Chemoreception & Tobacco

Centers for Disease Control and Prevention
October 6, 2014
Aspects of Oral Perception

- Taste (Gustation)
- Aroma (Olfaction)
- Mouthfeel
- Thermal & Chemesthetic (e.g. Trigeminal)

Cooling Ingredients

- Menthol Production
- Menthol & Perception
- Other Cooling Ingredients

Tobacco & Flavoring

- The Old Cigarette Companies
- The Changing Cigarette
- Filters - Lower Tar & Nicotine
- Smoke pH, Ammonia & DAP
- Tobacco Flavors

E-Cigarettes & Flavors

- The New Wild West
ASPECTS OF ORAL PERCEPTION

- Taste (Gustation)
- Aroma (Olfaction)
- Mouthfeel
- Trigeminal & Thermal
And is “Kokumi” the sixth taste?
ASPECTS OF ORAL PERCEPTION

Major Mouthfeel Attributes

- **Viscosity** (Thickness)
  - Glutathione (γ-Glu-Cys-Gly), γ-Glu-Val-Gly
  - Gums, Hydrocolloids, Sugars

- **Astringency**
  - Catechins, Tannins, Bark extracts

- **Particulates**
  - Grainy, Gritty, Crunchy, Chalky

- **Oily** (fat, creamy)
  - Butterfat, Chicken fat, Beef fat, Oils

- **Tingly**
  - Carbonation, Other Tingling agents

- **Slickness** (Gelatinous)
  - Gums, Gelatin, etc

- **Kokumi** (Heartiness, fullness)
  - Glutathione (γ-Glu-Cys-Gly), γ-Glu-Val-Gly

**Mouthfeel**
ASPECTS OF ORAL PERCEPTION

Major Thermal & Chemesthetic (e.g. Trigeminal) Attributes

- Chile pepper (capsaicin), Black pepper (piperine), Ginger (gingerols, shogaols), Jambu (Spilanthol), Guinea pepper (paradols), Sichuan pepper (sanshool), Mustard & Horseradish (isothicyanates)

- Menthol, Menthyl Carboxamides (WS-3, WS-5, G-180), Icilin and more

- Cold (Temperature)
- Hot (Temperature)
- Hot (Tingly) (Chemical)
- Cold (Chemical)
- Pain (Irritation)

All the above
Odorants are volatile chemicals carried by air to the Regio olfactoria (olfactory epithelium) located in the roof of the two nasal cavities of the human nose, just below and between the eyes. The olfactory region of each of the two nasal passages in humans is a small area of about 2.5 square centimeters containing in total approximately 50 million primary sensory receptor cells.
The olfactory region consists of cilia projecting down out of the olfactory epithelium. The olfactory cilia are the sites where molecular reception with the odorant occurs and sensory transduction (i.e., transmission) starts.

Odorants can reach the receptors either though the nostrils (orthonasal) or via the mouth cavity (retronasal).
October 4, 2004 - Richard Axel and Linda Buck honored with the 2004 Nobel Prize in Physiology or Medicine for pioneering studies that clarify how the olfactory system works

Understanding Scent

Elucidation of Olfactory G-Protein Receptor Structures - a result of Genome Data mining Research

Different Views of G-Protein Receptor Structures

Cooling Ingredients

• Menthol Production
• Menthol & Perception
• Other Cooling Ingredients
Production of Mentha arvensis Oil in India & China & Menthol Derived

Source: 2007-2010 - India Spice Board & Karvy Comtrade Ltd (July 2011) & Sushil Global Commodities
Source: 2011-2012 - Commodity Online India & MCX India
Major Commercial Routes to (-)-Menthol

**BASF Process**

1. Distillation
2. $\text{Rh}(\text{CO})_2\cdot((R,R)-\text{Chirophos})$
3. Cyclisation (cat.)
4. $\text{H}_2$ / cat.

**Symrise Process**

1. $\text{Al}_2\text{O}_3$ cat.
2. $\text{H}_2$ / cat.
3. Distillation & Recycle
4. Methyl benzoate trans-esterification
5. Menthol benzoate Resolution & Recycle

**Takasago Process**

1. Li + $(\text{C}_2\text{H}_5)\text{NH}$
2. (S)-SEPHOS-Rh or (S)-BINAP-Rh
3. $\text{H}_3\text{O}^+$
4. Cyclisation (cat.)

