*Article*

# Development of a Flavor Ingredient Wheel Linking E-Liquid Additives to the Labeled Flavor of Vaping Products

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**Table S1.** Integrated Peak Area Abundances for LOQ Estimation.

| Chemical Name/Ingredient | 3XLOD Estimate (Abundance) |
| --- | --- |
| 3-Hexen-1-ol, (Z)- | Resp. >3000 |
| 1,3-Dioxolane, 4-methyl-2-phenyl- Results | Resp. >1000 |
| a-Nicotine Results | Resp. >5000 |
| 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-, (R)- (Carvone)  (anise) Results | Resp. >1000 |
| 1,3-Benzodioxole, 5-(4-methyl-1,3-dioxolan-2-yl)- (Heliotropine propylene glycol acetal) (apple) Results | Resp. >1000 |
| Hexanoic acid, butyl ester (Butyl caproate- apricot) Results | Resp. >3000 |
| Butanoic acid, 2-methyl-, ethyl ester (apple, apricot, orange, grapefruit) Results | Resp. >1000 |
| Butanoic acid, 2-methyl- (Active Valeric Acid) (fruity) Results | Resp. >2000 |
| Butanoic acid, 3-methyl-, ethyl ester (apple) Results | Resp. >2000 |
| 1-Butanol, 3-methyl-, acetate (Banana/ pear) Results | Resp. >1000 |
| 4H-Pyran-4-one, 2-ethyl-3-hydroxy- Ethyl maltol (caramelized sugar and cooked fruit) Results | Resp. >2000 |
| Benzene, 1-methyl-2-(1-methylethyl)-  (o-Cymene) (citrusorange) Results | Resp. >1000 |
| 2H-1-Benzopyran-2-one, 6-methyl- (coconut) Results | Resp. >2000 |
| 1,3-Dioxolane-2-propanoic acid, 2,4-dimethyl-, ethyl ester Results | Resp. >2000 |
| Veratraldehyde propylene glycol acetal (ethyl vanillin) Results | Resp. >1000 |
| Ethyl Vanillin Results | Resp. >2000 |
| Benzyl Alcohol (flavor enhancer) Results | Resp. >500 |
| 1,3-Dioxan-5-ol, 2-phenyl- (Benzaldehyde glyceryl acetal derivitive) food flavor Results | Resp. >2000 |
| Acetic acid, pentyl ester (pear and apple scent) Results | Resp. >1000 |
| Acetic acid, hexyl ester (fruit essence) Results | Resp. >10000 |
| Pentanoic acid, 4-oxo-, 1-methylethyl ester (iso-Propyl levulinate) fruity Results | Resp. >10000 |
| Benzoic acid, 2-amino-, methyl ester (grape and many others) Results | Resp. >2000 |
| 2-Propenoic acid, 3-phenyl-, methyl ester  (Cinnamic acid, methyl ester, (E)-)  (guava, feijoa, strawberry) Results | Resp. >30000 |
| Butanoic acid, 3-methyl-, propyl ester (banana, jackfruit and gruyere) Results | Resp. >2000 |
| (S)-2-Hydroxypropanoic acid  (Lactic acid)  Results | Resp. >30000 |
| 1,4-Dioxane-2,5-dione, 3,6-dimethyl-  (lactide) Results | Resp. >50000 |
| Pentanoic acid, 4-oxo-, butyl ester (levulinic acid) Results | Resp. >50000 |
| Limonene (lemon) Results | Resp. >1000 |
| 5-Thiazoleethanol, 4-methyl-  (meaty flavor) Results | Resp. >2000 |
| Cyclohexanol, 1-methyl-4-(1-methylethyl)- (menthol) Results | Resp. >1000 |
| N-Acetyl-4-(2',3'-dihydroxypropoxy)phenylacetamide Results | Resp. >100000 |
| N-Ethyl-4-hydroxypiperidine Results | Resp. >100000 |
| Neonicotine Results | Resp. >2000 |
| (1's,2's)-Nicotine-N'-oxide Results | Resp. >500 |
| Nicotine Results | Resp. >500 |
| Non-7-enoic acid, dimethylamide Results | Resp. >15000 |
| Triacetin (papaya) Results | Resp. >2000 |

| | |
|---|---|
| (2(3H)-Furanone, 5-heptyldihydro-) Peach lactone Results | Resp. >500 |
| 2(3H)-Furanone, 5-hexyldihydro- (peach) Results | Resp. >1000 |
| Benzyl Benzoate (perfume fixative as well as: scabicide, an acaricide and a plant metabolite) Results | Resp. >1000 |
| 1,2,3-Propanetriol, monoacetate/ Acetin (perfume fixative) Results | Resp. >5000 |
| 1R-a-Pinene (pine or rosemary) Results | Resp. >1000 |
| Salicylic acid Results | Resp. >1000 |
| 2H-1-Benzopyran-2-one, 3,4-dihydro- (sour cherry, terragon) Results | Resp. >1000 |
| Oxiranecarboxylic acid, 3-methyl-3-phenyl-, ethyl ester, cis- (Hydrocinnamic acid)   (strawberry) Results | Resp. >500 |
| 1-Deoxy-d-arabitol (sugar alcohol) Results | Resp. >10000 |
| 2H-Pyran-2-one, 6-heptyltetrahydro-   (tropical) Results | Resp. >1000 |
| Pentanoic acid, 2-acetyl-4-methyl-, ethyl ester (valeric acid) Results | Resp. >10000 |
| Vanillin, acetate Results | Resp. >10000 |
| 3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (E)- (ionone)   (violets) Results | Resp. >1500 |

