561 | 6.1 | 1.32 |
| 800158 | 3 | Quest 3 | 3561 | 6.1 | 1.36 |
| 800158 | 13 | Quest 3 | 3561 | 6.2 | 1.31 |
| | | | **Average** | **6.1** | **1.34** |
| | | | **SD** | **0.1** | **0.03** |
| | | | **%RSD** | **1.5** | **2.1** |
| 800157 | 2 | 2R4F | 912 | 9.0 | 2.09 |
| 800157 | 10 | 2R4F | 912 | 9.1 | 1.91 |
| 800157 | 23 | 2R4F | 912 | 9.1 | 2.08 |
| 800158 | 2 | 2R4F | 912 | 9.3 | 2.19 |
| | | | **Average** | **9.1** | **2.07** |
| | | | **SD** | **0.1** | **0.12** |
| | | | **%RSD** | **1.4** | **5.6** |

Arista LABORATORIES

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# APPENDIX N

## Analysis of Mainstream Cigarette Smoke for Tobacco Specific N-Nitrosamines

The results in this test report relate only to the samples identified in this report. The information is confidential and is only to be used by the client identified in this report. Arista Laboratories accepts no liability in the use of this report or the results contained, herein. The original controlled report shall not be reproduced without written approval of Arista Laboratories, Inc.

Arista LABORATORIES

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*Certificate No. 1873.01*

# DETERMINATION OF TOBACCO SPECIFIC N-NITROSAMINES IN MAINSTREAM SMOKE

## I. PRINCIPLE OF METHOD

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

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

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

**Mainstream TSNAs Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-020
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run# | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | NAB (ng/cigt) | NAT (ng/cigt) | NNK (ng/cigt) | NNN (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00415 | B | Camel 100 | 3557 | 11.5 | 24.2 | 25.8 | 203 | 103 | 235 |
| C00415 | P | Camel 100 | 3557 | 11.0 | 22.4 | 27.6 | 200 | 114 | 197 |
| C00415 | R | Camel 100 | 3557 | 11.0 | 20.8 | 25.0 | 186 | 103 | 207 |
| C00415 | T | Camel 100 | 3557 | 11.3 | 22.9 | 26.7 | 213 | 111 | 216 |
| C00418 | I | Camel 100 | 3557 | 11.3 | 22.9 | 26.1 | 200 | 106 | 204 |
| C00418 | O | Camel 100 | 3557 | 11.4 | 23.9 | 23.3 | 201 | 112 | 223 |
| | | | **Average** | **11.3** | **22.9** | **25.8** | **201** | **108** | **214** |
| | | | **SD** | **0.2** | **1.2** | **1.5** | **9** | **5** | **14** |
| | | | **%RSD** | **1.8** | **5.3** | **5.8** | **4.3** | **4.6** | **6.5** |
| C00415 | E | Marlboro Light | 3558 | 8.4 | 12.9 | 16.8 | 127 | 75.5 | 138 |
| C00415 | I | Marlboro Light | 3558 | 8.2 | 13.4 | 17.6 | 135 | 89.6 | 144 |
| C00415 | K | Marlboro Light | 3558 | 7.8 | 12.6 | 16.0 | 115 | 79.9 | 144 |
| C00415 | S | Marlboro Light | 3558 | 8.3 | 12.6 | 18.9 | 138 | 84.5 | 138 |
| C00418 | J | Marlboro Light | 3558 | 8.1 | 12.6 | 17.1 | 135 | 83.5 | 128 |
| C00418 | M | Marlboro Light | 3558 | 7.8 | 12.0 | 14.0 | 119 | 77.3 | 138 |
| | | | **Average** | **8.1** | **12.7** | **16.7** | **128** | **81.7** | **138** |
| | | | **SD** | **0.3** | **0.4** | **1.7** | **10** | **5.2** | **6** |
| | | | **%RSD** | **3.3** | **3.5** | **9.9** | **7.5** | **6.4** | **4.3** |
| C00415 | C | Quest 1 | 3559 | 6.7 | 12.5 | 6.59 | 41.5 | 27.3 | 62.7 |
| C00415 | L | Quest 1 | 3559 | 6.6 | 10.6 | 6.20 | 40.6 | 25.6 | 64.9 |
| C00415 | N | Quest 1 | 3559 | 6.0 | 9.84 | 6.39 | 37.9 | 26.3 | 56.1 |
| C00418 | F | Quest 1 | 3559 | 7.0 | 11.4 | 6.27 | 37.7 | 27.6 | 56.5 |
| C00418 | H | Quest 1 | 3559 | 6.6 | 10.3 | 5.39 | 39.1 | 24.6 | 51.3 |
| C00418 | L | Quest 1 | 3559 | 6.6 | 10.0 | 5.90 | 41.9 | 26.5 | 58.4 |
| | | | **Average** | **6.6** | **10.8** | **6.13** | **39.8** | **26.3** | **58.3** |
| | | | **SD** | **0.3** | **1.0** | **0.43** | **1.8** | **1.1** | **4.9** |
| | | | **%RSD** | **4.8** | **9.2** | **7.0** | **4.6** | **4.2** | **8.4** |