Meta-Cresol

Thymol

$(\pm)$-Menthol (Racemic)

(-)-Menthol

Myrcene

(R)-Citronellal enamine

(+)-Citronellal

(-)-Isopulegol

*Mentha arvensis* ex India/China
**Worldwide Estimated L-Menthol Production (Metric tons)**

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (natural)</td>
<td>9,700</td>
<td>13,000</td>
</tr>
<tr>
<td>China (natural)*</td>
<td>2,120</td>
<td>4,000</td>
</tr>
<tr>
<td>Symrise (synthetic)</td>
<td>3,600</td>
<td>5,500</td>
</tr>
<tr>
<td>Takasago (synthetic)</td>
<td>1,500</td>
<td>2,000</td>
</tr>
<tr>
<td>BASF</td>
<td>0</td>
<td>1,000</td>
</tr>
<tr>
<td>Other synthetic</td>
<td>1,200</td>
<td>2,000</td>
</tr>
<tr>
<td>Brazil (natural)*</td>
<td>450</td>
<td>300</td>
</tr>
<tr>
<td>Taiwan (natural)*</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Japan (natural)*</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19,170</strong></td>
<td><strong>28,400</strong></td>
</tr>
</tbody>
</table>

*Primarily produced from crude menthol and/or Mentha arvensis oil from India

Source: 2012 – J.C. Leffingwell estimate

Assuming a menthol price of US $25/kilo = ~$700 million Market
In 2011 USA Menthol Cigarettes used ~ 252 tons of Menthol
## Thermo TRP Receptors & Agonists

### Thermoreceptor Agonists

<table>
<thead>
<tr>
<th>Chemical agonist (botanical source)</th>
<th>ThermoTRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin (hot chilli peppers, e.g., Tabasco)</td>
<td>TRPV1</td>
</tr>
<tr>
<td>Piperine (black pepper corns)</td>
<td>TRPV1</td>
</tr>
<tr>
<td>Allicin (fresh garlic)</td>
<td>TRPV1, TRPA1</td>
</tr>
<tr>
<td>Camphor (Cinnamomum camphora)</td>
<td>TRPV3, TRPV1</td>
</tr>
<tr>
<td>D-9-Tetrahydrocannabinol (Cannabis sativa)</td>
<td>TRPV2, TRPA1</td>
</tr>
<tr>
<td>Cannabidiol (Cannabis sativa)</td>
<td>TRPV2</td>
</tr>
<tr>
<td>Thymol (thyme)</td>
<td>TRPV3</td>
</tr>
<tr>
<td>(-)-Menthol (peppermint)</td>
<td>TRMP8, TRPA1, TRPV3</td>
</tr>
<tr>
<td>1,8-Cineole, eucalyptol (eucalyptus)</td>
<td>TRPM8, TRPV3</td>
</tr>
<tr>
<td>WS-3 (synthetic)</td>
<td>TRPM8, TRPA1</td>
</tr>
<tr>
<td>Icilin (synthetic)</td>
<td>TRPM8</td>
</tr>
<tr>
<td>WS-12 (synthetic)</td>
<td>TRPV3, TRPA1, TRPV1</td>
</tr>
<tr>
<td>Eugenol (clove)</td>
<td>TRPA1, TRPV3</td>
</tr>
<tr>
<td>Cinnamaldehyde (cinnamon, cassia)</td>
<td>TRPA1</td>
</tr>
<tr>
<td>Allyl isothiocyanate (mustard, horseradish)</td>
<td>TRPA1</td>
</tr>
<tr>
<td>Phenethyl isothiocyanate (mustard, horseradish)</td>
<td>TRPA1</td>
</tr>
<tr>
<td><strong>Nicotine</strong> (Tobacco)</td>
<td><strong>TRPA1</strong></td>
</tr>
</tbody>
</table>

