Possible Health Effects of Cigarette Mentholation

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Tobacco Products Scientific Advisory Committee (TPSAC)
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Sources

• 343 articles in the NCI Bibliography of Literature on Menthol and Tobacco (2009) + 23 recent additions

Not directly relevant

Reviews (relied on primary sources)

Didn’t evaluate menthol separately

65 articles

Note: Red and * denotes tobacco industry-funded study
Overview

• Introduction to menthol
• Biomarkers of tobacco smoke exposure
• Toxicity and cellular effects
• Respiration
• Cardiovascular function
• Allergic reactions and inflammation
• Tobacco-related disease
• Discussion
• Summary
Introduction to Menthol
What is Menthol?

• Found naturally in peppermint and cornmint essential oils
• Saturated cyclic monoterpinoid alcohol with the molecular formula $\text{C}_{10}\text{H}_{20}\text{O}$

1 http://chemistry.umeche.maine.edu/CHY556/Models.html
Department of Chemistry, University of Maine, Orono, ME
Biomarkers of Tobacco Smoke Exposure**

** NOTE: Not including nicotine/cotinine (covered in presentation on Menthol and Nicotine Dependence)
# Carbon Monoxide (CO)\(^1\)

<table>
<thead>
<tr>
<th>Decreased CO</th>
<th>No Effect</th>
<th>Increased CO</th>
</tr>
</thead>
</table>

\(^1\) As recorded by expired CO, CO boost or carboxyhemoglobin (COHb)

\(^2\) When adjusted for cigarettes per day and amount of cigarette smoked

\(^3\) Borderline significant difference (p=0.053) for COHb boost; no significant difference in exhaled CO boost
Carbon Monoxide (CO) (cont.)

• Possible confounding variables:
  – Physiologic variables\textsuperscript{1}
    • Mucous layers in mucosal cold nerve endings
    • Differences in how the cigarette burns
      – Menthol in mainstream smoke may be reduced by pyrolysis
    – Other chemicals present in smoke\textsuperscript{2}

\textsuperscript{1} Ahijevych et al. 1996 \hspace{2em} \textsuperscript{2} Rabinoff et al. 2007
Tobacco-Specific Nitrosamines

• Tobacco-specific nitrosamines are known carcinogens
  – 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL)
  – 4-(methylNitrosamino)-1-(3-pyridyl)-1-butanone (NNK; metabolized into NNAL)
• Menthol inhibited metabolism of NNAL in human microsomes in vitro\(^1\)
• Menthol administered to NNK-treated rats had increased levels of NNAL metabolites\(^2\)
  – Suggests enhanced metabolism in vivo

\(^1\) Muscat et al. 2009  \(^2\) Ritchie et al. 1997
Does Menthol Inhibit Metabolism of NNAL in Smokers?

**NO**
- $\geq 15$ cpd
- $n = 112$ subjects
- Smoking as desired
- “Light” cigarettes only (defined by author as 7-15 mg “tar”)

**YES**
- $\geq 5$ cpd
- $n = 147$ subjects
- Overnight abstinence (food and cigarettes)
- Cigarettes had to be classifiable according to FTC menthol status

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1 Heck 2009*  
2 Muscat et al. 2009
Toxicity and Cellular Effects of Menthol
Toxicity

• Animal study with nose-inhalation of tobacco smoke from tobacco smoke with or without menthol by rats¹
  – Exposure to either cigarette produced:
    • Reduced body weights
    • Histopathological changes, such as
      – Epithelial hyperplasia and/or squamous metaplasia in the nasal passages, trachea and larynx, lungs and bronchi
      – Olfactory epithelial degeneration
    • **No difference** between type of cigarette smoke
  – Non-menthol tobacco smoke exposed rats had slightly higher incidence of nasal discharge

¹ Gaworski et al. 1997*
Cell Membrane Permeability

• Tobacco smoke alters cell membranes
  – Transepithelial electrical resistance between human bronchial epithelial cells was reduced by tobacco smoke¹
    • Indicates that the gap junctions between the cells were “loosened” up and integrity was lost (cell irritation)
    • **No difference** between menthol versus non-menthol smoke

¹ Alakayak and Knall 2008
Cell Membrane Permeability (cont.)

