Clinical Effects

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Clinical Effects

- Analytical and Health Sciences Capabilities
- Mechanistic Studies on Sensory Effects of Menthol
- Health Effects
- Dependence and Cessation
- Summary
Analytical and Health Sciences Capabilities

- Expertise and experience
- Evaluation of ingredients
  - More than 600 studies performed
  - Many peer-reviewed publications in press or in preparation
- Peer-reviewed publications
- Presentations and posters
- Analysis of published literature
Clinical Effects

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Mechanistic Studies on Sensory Effects of Menthol

- Hundreds of studies have focused on menthol per se
- In airways, studies have focused on:
  - Local anesthetic effects
  - Cooling sensation
  - Desensitization to irritation or pain
Mechanistic Studies on the Local Anesthetic Effects of Menthol per se

The salient features of local anesthetics* are:

- blocks Na\(^+\) ion movement through Na\(^+\) ion channels in nerves
- thereby blocking the action potentials responsible for nerve conduction

* (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Catterall & Mackie 2006)

Mechanistic evidence from a PM USA-funded study (Hans, publication planned)
- menthol does not block current-induced neuronal action potentials
- menthol does not block neuronal sodium channels

Primary cultures of rat trigeminal neurons
Mechanistic Studies

Menthol per se causes a cooling sensation

TRPM8

Menthol per se causes an irritation / pain sensation

TRPA1

(Mckemy, et al. 2002; Peier, et al. 2002; Gerhold and Bautista 2009)

(Cliff and Green 1994; Karashima, et al. 2007)
Mechanistic Studies on the Desensitization Effect of Menthol per se

- **Evidence from cell culture studies**
  - Menthol desensitization of nicotine at the TRPA1 channel
  - Other compounds can irreversibly bind the TRPA1 channel

- **Evidence from clinical studies**
  - Menthol pretreatment of the tongue
    (Dessirier, et al. 2001)
  - Menthol vapor in the nose
    (Renner, et al. 2008 PM USA-funded study, publication planned)
Mechanistic Studies on the Desensitization Effect of Menthol per se

Menthol per se does not desensitize the nose to pain caused by nicotine, even in the presence of a cooling sensation.

Stimuli administered as a vapor with an olfactometer.

Study Information
PM USA-funded study, Renner et al., publication is planned.

Data represents the average of results from 20 adult smokers.

[EU] is Estimation Units.

**CO₂**

**Visual Analog Scale (VAS) [EU]**

**Menthol:**
- Cooling level
- VAS (mean ± SEM)
  - Menthol 44.8 ± 7.8
  - Placebo 48.6 ± 7.0
- Menthol 26.0 ± 8.2
- Placebo 28.7 ± 8.1

**Low level of Nicotine:**
- Measuring: Burning Pain
- VAS (mean ± SEM)
  - Menthol
  - Placebo
**Summary: Mechanistic Studies on Sensory Effects of Menthol**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Menthol per se</th>
<th>Menthol in Smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetic effect</td>
<td>No effect</td>
<td>No studies</td>
</tr>
<tr>
<td>Desensitization in cell culture</td>
<td>Mixed results</td>
<td>No studies</td>
</tr>
<tr>
<td>Airway desensitization in clinical studies</td>
<td>Mixed results</td>
<td>No studies</td>
</tr>
</tbody>
</table>
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Health Effects, Dependence and Cessation

- Important variables to consider
- The proportion of smokers who smoke menthol cigarettes varies by:
  - race
  - gender
  - age groups
  - socioeconomic status

(Tobacco Use Supplement to the Current Population Survey)

Studies of health effects, dependence and cessation comparing menthol and non-menthol smokers should consider these potential confounding variables
## Epidemiological Studies Comparing Health Effects of Menthol vs. Non-Menthol Cigarettes