Thermoreceptors belong to the class of **transient receptor potential (TRP) channels**

ThermoTRPs are gated Ca++ channels consisting of six transmembrane domains (TM1–TM6) flanked by large N- and C-terminal cytoplasmic domains. The schematic representation is shown with the putative ion channel between TM5–TM6 in TRPM8, which is activated by menthol and other cold stimuli. TRP channels modulate the calcium ion gating processes resulting in the stimulus signal.

Much of the knowledge gained on TRP activation by chemical stimuli has been derived by genetic expression of putative receptor domains and measurement of Ca++ flux intensity by fluorometric imaging assays.
Wilkinson Sword Design of Non-Menthol Cooling Agents
(late ‘60’s – early 70’s)

Used Pharmaceutical Approach

A - Examined cooling activity of over 1200 compounds
B - Developed Structure Activity Relationships for predicting cooling

The Wilkinson-Sword model lists four requirements for cooling compounds:

1 - A hydrogen bonding group.
2 - A compact hydrocarbon skeleton.
3 - A logP between 1.0 and 5.0 (solubility coefficient in octanol/water)
4 - A molecular weight between 150 and 350

* - Chirality can play a major role when present

Although refined over the years, these factors are still valid.

Today, the major approach to discovery of new coolants (and other tastants) utilizes the genetic approach of receptor expression and calcium fluorometric imaging assays to measure binding intensity.
Approximate Relative Cooling Strengths vs Menthol (as 100)

Note – WS-30, WS-4 & WS-14 are not GRAS as of 2014
Relative Potency of TRPM8 agonists based on EC$_{50}$ values (mean) with (-)-Menthol = 100

Adapted from Behrendt et al., Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging plate reader (FLIPR) assay, Brit J Pharm 2004; 141(4):737–745.
Wilkinson Sword Coolants

**WS-3 = N-Ethyl-p-menthane-3-carboxamide**

- Approximate cooling intensity vs. L-Menthol (as 100)
- 150 = 1.5X menthol

- FEMA 3455 (1975)
- FLAVIS 16.013

**WS-23 = N,2,3-trimethyl-2-Isopropylbutyramide**

- Approximate cooling intensity vs. L-Menthol (as 100)
- 75 = 0.75X menthol

- FEMA 3804 (1996)
- FLAVIS 16.013

**WS-12 = N-(4-Methoxyphenyl)-p-menthane-3-carboxamide**

- Approximate cooling intensity vs. L-Menthol (as 100)
- ~100 – 150 = ~1.0-1.5X menthol

- FEMA 4681 (2011)
- FLAVIS --
WS-14 = N-t-Butyl-p-menthane-3-carboxamide (NOT GRAS)

Approximate cooling intensity vs. L-Menthol (as 100)

75 = 0.75X menthol

Investigated by both RJRT and Philip Morris for a “Cool without Menthol” concept. Considered the best of the WS non-menthol coolants by both companies.

Introduced into test market by PM in 1981 – rather rapidly withdrawn! Was that because of market acceptance OR because of legal concerns?
Tobacco & Flavoring

• The Old Cigarette Companies
• The Changing Cigarette
• Filters - Lower Tar & Nicotine
• Smoke pH, Ammonia & DAP
• Tobacco Flavors
The Old Cigarette Companies

- At the beginning of 1911, J.B. Duke's American Tobacco Co. controlled 92% of the world's tobacco business. But the trust is broken up as violation of the 1890 Sherman Antitrust Act. The major companies to emerge were: American Tobacco Co., R.J. Reynolds, Liggett & Myers Tobacco Company, Lorillard and BAT.
- Liggett & Myers got about 28% of the cigarette market
- P. Lorillard received 15% of the cigarette business
- American Tobacco retained 37 per cent of the market
- R. J. Reynolds received no cigarette line but was awarded 20 per cent of the plug chewing trade
The Old Cigarette Companies

1912: RJR Introduces Red Kamel ... a blend of Turkish & Virginia Tobaccos AND Prepares the Introduction of another cigarette
1913: Birth of the "modern" cigarette: R.J. Reynolds introduces Camel, the first “American Blend” cigarette - made of a blend of Virginia, Burley and Oriental tobaccos.