• Porcine esophageal tissue bathed in a solution containing menthol and NNK\(^1\)
  – *Markedly lower* permeation rate for NNK
  – Increase in tissue reservoir formation
  – Result: significantly more NNK bound within the esophageal mucosa, possibly increasing cell exposure to NNK
    • Increase the likelihood of cancer of the esophagus?
    • Limited evidence
      – Single *in vitro* animal study (not whole animal)
      – Non-human study
      – Epidemiological studies are inconclusive

\(^1\) Azzi et al. 2006
Cytotoxicity or Reduced Cell Proliferation

- **Toxic** in *in vitro* biologic model systems in normal tissue\(^1\)
- Cancer cell cultures: menthol dose- and time-dependently *inhibits* cell proliferation and/or *induces* cell death\(^2\)
- Does *not appear to enhance* the cytotoxicity already produced by tobacco smoke exposure\(^3\)

1 Bernson and Pettersson 1983  
3 Doolittle et al. 1990a*; Doolittle et al. 1990b*; Lee et al. 1990*
Menthol and Respiration
Respiration

• Published article on publicly available industry documents\(^1\)
  – An early tobacco industry study reported that mentholation of cigarettes appeared to exert an adverse effect on respiratory function
• Most studies have failed to find any effects of menthol on respiration (e.g., breathing patterns, nasal resistance)\(^2\)
• Inhaled menthol vapor has been associated with reduced ratings of respiratory discomfort\(^3\)

\(^1\) Wayne and Connolly, 2004   \(^2,3\) Eccles et al. 1987; Eccles et al. 1990; Nishino et al. 1997
Menthol and Cardiovascular Function
Cardiovascular Function

• CARDIA study\(^1\): as compared to non-menthol smokers, menthol smokers do not have significantly different rates of:
  – Coronary calcification
  – Reduced pulmonary function
• Rapid smoking study found only a single racial/ethnic difference\(^2\)
  – Black menthol smokers had lower increases in heart rate as compared to Black non-menthol smokers
    • 4.4% increase as compared to 12.2% increase (p>0.05)

\(^1\) Pletcher et al. 2006  \(^2\) Caskey et al. 1993
Cardiovascular Function (cont.)

• Small (n=22) within-subject laboratory study using denicotinized test cigarettes¹
  – Menthol smokers had greater increase in heart rate (p=.011) following both types of cigarettes
    • Menthol smokers ΔHR=5.3 bpm
    • Non-menthol smokers ΔHR=1.65 bpm
  – Smoker difference, not a difference between the menthol and non-menthol test cigarettes

¹ Pritchard et al. 1999
Cardiovascular Function (cont.)

- Three cross-over laboratory studies: acute effects following test two cigarettes (menthol compared to non-menthol)
  - **No** difference on measures of coronary flow reserve\(^1\)
  - **Worse** ventricular diastolic function\(^2\)
  - **Greater** increase in heart rate (101.2 versus 83.05 bpm)\(^3\)
  - **Greater** increase systolic blood pressure (130.7 versus 118.0 mmHG)\(^3\)
  - **Greater** stiffness of the carotid artery (stiffness index = 5.7 versus 2.2)\(^3\)

\(^1\) Ciftci et al. 2008b  \(^2\) Ciftci et al. 2008a  \(^3\) Ciftci et al. 2009
Menthol-Induced Allergic Reactions and Inflammation
Allergic Reactions and Inflammation

• An early example of menthol sensitivity: 1951 case study of a woman with nonthrombocytopenic purpura\(^1\)
  – Alleviation with cessation
  – Return with challenge
  – Alleviation with cessation

• A case series described three young women with acute eosinophilic pneumonia associated with the initiation of smoking menthol cigarettes\(^2\)

\(^1\) Highstein and Zeligman 1951  \(^2\) Miki et al. 2003
Menthol and Tobacco-Related Disease: Animal Studies
Tobacco-Related Disease

• No evidence that menthol (by itself) causes cancer\(^1\)

• May affect cancers induced by other agents

\(^1\) Ashby and Tennant 1991
Tobacco-Related Disease (cont.)

- Orally administered menthol did not significantly alter cancer induced in the large bowel and duodenum in rats\(^1\)

<table>
<thead>
<tr>
<th>Test compound</th>
<th>% rats with tumors</th>
<th># tumors/rat</th>
<th>% rats with tumors</th>
<th># tumors/rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>82</td>
<td>1.5 ± 1.2</td>
<td>50</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>Menthol</td>
<td>88</td>
<td>1.2 ± 0.7</td>
<td>42</td>
<td>0.4 ± 0.5</td>
</tr>
</tbody>
</table>

\(^1\) Wattenberg 1991, table redrawn
Tobacco-Related Disease (cont.)