Note. LOQ estimation based on manual LOD peak area determinations. Any response greater than the listed response would theoretically be quantifiable and was thus counted as a "positive detection" for that ingredient.

**Figure S1.** Average Chemical Classification Breakdown of Ingredients by Labeled Flavor Category.
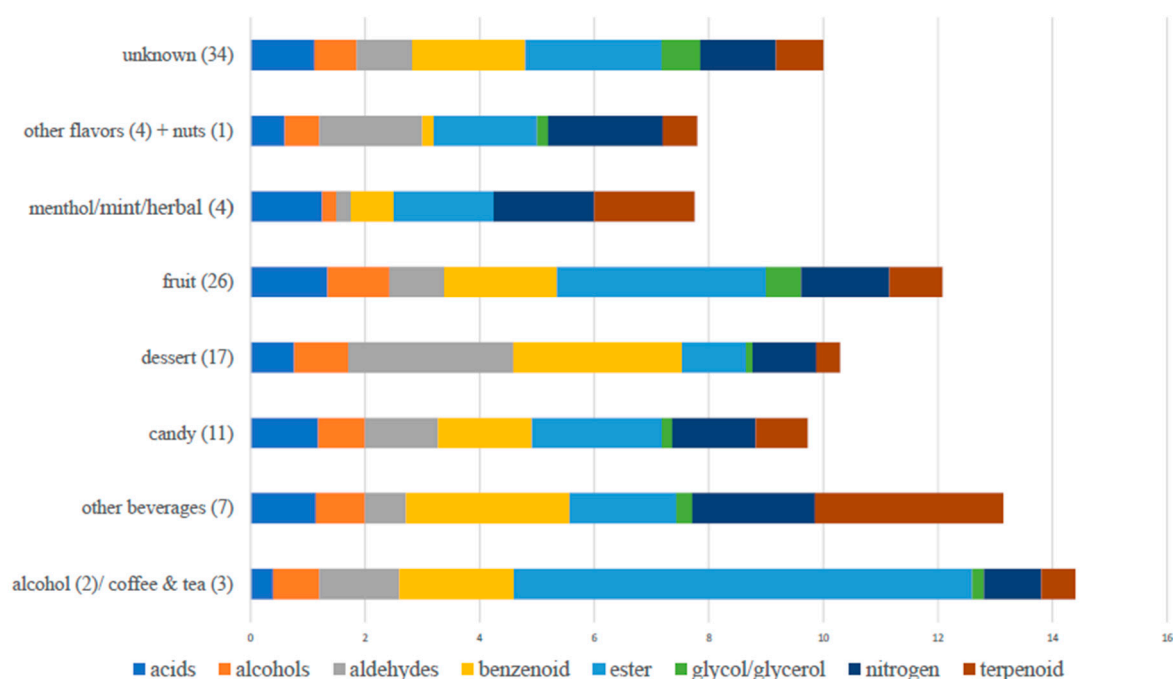


Note. Using the root chemical class for each ingredient and the generalized flavor category of the samples, the mean number of ingredients for each flavor are represented as a stacked bar plot. For each flavor category, the mean number of ingredients belonging to each root chemical class was determined and plotted to represent the average makeup of each flavor.