1917: There are now 3 standard brands of cigarettes on the US market: Camel, Lucky Strike and Chesterfield.
The Old Cigarette Companies

1926: Lloyd (Spud) Hughes' menthol Spud Brand and recipe sold to Axton-Fisher Tobacco Co., which markets it nationally.

1932: B&W introduces "Kool" cigarettes to compete with Axton-Fisher's Spud, the only other mentholated brand.
The Old “Original” Major Brands
U.S. Sales
1938-2010

Source: RAI 2010-2013; Maxwell Reports 1983-2009; Philip Morris USA 1938-81
The Changing Cigarette

Filter Cigarettes:
1951 - Filters are 0.8% of sales

1952 – B&W’s 70mm Viceroy with the new cellulose acetate filter is introduced.

1952: Lorillard introduces Kent cigarettes with the "Micronite Filter"; but the filter contains asbestos.


1955 - Filters are 19.6% of sales

1956: P. Lorillard discontinues use of "Micronite" filter (with asbestos) in its Kent cigarettes. With a conventional cellulose acetate filter Kent sales increase by 33 billion units between 1956-1958.

1960 - Filters are 52.5% of sales
The Changing Cigarette

**Reconstituted Tobacco:**

Early 1950's - RJR constructs plant to produce reconstituted tobacco and incorporates low levels (i.e., 1%) into cigarettes in 1954. This utilizes Tobacco waste & stems in a classic paper making process.

By the late 1950’s all manufacturers were utilizing reconstituted tobacco.

1964 –1965: Philip Morris implements a new “hot belt” or “band cast” recon process, with improved flavor, using diammonium phosphate to solubilize the tobacco pectins. Immediately, sales of Marlboro sky rocketed. In the next 10 years Marlboro volume in the U.S. increased by 64.4 billion units at an average annual growth of 14.5%/year.

By 1969 -1970 – Competitors were investigating “why?”. And the possibility of “Free-Base” nicotine was being discussed.
Cigarette Paper Porosity:
1956 - 1964: The use of more porous cigarette paper allows the industry to reduce average tar & nicotine levels by nearly 50%.

Expanded Tobacco:
1967: an eccentric chemist buried in the RJR labs proposes a method of expanding tobacco by impregnating tobacco with a volatile solvent and heating it.

Circa 1970 - the first expanded tobacco quietly is introduced into RJR cigarettes; the volatile solvent utilized commercially for expansion was Freon.

Expanded tobacco would play an important role in product cost reduction and also become important in designing “low tar” cigarettes.
**The Changing Cigarette**

**Expanded Tobacco:**
mid-70's: Philip Morris begins using an expansion process utilizing ammonium carbonate that circumvents the RJR patents.

1979: A Philip Morris / Airco process now known as DIET utilizing carbon dioxide in a pressurized vessel followed. This process gave a superior tasting product as compared to using ammonium carbonate.

Late 70's: concern over Freon’s effect on the ozone layer becomes an issue to face RJR.

1980's: RJR develops a propane expansion process, but only built a pilot plant.