**Mainstream TSNAs Test Report for:**
**Liggett Group Inc.**
**100 Maple Lane**
**Mebane, NC 27302**
**Q14615R2**

**Project Code:** 1808
**Project Start Date:** 27-Aug-04
**Arista SOP #:** T-020
**Smoking Protocol:** FTC
**Authorized By:** A. Martin
**Title:** QA Mgr

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

| Run# | Port | Client Code | Arista Code | Puffs/Cigt | MS TPM (mg/cigt) | NAB (ng/cigt) | NAT (ng/cigt) | NNK (ng/cigt) | NNN (ng/cigt) |
|---|---|---|---|---|---|---|---|---|---|
| C00415 | D | Quest 2 | 3560 | 6.3 | 9.72 | 3.64 | 26.3 | 29.5 | 62.2 |
| C00415 | G | Quest 2 | 3560 | 6.0 | 9.80 | 3.34 | 23.8 | 29.6 | 52.4 |
| C00415 | J | Quest 2 | 3560 | 6.2 | 10.4 | 3.67 | 23.5 | 31.3 | 59.4 |
| C00418 | N | Quest 2 | 3560 | 6.1 | 10.6 | 3.72 | 23.4 | 31.4 | 58.3 |
| C00418 | P | Quest 2 | 3560 | 6.3 | 10.5 | 3.53 | 22.4 | 31.3 | 56.1 |
| C00418 | R | Quest 2 | 3560 | 6.4 | 10.9 | 3.91 | 21.5 | 38.2 | 54.1 |
| | | | **Average** | **6.2** | **10.3** | **3.63** | **23.5** | **31.9** | **57.1** |
| | | | **SD** | **0.1** | **0.5** | **0.19** | **1.6** | **3.2** | **3.6** |
| | | | **%RSD** | **2.1** | **4.5** | **5.3** | **7.0** | **10.1** | **6.3** |
| C00415 | F | Quest 3 | 3561 | 6.0 | 8.64 | [redacted] | 5.34 | 10.4 | 78.4 |
| C00415 | H | Quest 3 | 3561 | 6.0 | 8.46 | [redacted] | 6.13 | 13.2 | 79.0 |
| C00415 | O | Quest 3 | 3561 | 6.1 | 8.68 | [redacted] | 6.63 | 14.6 | 76.0 |
| C00418 | C | Quest 3 | 3561 | 6.2 | 9.76 | [redacted] | 6.66 | 11.6 | 78.9 |
| C00418 | E | Quest 3 | 3561 | 6.2 | 8.88 | [redacted] | 6.31 | 14.5 | 81.1 |
| C00418 | K | Quest 3 | 3561 | 6.0 | 8.94 | [redacted] | 6.42 | 16.0 | 81.9 |
| | | | **Average** | **6.1** | **8.89** | [redacted] | **6.25** | **13.4** | **79.2** |
| | | | **SD** | **0.1** | **0.46** | **0.1** | **0.49** | **2.1** | **2.1** |
| | | | **%RSD** | **1.3** | **5.2** | **7.4** | **7.8** | **15.6** | **2.7** |
| C00415 | M | 2R4F | 912 | 9.0 | 11.1 | 17.2 | 124 | 137 | 145 |
| C00415 | Q | 2R4F | 912 | 9.1 | 10.8 | 17.2 | 141 | 146 | 147 |
| C00418 | D | 2R4F | 912 | 9.2 | 11.8 | 16.5 | 126 | 143 | 153 |
| C00418 | G | 2R4F | 912 | 9.0 | 11.9 | 17.2 | 137 | 150 | 146 |
| | | | **Average** | **9.1** | **11.4** | **17.0** | **132** | **144** | **148** |
| | | | **SD** | **0.1** | **0.5** | **0.4** | **8** | **5** | **4** |
| | | | **%RSD** | **1.0** | **4.8** | **2.2** | **6.1** | **3.8** | **2.5** |
| | | | | | ***LOD:*** | ***0.8*** | ***1.4*** | ***0.4*** | ***1.0*** |
| | | | | | ***LOQ:*** | ***2.5*** | ***4.5*** | ***1.4*** | ***3.5*** |

Note: Shaded cells contain values between the Limit of Detection (LOD) and Limit of Quantitation (LOQ) for the method.