**Figure S2.** Ingredients by Flavor Classification.
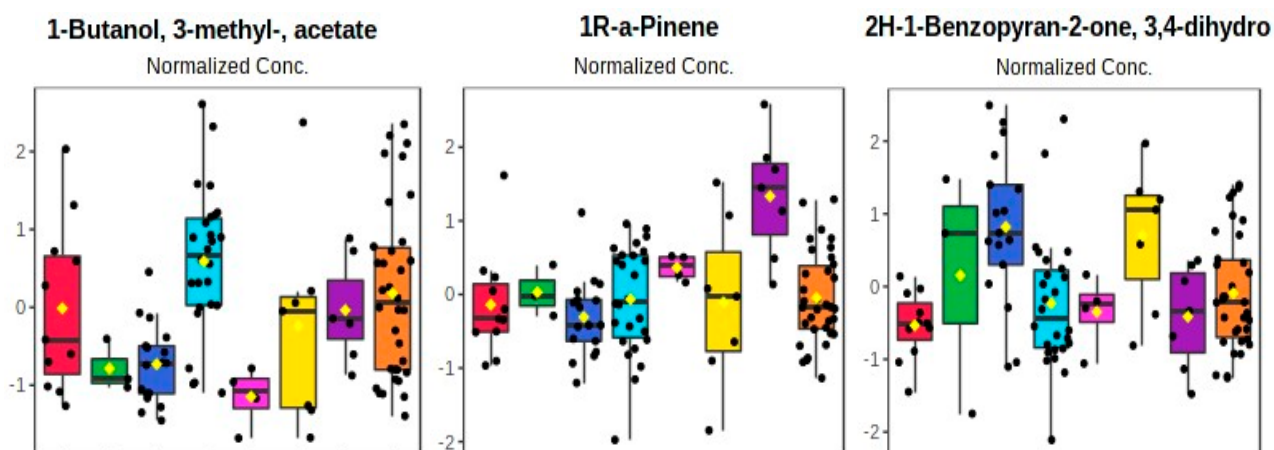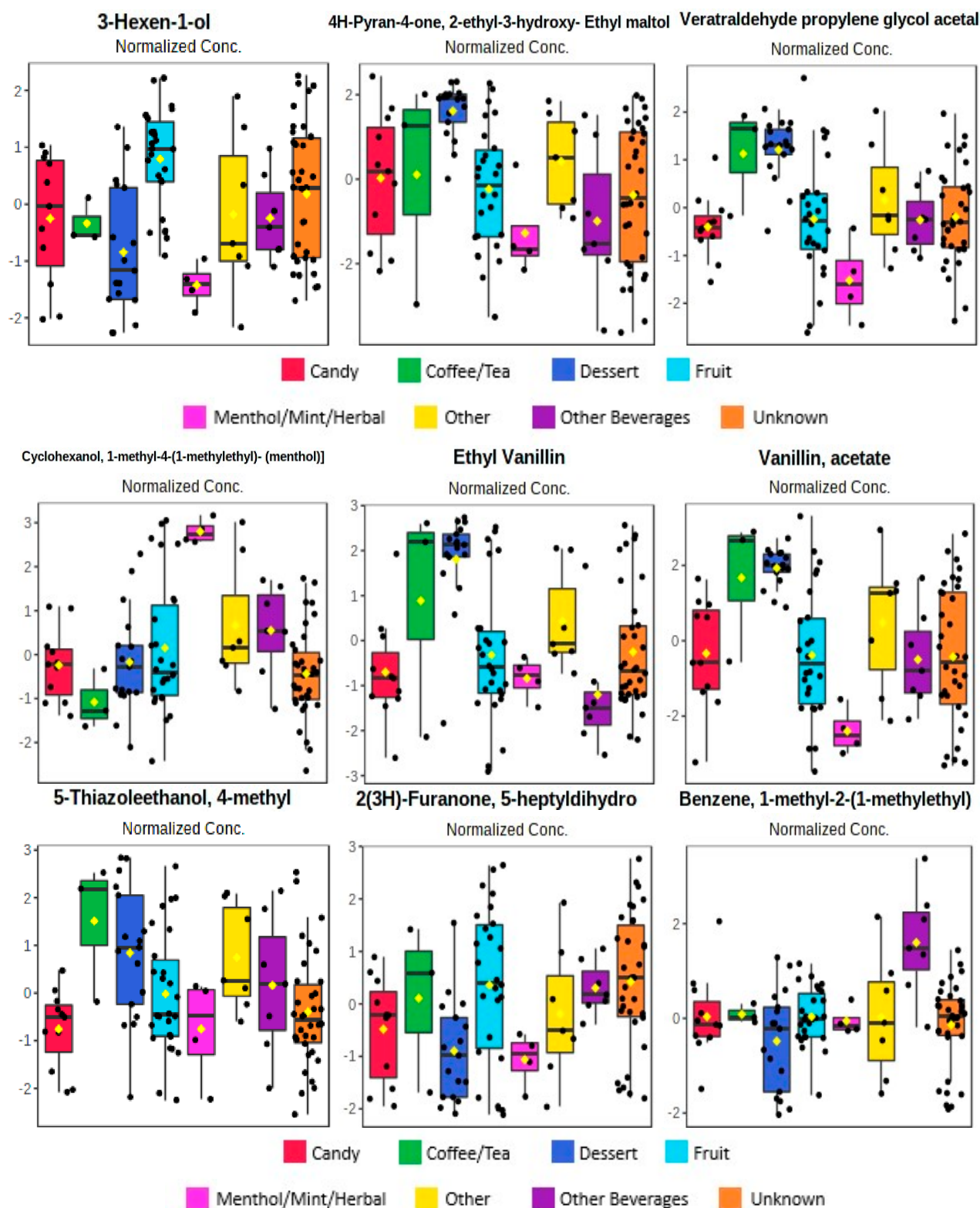
Note. The 15 significantly different ingredients by analysis of variance (ANOVA) test represented as box plots, with their common name