1990's: RJR implements DIET expansion.
The New Filter Brands of the 50’s
U.S. Sales
1945-2010

Source: Altria 2009-2013; Maxwell Reports 1983-2009; Philip Morris USA 1938-81
The Major Menthol Brands
U.S. Sales
1938-2010

UNITS (IN BILLIONS)

Year

Source: Lorillard 2010-2013; Maxwell Reports 1983-2009; Philip Morris USA 1938-81
The Changing Cigarette

1951 - Filters are 0.8% of sales
1955 - Filters are 19.6% of sales
1960 - Filters are 52.5% of sales
1970 - Filters are 79.4% of sales
1980 - Filters are 91.7% of sales
1990 - Filters are 96.0% of sales
2000 - Filters are 98.2% of sales
2010 - Filters are 99.5% of sales

Source: Maxwell Reports; FTC
Prior to 1950:
Less than 1% with filter, No Porous cigarette paper
No reconstituted or Expanded tobacco
Most were 70 mm in length;
Tobacco wt. per cigarette ~1000-1200 mg.
Less than 1% were mentholated

Today’s Cigarette:
99.6% with filter, all with Porous cigarette paper,
15-29% Reconstituted tobacco
15-29% Expanded tobacco
Most 85 mm in length
Tobacco wt. per cigarette ~725 mg.
32+% are mentholated
Sales Weighted Average Tar & Smoke Nicotine
USA

Tar (TPM) - mg/cigarette
Nicotine - mg/cigarette

Year

Leffingwell & Associates
Smoke pH, Ammonia & DAP

Alkalinity of Smoke – Air-Cured vs. Flue-Cured

Cigarette Smoke pH
(Cumulative Puffs)

Butt Length in Millimeters

Virginia (15.5% Sugar)  Air-Cured (2% Sugar)
Blended (4.7% Sugar)  Cigarillo (0.5% Sugar)

[Adapted from Elson, 1972]

Smoke pH, Ammonia & DAP

Thermal Generation of Formic Acid – Burley vs. Flue-Cured

Thermal Generation of Formic Acid

Adapted from Fenner, TCRC, 1988

Smoke pH, Ammonia & DAP

Thermal Generation of Ammonia – Burley vs. Flue-Cured

Adapted from Fenner, TCRC, 1988

Since pH of smoke in air-cured tobacco is more alkaline than flue-cured or Oriental, the ratio of nicotine base to nicotine salts increases. This causes the sensory and physiological perception of increased nicotine strength (and harshness) on inhalation. Accordingly, the increased alkalinity of straight air-cured cigarettes renders them virtually unacceptable to nearly all smokers as the higher smoke pH imparts an alkaloid harshness (nicotine “impact” or “kick”) with a flavor distortion which can be extremely unpleasant. Conversely, many smokers find the acidic smoke of straight Virginia cigarettes to be unbalanced.

The addition of sugars to air-cured tobacco mitigates the alkaloid harshness.
Smoke pH, Ammonia & DAP

Nicotine

Diprotanated $\leftrightarrow$ Monoprotanated $\leftrightarrow$ Free Base

- Diprotanated $\text{pH} 2.0$
- Monoprotanated $\text{pH} 5.5$
- Free Base $\text{pH} 9.2$

Smoke pH, Ammonia & DAP

### Tobacco Smoke pH, Ammonia & DAP

<table>
<thead>
<tr>
<th>Tobacco Smoke</th>
<th>“Smoke pH”</th>
<th>Free nicotine (calc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flue-cured</td>
<td>5.0 – 6.0</td>
<td>0 – 1%</td>
</tr>
<tr>
<td>American blend</td>
<td>5.5 – 6.5</td>
<td>0.3 – 3%</td>
</tr>
<tr>
<td>Dark-air cured</td>
<td>7.0 – 7.5</td>
<td>9 – 25%</td>
</tr>
<tr>
<td>Cigar</td>
<td>8.0 – 8.5</td>
<td>50 – 80%</td>
</tr>
<tr>
<td>Recon Tob.</td>
<td>5.9 – 6.0</td>
<td>~1%</td>
</tr>
<tr>
<td>Recon Tob. (NH₃)</td>
<td>6.0 – 6.2</td>
<td>~1 – 2%</td>
</tr>
<tr>
<td>Recon Tob. (DAP)*</td>
<td>6.0 – 6.5</td>
<td>~2 – 3%</td>
</tr>
</tbody>
</table>