- DBMA-induced rat model of mammary carcinogenesis\(^1\)
  - Orally administered menthol *inhibited* tumor formation and *increased* tumor latency (chemopreventive)

<table>
<thead>
<tr>
<th>Treatment</th>
<th># rats per group</th>
<th>Average # tumors/rat</th>
<th>Median tumor latency (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>46</td>
<td>3.3</td>
<td>63</td>
</tr>
<tr>
<td>Menthol</td>
<td>52</td>
<td>2.0</td>
<td>80 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

\(^1\) Russin et al. 1989; table re-drawn
Tobacco-Related Disease (cont.)

- Cigarette smoke condensate from menthol cigarettes painted on mouse skin *did not* significantly alter tumor incidence, latency or multiplicity as compared to that from non-menthol cigarettes\(^2\)
  - SENCAR mouse skin painting bioassays with TPA-induced tumors
  - Wasn’t menthol specific → combination of flavors that included menthol

\(^1\) Gaworski et al. 1999*
Menthol and Tobacco-Related Disease: Human Studies
Tobacco-Related Disease (cont.)

• To date, case-control studies\(^1\) and surveys\(^2\) have not shown that menthol alters smokers’ likelihood of developing:
  – Several kinds of cancers, including lung and non-lung smoking related cancers
  – Cardiovascular disease or coronary heart disease

  But, may not be so straightforward…

\(^1\) Brooks et al., 2003; Hebert and Kabat 1988; Kabat and Hebert 1991  \(^2\) Friedman et al. 1998; Murray et al. 2007
Tobacco-Related Disease (cont.)

• Menthol x Gender x Disease Interaction
  – 2 case control studies failed to find an interaction\(^1\)
  – 1 case control study: male menthol smokers had modestly increased risk of lung cancer\(^2\)
    • Relative risk for male menthol smokers = 1.45 (95% CI 1.03-2.02)
  – 1 case control study: authors suggested an increased risk for male menthol smokers and lung cancer\(^3\)
    • OR for 32+ pack years = 1.48 (95% CI = 0.71-3.05) – not statistically significant

\(^1\) Brooks et al. 2003; Hebert and Kabat 1988  \(^2\) Sidney et al. 1995  \(^3\) Carpenter et al. 1999
Tobacco-Related Disease (cont.)

- 1 case control study: authors suggested that male menthol smokers have an *modestly increased* risk of pharyngeal cancer\(^1\)
  - OR = 1.7 (95% CI = 0.8-3.4) – not statistically significant
- 1 case control study: authors suggested that female menthol smokers had a *modestly increased* risk (p=0.07) for esophageal cancer\(^2\)
  - OR = 2.3 (95% CI = 0.93-5.72) – not statistically significant

\(^1\) Kabat and Hebert 1994  \(^2\) Hebert and Kabat 1989
Discussion
Discussion

- Published analysis of publicly available tobacco industry documents
  - Botanicals and additives (e.g., menthol) can “reduce, mask, or prevent smokers’ awareness of the adverse symptoms caused by smoking”
- Smokers of menthol cigarettes may not be as able to perceive changes in health

- During delays, smokers may also continue to smoke
  - May itself exacerbate illness due to extended exposure to carcinogens and smoke particulate.

1 Rabinoff et al. 2007  2 Garten et al. 2003
Summary
Summary

• The data on biomarkers (CO and tobacco-specific nitrosamines) are inconclusive.
• Menthol is a biologically active compound that may damage or kill cells.
• Menthol does not appear to alter the cytotoxic effects of tobacco smoke.
Summary (cont.)

- Menthol **reduces** feelings of respiratory discomfort, but no corresponding physiological effects.
- The data regarding the effects of menthol and the cardiovascular effects of cigarette smoke are inconclusive.
- The data regarding menthol and cancer suggest a possible menthol x gender x disease interaction.
- Menthol added to tobacco has been known to **produce** allergic reactions in rare cases.
Clarifying Questions?

References are listed in subsequent slides
References


References (cont.)

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