displayed, groups: candy 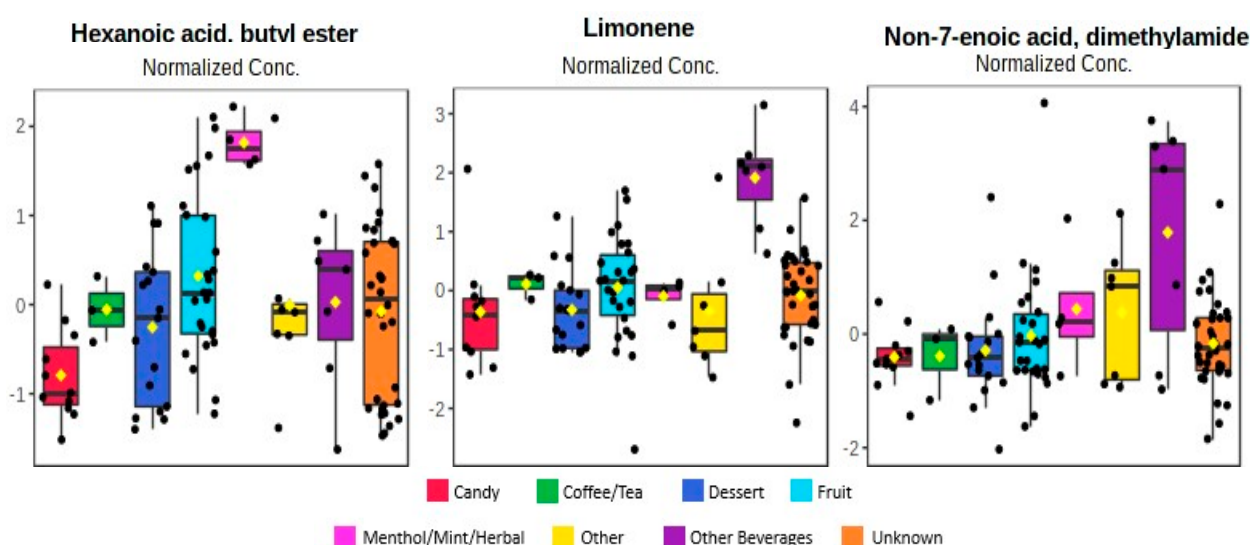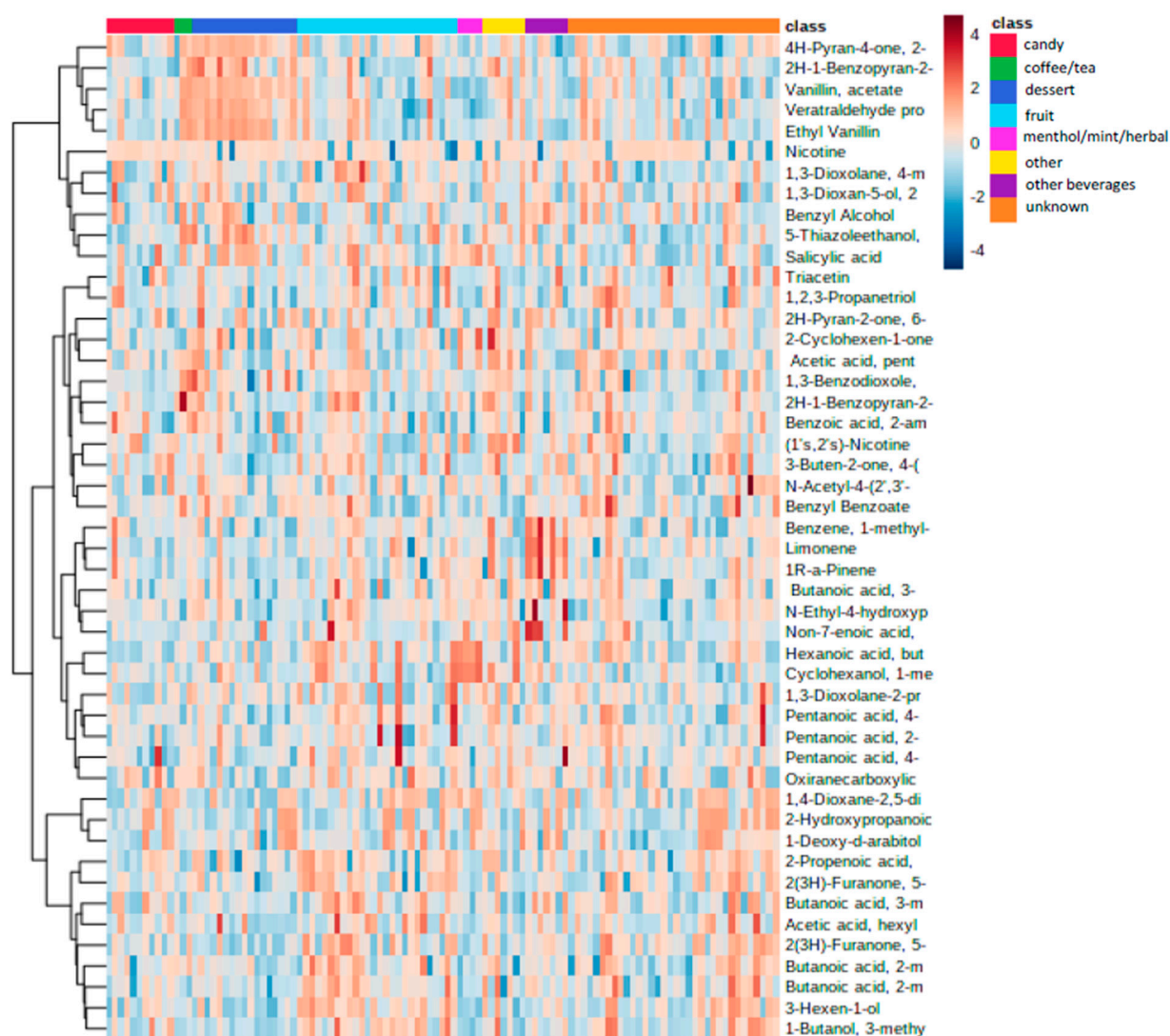= red, coffee/tea = green, dessert = blue, fruit = aqua, menthol/mint/herbal = purple, other = yellow, other beverages = purple, and unknown = orange. Conc. = concentration.