* DAP = (NH₄)₂HPO₄ = Diammonium phosphate

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Rodgman, A., Smoke pH: A Review, Beiträge zur Tabakforschung Int., Volume 19, No. 3, 2000, pp.128-131
Ammoniation of Sugars

Cigarette 2,6-DF (μg/g) 2,5-DF (μg/g) Glucosamine (μg/g)
Newport*? 225.24 355.05 1093.27
Marlboro Red* 167.22 286.32 1008.97
Camel* 140.99 227.51 992.83
Am. Blend Reference 2R4F 117.58 174.74 882.07
Flue-cured (avg. 6 Samples) 57.97 66.13 420.67
Izmir (Oriental) 36.97 35.10 255.03
Burley (avg. 6 Samples) 0.76 18.87 145.83

* Ammoniated Recon

Moldoveanu et al., Beiträge zur Tabakforschung Int., Volume 24, No. 5, 2011. p 239
Pyrolysis of Deoxyfructosazines

Tobacco Flavors

Evolution of American Blend Cigarette Flavors

(The American Tobacco Trust - Dissolved in 1911)

Emerging U.S. Companies were:
American Tobacco
R.J. Reynolds Tobacco
Lorrilard Tobacco
Liggett & Myers Tobacco

All of these companies used the same types of master flavor formulas developed by the American Tobacco Trust for Pipe tobaccos such as Prince Albert, Dukes Mixture and Bull Durham - all were based on Nutmeg or Mace, Cardamom and Coriander.
## Tobacco Flavors

### Alcoholic extracts (Lucky Strike Type) - Historical

(Merory, Food Flavorings, 1960)

<table>
<thead>
<tr>
<th>PARTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonka beans</td>
<td>125</td>
</tr>
<tr>
<td>Coriander seed</td>
<td>125</td>
</tr>
<tr>
<td>Cardamom seed</td>
<td>8</td>
</tr>
<tr>
<td>Mace</td>
<td>1.2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>357</td>
</tr>
<tr>
<td>Water</td>
<td>773</td>
</tr>
</tbody>
</table>

Casing of sugar, maple, licorice, cocoa with Balsam Peru, Balsam Tolu and Styrax
Tobacco Flavors

Alcoholic extracts (Camel Type) - Historical

(Merory, Food Flavorings, 1960)

<table>
<thead>
<tr>
<th>PARTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deer tongue</td>
<td>125</td>
</tr>
<tr>
<td>Tonka beans</td>
<td>125</td>
</tr>
<tr>
<td>Coriander seed</td>
<td>125</td>
</tr>
<tr>
<td>Angelica root</td>
<td>64</td>
</tr>
<tr>
<td>Cardamom seed</td>
<td>8</td>
</tr>
<tr>
<td>Mace</td>
<td>16</td>
</tr>
<tr>
<td>Alcohol</td>
<td>390</td>
</tr>
<tr>
<td>Water</td>
<td>840</td>
</tr>
</tbody>
</table>

Casing of sugar, maple, licorice, cocoa
Tobacco Flavors

Typical Components of American Blend Flavors

(Philip Morris - Marlboro Type circa 1960 - 1998)

Chocolate Flavor (pre-1960 type) supplied originally by Fritzsche-D&O (now Givaudan)

- Anise extract or oil (~2-5 ppm anethole)
- Menthol (~25 ppm)
- Valerian oil (probably oil at low level)

Casing of sucrose, invert sugar, licorice, cocoa, chocolate liquor & Benzoin resinoid

- Originally contained coumarin until ~1970 (after 1954 FDA food ban)
- Notes were predominantly chocolate, some vanilla with a fruity pack aroma

In the late 1990’s PM reformulated the Marlboro Flavor to remove anethole – it now has an anisic aldehyde, acetanisole, chocolate, vanilla type flavor.
Tobacco Flavors

Typical Components of American Blend Flavors

(RJR – Old Camel / Winston Types)

- Nutmeg oil (~2-5 ppm)
- Cardamom Oil (~1 ppm)
- Coriander Oil (~0.5 ppm)
- Vanillin (~10 ppm) (optional)

Casing of invert sugar, licorice, cocoa.