<table>
<thead>
<tr>
<th>Study authors, date, page no.</th>
<th>Health outcome investigated</th>
<th>Study design</th>
<th>Number of subjects</th>
<th>Menthol associated with increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebert &amp; Kabat, 1988, p.986</td>
<td>Esophageal cancer</td>
<td>Case-control</td>
<td>Cases = 312; Controls = 462</td>
<td>NO</td>
</tr>
<tr>
<td>Hebert &amp; Kabat, 1989, p. 41</td>
<td>Esophageal cancer</td>
<td>Case-control</td>
<td>Cases = 311; Controls = 462</td>
<td>NO</td>
</tr>
<tr>
<td>Kabet &amp; Hebert, 1991, p. 6511</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 1044; Controls = 1324</td>
<td>NO</td>
</tr>
<tr>
<td>Kabet &amp; Hebert, 1994, p. 183</td>
<td>Oropharyngeal cancer</td>
<td>Case-control</td>
<td>Cases = 276; Controls = 1265</td>
<td>NO</td>
</tr>
<tr>
<td>Sidney, et al., 1995, p. 727</td>
<td>Lung cancer</td>
<td>Cohort</td>
<td>Menthol: 3654 Non-menthol: 8107</td>
<td>YES in men only. (RR=1.45; 95% CI 1.03-2.02)</td>
</tr>
<tr>
<td>Carpenter, et al., 1999, p. 114</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 337; Controls = 478</td>
<td>NO</td>
</tr>
<tr>
<td>Brooks, et al., 2003, p. 609</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 643; Controls = 4110</td>
<td>NO</td>
</tr>
<tr>
<td>Stellman, et al., 2003, p. 294</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 3448; Controls = 8151</td>
<td>NO</td>
</tr>
<tr>
<td>Jockel, et al., 2004, p. 33</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 1004; Controls = 1004</td>
<td>NO</td>
</tr>
<tr>
<td>Pletcher, et al., 2006, p. 1919</td>
<td>Coronary calcification, pulmonary function decline</td>
<td>Longitudinal, prospective</td>
<td>Menthol: 972 Non-menthol: 563</td>
<td>NO</td>
</tr>
<tr>
<td>Murray et al., 2007, p. 101</td>
<td>Mortality from coronary heart disease, cardiovascular disease, lung cancer, and all causes</td>
<td>Prospective</td>
<td>Menthol: 1216 Non-menthol: 4665</td>
<td>NO</td>
</tr>
<tr>
<td>Etzel, et al., 2008, p. 261</td>
<td>Lung cancer</td>
<td>Case-control</td>
<td>Cases = 491; Controls = 497</td>
<td>NO</td>
</tr>
</tbody>
</table>
Health Effects*

- Menthol cigarettes do not result in increased toxicity in non-clinical toxicity testing compared with non-menthol cigarettes.
- Smoking menthol cigarettes produces no consistent effect on human puffing and inhalation behavior.
- Findings from the PM USA Total Exposure Study (TES) show no difference in biomarkers of exposure (BOE) and biomarkers of potential harm (BOPHs) between menthol and non-menthol cigarette smokers.
- Findings from the TES suggest no effect of smoking menthol cigarettes on the metabolism of nicotine or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).
- Epidemiological evidence suggests no effect of menthol on smoking-related disease risks.

* Refer to ALCS submissions to the TPSAC dated March 22, 2010 and June 30, 2010.
Overall, our analysis of the published scientific literature and internal studies concludes that menthol added to cigarettes does not increase the inherent health risks of smoking.
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Dependence

- Fagerström Test for Nicotine Dependence (FTND)
  - Most widely reported measurement tool for nicotine dependence
    (Heatherton, et al. 1991)
    - cigarettes per day (CPD)
    - time to first cigarette (Baker, et al. 2007; Fagerstrom 2003)
  - No statistically significant effect of menthol status on the FTND in the TES
    (Muhammad-Kah, et al. 2010)
  - Four other studies using the FTND also found no significant difference between menthol and non-menthol smokers

- Other measures showed no difference in dependence by menthol status:
  - DSM-IV criteria for Dependence
  - Fagerström Tolerance Questionnaire
  - Nicotine Dependence Syndrome Scale
  - Minnesota Withdrawal Scale scores
Cessation Treatment

- HHS published *Clinical Practice Guidelines for Treating Tobacco Use and Dependence: 2008 Update*
  - Comprehensive review of treatment effectiveness for smokers
  - No mention of menthol in relation to dependence, cessation or relapse

- The weight of evidence from nine published smoking cessation treatment studies show no difference between menthol and non-menthol smokers on cessation outcomes
  
Cessation

- Six published peer-reviewed studies from national surveys and health risk studies have generally found no difference in cessation outcomes between menthol and non-menthol smokers
  - higher odds of relapse, but no difference in odds of not currently smoking, recent quit attempt, cessation if recent quit attempt or sustained smoking cessation (n=1,535) *(Pletcher, et al. 2006)*
  
  - no significant difference in becoming a sustained quitter, intermittent quitter, or continuing smoker over five years of follow-up (n=5,887) *(Murray, et al. 2007)*
  
  - no difference in odds of having one or more quit attempts in the last 12 months and no difference in serious intention to quit in the next six months (n=7,912) *(Fagan, et al. 2007)*
  
  - higher (Whites), lower (Hispanics) and no difference (African-Americans and overall) in odds of cessation (n=7,815) *(Gundersen, et al. 2009)*
  
  - no difference in relative risk of quitting over five years (n=13,268) *(Hyland, et al. 2002)*
  
  - no difference in odds of quitting by menthol status among Whites or African-Americans (n=19,545) *(Muscat, et al. 2002)*
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Clinical Effects – Summary

- Based on an evaluation of published and unpublished information about menthol we conclude:
  - Menthol per se has airway sensory effects (cooling and irritation or pain)
  - Menthol per se in desensitization studies showed mixed results
  - Menthol added to cigarettes does not increase health risks of smoking as shown in:
    - Non-clinical studies
    - Clinical studies
    - Epidemiology studies
  - Menthol does not increase cigarette dependence
  - Menthol does not affect smoking cessation
References