**Table S2.** Ingredients With Significant Mean Abundance Differences Among Flavor Categories.

| Ingredient | *p* value |
|:---:|:---:|
| Ethyl vanillin | $2.48 \times 10^{-6}$ |
| Limonene | **$3.40 \times 10^{-6}$** |
| Vanillin, acetate | $4.35 \times 10^{-6}$ |
| Veratraldehyde propylene glycol acetal | $4.50 \times 10^{-6}$ |
| Cyclohexanol, 1-methyl-4-(1-methylethyl)- (menthol)] | $8.39 \times 10^{-5}$ |
| 3-hexen-1-ol | 0.00011589 |
| 1R-a-pinene | 0.00022557 |
| Hexanoic acid, butyl ester | 0.00023269 |
| 4H-pyran-4-one, 2-ethyl-3-hydroxy- ethyl maltol | 0.00037063 |
| 1-butanol, 3-methyl-, acetate | 0.00047774 |
| 2H-1-benzopyran-2-one, 3,4-dihydro | 0.00063365 |
| Benzene, 1-methyl-2-(1-methylethyl) | 0.00064589 |
| Non-7-enoic acid, dimethylamide | 0.00098517 |
| 5-thiazoleethanol, 4-methyl | 0.0026388 |
| 2(3H)-furanone, 5-heptyldihydro | 0.0086826 |

Note. *p* values determined using one-way analysis of variance.

**Figure S3.** Heatmap of Flavor Category.



Note. Heatmap showing the relative abundances using the red/blue color scale of ingredients detected in e-liquids. All ingredients and all 109 samples are represented, with grouping based on flavor description (candy = red, coffee/tea = green, dessert = blue, fruit = teal, menthol/mint/herbal = pink, other = yellow, other beverages = purple, and unknown =orange).
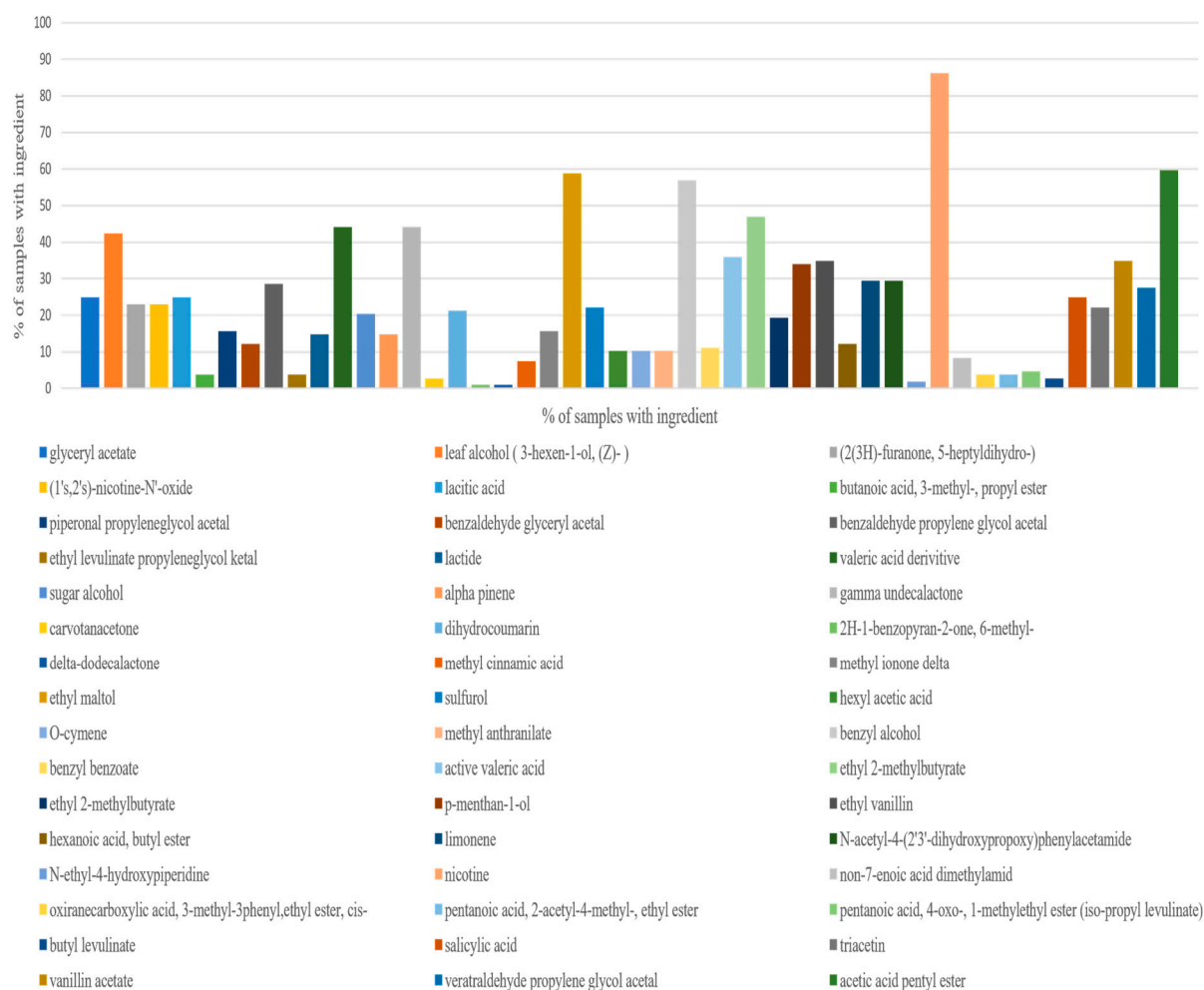
**Table S3.** Ingredients Significantly Different Between Groups Based on Cooling Claim.