Originally contained coumarin until ~1965 (after 1954 FDA food ban)
(Still used in some low-tar brands until early 1980’s)

Note: By 1972 Camel Filter was modified to mimic Marlboro

Note – some companies have removed Nutmeg & Mace oils for potential regulatory reasons (e.g. myristicin)
Tobacco Flavors

Typical Components of American Blend Flavors
(Old Kent Types)

Nutmeg or Mace oil
Cardamom Oil
Chamomile Oil?

Casing of invert sugar, corn syrup, licorice, cocoa, Balsam Tolu, Balsam Peru, Styrax.

Originally contained coumarin until ~1974 (after 1954 FDA food ban)
Tobacco Flavors
Key Tobacco Flavoring Materials

COUMARIN NOTES:
- VANILLIN
- HELIOTROPIN
- C-18 ALDEHYDE
- IMMORTELLE ABSOLUTE
- OAKMOSS ABSOLUTE
- OCTALACTONES
- HEPTALACTONE
- METHYL HEPTADIENONE
- CHAMOMILE EXTRACT
- ANISYL ALCOHOL
- ANISE ALDEHYDE
- ACETANISOLE
- BENZALDEHYDE GLYCERIN ACETAL

BURNT SUGAR NOTES:
- MAPLE FURANONE
- STRAWBERRY FURANONE
- SOTOLON
- MALTOL
- ETHYL MALTOL
- CYCLOTENE

NUTTY NOTES
- ACETYLPYRAZINE
- METHOXYMETHYLPYRAZINE
Tobacco Flavors
Key Tobacco Flavoring Materials

HONEY:
- PHENYLACETIC ACID
- ETHYL PHENYL ACETATE
- METHYL PHENYL ACETATE

BUTTER:
- DIACETYL
- ACETYL VALERYL
- ACETYL PROPIONYL
- DELTA-DODECALACTONE
- DELTA-DECALACTONE

SMOOTHING AGENTS:
- PHENYLACETIC ACID
- LACTIC ACID

VANILLA NOTES:
- VANILLIN
- ETHYL VANILLIN
- HELIOTROPIN
- PROPENYL GUAETHOL
- GUAIAACOL

SWEET SMOKEY:
- GUAIAACOL
- 4-METHYL GUAIAACOL
Tobacco Flavors
Key Tobacco Flavoring Materials

**FLORAL (ROSE):**
- Phenyl Ethyl Alcohol
- Phenyl Acetaldehyde
- Bulgarian Rose Oil

**SWEET/FLORAL:**
- Linalool
- Methyl DiHydroJasmonate
- Isoamyl Salicylate
- Coriander Oil

**CHOCOLATE:**
- Isobutyraldehyde
- Isovaleraldehyde
- Vanillin
- Trimethyl Pyrazine
- Tetramethyl Pyrazine
- Dimethyl Pyrazines
- Trimethyl Thiazoyle
- Ethyl Dimethyl Pyrazine
- Butyric Acid
- Carob Extracts
### Tobacco Flavors