| Ingredient | FC | *p*-value |
|---|---|---|
| cyclohexanol, 1-methyl-4-(1-methylethyl)- (menthol)] | −41.848 | $7 \times 10^{-10}$ |
| hexanoic acid, butyl ester | −8.78735 | $7.10 \times 10^{-6}$ |
| vanillin, acetate | 26.187 | $4.80 \times 10^{-4}$ |
| non-7-enoic acid, dimethylamide | −31.2061 | $3.00 \times 10^{-3}$ |
| 2H-1-benzopyran-2-one, 3,4-dihydro | 13.64 | $6.90 \times 10^{-3}$ |
| 4H-pyran-4-one, 2-ethyl-3-hydroxy- ethyl maltol | 10.142 | $1.00 \times 10^{-2}$ |
| veratraldehyde propylene glycol acetal | 7.7431 | $1.40 \times 10^{-2}$ |
| benzoic acid, 2-amino-, methyl ester | 20.09 | $3.00 \times 10^{-2}$ |
| butanoic acid, 2-methyl-, ethyl ester | 3.6975 | $4.80 \times 10^{-2}$ |

Note. The log fold change and p-value for ingredients with significant differences ($p < 0.05$) in mean relative abundance between samples with a cooling claim and those without a cooling claim.

**Figure S4.** Partial Least Squares Discriminant Analysis and Variable of Importance in Projection Ingredients Based on Cooling Claim on Packaging.
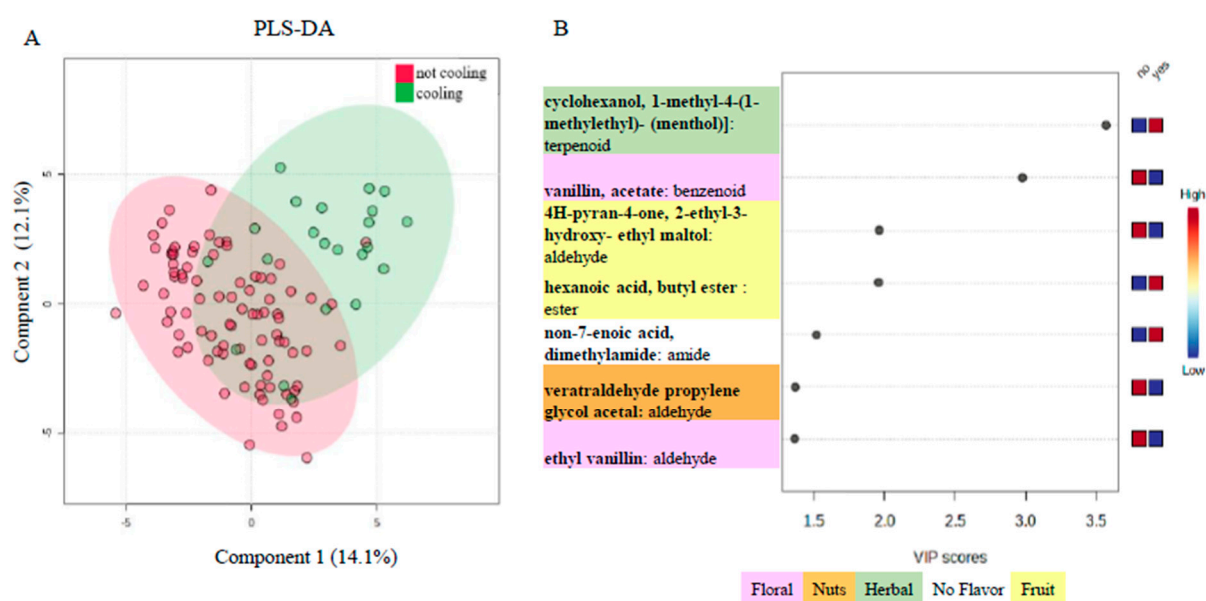


Note. (**A**) A partial least squares discriminant analysis (PLS-DA) demonstrating the dimensional reduction of the patterns in the ingredient data based on cooling description. Samples that claim no cooling (red) cluster closer together with less variability than samples that claim a cooling effect (green). (**B**) Variable importance in projection (VIP) scores of ingredients in e-liquid that contribute to the variation between liquid type as displayed in the PLS-DA plot. Relative abundances of ingredients are displayed in the blue/red gradient to the right of the chart. Ingredient and root chemical class are displayed, with flavor profile represented by color as shown below the plot.

**Figure S5.** Bar Plot of Distribution of Detected E-Liquid Ingredients.



■ glyceryl acetate
■ leaf alcohol ( 3-hexen-1-ol, (Z)- )
■ (2(3H)-furanone, 5-heptyldihydro-)

■ (1's,2's)-nicotine-N'-oxide
■ lacitic acid
■ butanoic acid, 3-methyl-, propyl ester

■ piperonal propyleneglycol acetal
■ benzaldehyde glyceryl acetal
■ benzaldehyde propylene glycol acetal

■ ethyl levulinate propyleneglycol ketal
■ lactide
■ valeric acid derivitive

■ sugar alcohol
■ alpha pinene
■ gamma undecalactone

■ carvotanacetone
■ dihydrocoumarin
■ 2H-1-benzopyran-2-one, 6-methyl-

■ delta-dodecalactone
■ methyl cinnamic acid
■ methyl ionone delta

■ ethyl maltol
■ sulfurol
■ hexyl acetic acid

■ O-cymene
■ methyl anthranilate
■ benzyl alcohol

■ benzyl benzoate
■ active valeric acid
■ ethyl 2-methylbutyrate

■ ethyl 2-methylbutyrate
■ p-menthan-1-ol
■ ethyl vanillin

■ hexanoic acid, butyl ester
■ limonene
■ N-acetyl-4-(2'3'-dihydroxypropoxy)phenylacetamide

■ N-ethyl-4-hydroxypiperidine
■ nicotine
■ non-7-enoic acid dimethylamid

■ oxiranecarboxylic acid, 3-methyl-3phenyl,ethyl ester, cis-
■ pentanoic acid, 2-acetyl-4-methyl-, ethyl ester
■ pentanoic acid, 4-oxo-, 1-methylethyl ester (iso-propyl levulinate)

■ butyl levulinate
■ salicylic acid
■ triacetin

■ vanillin acetate
■ veratraldehyde propylene glycol acetal
■ acetic acid pentyl ester

Note. Bar plot showing the percentage of analyzed products (out of 109 samples) that were positive for individual ingredients.

**Table S4.** Detected Acid Ingredients.

| | Samples, n (%) | Nicotine Type (based on product label) | | | Proportion of + salt samples, % | Proportion of + free-base samples, % | Proportion of + 0 nicotine samples, % |
|---|---|---|---|---|---|---|---|
| | | Salt, n | Free-base, n | 0 nicotine, n | | | |
| **levulinic acid** | **3 (2.8)** | **3** | **0** | 0 | 100 | 0 | 0 |
| **lactic acid** | 27 (24.8) | 26 | 1 | 0 | 96.3 | 3.7 | 0 |
| **salicylic acid** | 27 (24.8) | 11 | 10 | 6 | 40.7 | 37 | 22.2 |
| **benzoic acid** | 11 (10.1) | 5 | 4 | 2 | 45.5 | 36.4 | 18.2 |
| **levulinic + salicylic** | 1 (0.9) | | | | | | |
| **lactic + salicylic** | 8 (7.3) | | | | | | |
| **lactic + benzoic** | 1 (0.9) | | | | | | |
| **salicylic +benzoic** | 2 (1.8) | | | | | | |

| lactic + salicylic + benzoic | 2 (1.8) | |
|---|---|---|

Note. Each identified acid ingredient and the number of samples that had a positive detection were determined, and the proportions of each sample relative to a total number of samples and different sample groups.