#### Key Tobacco Flavoring Materials – Tobacco-Like

<table>
<thead>
<tr>
<th>Tobacco-Like Flavoring Materials</th>
<th>Tobacco-Like Flavoring Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>KETO ISOPHORONE</td>
<td>DAMASCENONE</td>
</tr>
<tr>
<td>BETA-DAMASCONE</td>
<td>MACE OIL</td>
</tr>
<tr>
<td>4-ETHYL GUAIACOL</td>
<td>CARDAMOM OIL</td>
</tr>
<tr>
<td>NUTMEG OIL</td>
<td>2.5-DIMETHYL PYRAZINE</td>
</tr>
<tr>
<td>CIS-3-HEXENYL BENZOATE</td>
<td>2.6-DIMETHYL PYRAZINE</td>
</tr>
<tr>
<td>PHENYLACETIC ACID</td>
<td>ISOVALERALDEHYDE</td>
</tr>
<tr>
<td>GERMAN CHAMOMILE</td>
<td>ISOBUTYRALDEHYDE</td>
</tr>
<tr>
<td>MATE ABSOLUTE</td>
<td>OCTALACTONES</td>
</tr>
<tr>
<td>OAKMOSS ABSOLUTE</td>
<td>HEXALACTONE</td>
</tr>
<tr>
<td>2,3-DIETHYL PYRAZINE</td>
<td>CAROB EXTRACT</td>
</tr>
<tr>
<td>TRIMETHYL PYRAZINE</td>
<td>MALTOL</td>
</tr>
<tr>
<td>TETRAMETHYL PYRAZINE</td>
<td>SOTOLON</td>
</tr>
<tr>
<td>IMMORTELLE ABSOLUTE</td>
<td>ETHYL ISOVALERATE</td>
</tr>
<tr>
<td>3-ETHYL PYRIDINE</td>
<td>VALERIAN OIL</td>
</tr>
<tr>
<td>2,6-DIMETHYL PYRIDINE</td>
<td>PHENYLACETALDEHYDE</td>
</tr>
<tr>
<td>CAPROIC ACID</td>
<td>ACETIC ACID</td>
</tr>
<tr>
<td>ISOVALERIC ACID</td>
<td>FENUGREEK EXTRACTS</td>
</tr>
<tr>
<td>VALERIAN OIL and/or EXTRACT</td>
<td>4-METHYL GUAIACOL</td>
</tr>
</tbody>
</table>
E-Cigarettes & Flavors

- The New Wild West
Electronic Cigarettes
Manufacturers of e-cigarettes, including the major tobacco companies, such as RAI, Altria, PMI and Imperial are “not experts” in designing the many types and varieties of flavors being sold.

For this, flavor companies are being used – many of which are simply adapting existing “food flavors” which may contain flavor ingredients never used previously in tobacco products or other inhalation devices. In fact, only about 5% of available GRAS flavor additives are currently used in conventional tobacco products.
Electronic Cigarettes
Flavors

In the case of conventional cigarettes & cigarillos, while one can add flavor to the tobacco which imparts a characteristic aroma (to the tobacco) – when smoked, the flavor/taste is rarely perceived in the same manner due to the tobacco combustion products.

In contrast, since e-cigarettes simply “vaporize” the e-liquid, a truer “flavor” impression can be experienced.

Thus flavors like strawberry, coffee, cream soda, cola, walnut, pineapple and many more are available.
Electronic Cigarettes

Flavors

The Flavor Manufacturers Association (FEMA) states:

1. **There is no apparent direct regulatory authority in the United States to use flavors in e-cigarettes.**

2. None of the primary safety assessment programs for flavors, including the GRAS program sponsored by the Flavor and Extract Manufacturers Association of the United States (FEMA), evaluate flavor ingredients for use in products other than human food. **FEMA GRAS™ status for the uses of a flavor ingredient in food does not provide regulatory authority to use the flavor ingredient in e-cigarettes in the U.S.**

   The FEMA Expert Panel does not evaluate flavor ingredients for use in tobacco products including e-cigarettes.
Electronic Cigarettes
Flavors

I liken this to the “Wild, Wild West” of old! – An opportunity for a great and possibly very useful alternative to smoking and for smoking cessation – but without a sheriff in site (yet).

The American Heart Association states: “As of early 2014, there were 466 brands and 7764 unique flavors of e-cigarette products in the marketplace”.

There are about 42 million smokers in the U.S., of which more than 50% have made attempts to quit (CDC). And e-cigarettes may be one of the best solutions.

Obviously, adequate scientific assessments & regulations are needed. This should ultimately include levels of Nicotine delivery and “inhalation toxicological” assessment of the many flavor additives used in this new type of inhalation device (e.g. LSRO).