**Table S5.** Comparison of Primary Flavor Categories.

| | **Krüsemann et al.'s Flavor Wheel** | **Proposed in the Ingredient Wheel** |
|---|---|---|
| 1 | Tobacco | Not included |
| 2 | Menthol/Mint | Menthol/mint/herbal |
| 3 | Nuts | Not included |
| 4 | Spices | Not included |
| 5 | Coffee/Tea | Not included |
| 6 | Alcohol | Not included |
| 7 | Other Beverages | Not included |
| 8 | Fruit | Fruit |
| 9 | Dessert | Dessert |
| 10 | Candy | Candy |
| 11 | Other Sweets | Floral |
| 12 | Other Flavors | Other |
| 13 | Unflavored | Not included |
| | Not included | Nicotine |

Note. Krüsemann EJZ, Boesveldt S, de Graaf K, Talhout R. An e-liquid flavor wheel: a shared vocabulary based on systematically reviewing e-liquid flavor classifications in literature. *Nicotine & Tobacco Research*. 2019;21(10):1310-1319. doi: 10.1093/ntr/nty101 *Characterizing Product Flavors Using the Flavor Ingredient Wheel.*

**Table S6.** Characterizing Product Flavors Using the Flavor Ingredient Wheel.

| **Fruit/Berry - Not Cooling** | |
|---|---|
| 3-hexen-1-ol: alcohol | |
| Benzoic acid, 2-amino-, methyl ester: ester | |
| 2(3H)-furanone, 5-heptyldihydro: benzenoid | |

| **Dessert 1 - Cooling** | **Dessert 2 - Not Cooling** |
|---|---|
| 1,3-dioxolane, 4-methyl-2-phenyl: acid | 1,3-dioxolane, 4-methyl-2-phenyl: acid |
| Hexanoic acid, butyl ester: ester | 1,3-benzodioxole, 5-(4-methyl-1,3-dioxolan-2-yl): glycol |
| 4H-pyran-4-one, 2-ethyl-3-hydroxy- Ethyl maltol: aldehyde | 4H-pyran-4-one,2-ethyl-3-hydroxy-Ethyl maltol: aldehyde |
| Veratraldehyde propylene glycol acetal: aldehyde | Veratraldehyde propylene glycol acetal: aldehyde |
| Ethyl vanillin: aldehyde | Ethyl vanillin: aldehyde |
| Benzyl alcohol: benzenoid | Benzyl alcohol: benzenoid |
| 1,3-dioxan-5-ol, 2-phenyl- (benzaldehyde glyceryl acetal derivative): aldehyde | Benzoic acid, 2-amino-, methyl ester: ester |
| 2-hydroxypropanoic acid: acid | Salicylic acid: acid |
| Cyclohexanol,1-methyl-4-(1-methylethyl)- (menthol)]: terpenoid | Vanillin, acetate: benzenoid |
| Triacetin: glycerol | |

| | |
|---|---|
| 1,2,3-propanetriol,monoacetate: glycol/glycerol/sugar | |
| Salicylic acid: acid | |
| 1-deoxy-d-arabitol (sugaralcohol): glycol/glycerol/sugar | |
| Vanillin, acetate: benzenoid | |
| **Fruit - Other 1** | **Fruit - Other 2** |
| 1,3-dioxolane, 4-methyl-2-phenyl: acid | 3-hexen-1-ol: alcohol |
| 1,3-benzodioxole, 5-(4-methyl-1,3-dioxolan-2-yl): glycol | Butanoic acid, 2-methyl-, ethyl ester: ester |
| Butanoic acid, 2-methyl-, ethyl ester: ester | Butanoic acid, 2-methyl-: ester |
| Butanoic acid, 2-methyl-: ester | Butanoic acid, 3-methyl-, ethyl ester: ester |
| 1-butanol, 3-methyl-, acetate: ester | 1-butanol, 3-methyl-, acetate: ester |
| 4H-pyran-4-one, 2-ethyl-3-hydroxy- Ethyl maltol: aldehyde | 4H-pyran-4-one,2-ethyl-3-hydroxy-Ethyl maltol: aldehyde |
| 1,3-dioxan-5-ol, 2-phenyl- (benzaldehyde glyceryl acetal derivative): aldehyde | Benzyl Alcohol: benzenoid |
| Benzoic acid, 2-amino-, methyl ester: ester | 2-propenoic acid, 3-phenyl-, methyl ester (cinnamic acid): ester |
| 2-hydroxypropanoic acid: acid | 2-hydroxypropanoic acid: acid |
| Triacetin: glycerol | 1,4-dioxane-2,5-dione, 3,6-dimethyl: acid |
| 1,2,3-propanetriol, monoacetate: glycol/glycerol/sugar | 1-deoxy-d-arabitol (sugar alcohol): glycol/glycerol/sugar |

Legend:

| Floral | Nuts | Herbal | No Flavor | Fruit |
|---|---|---|---|---|