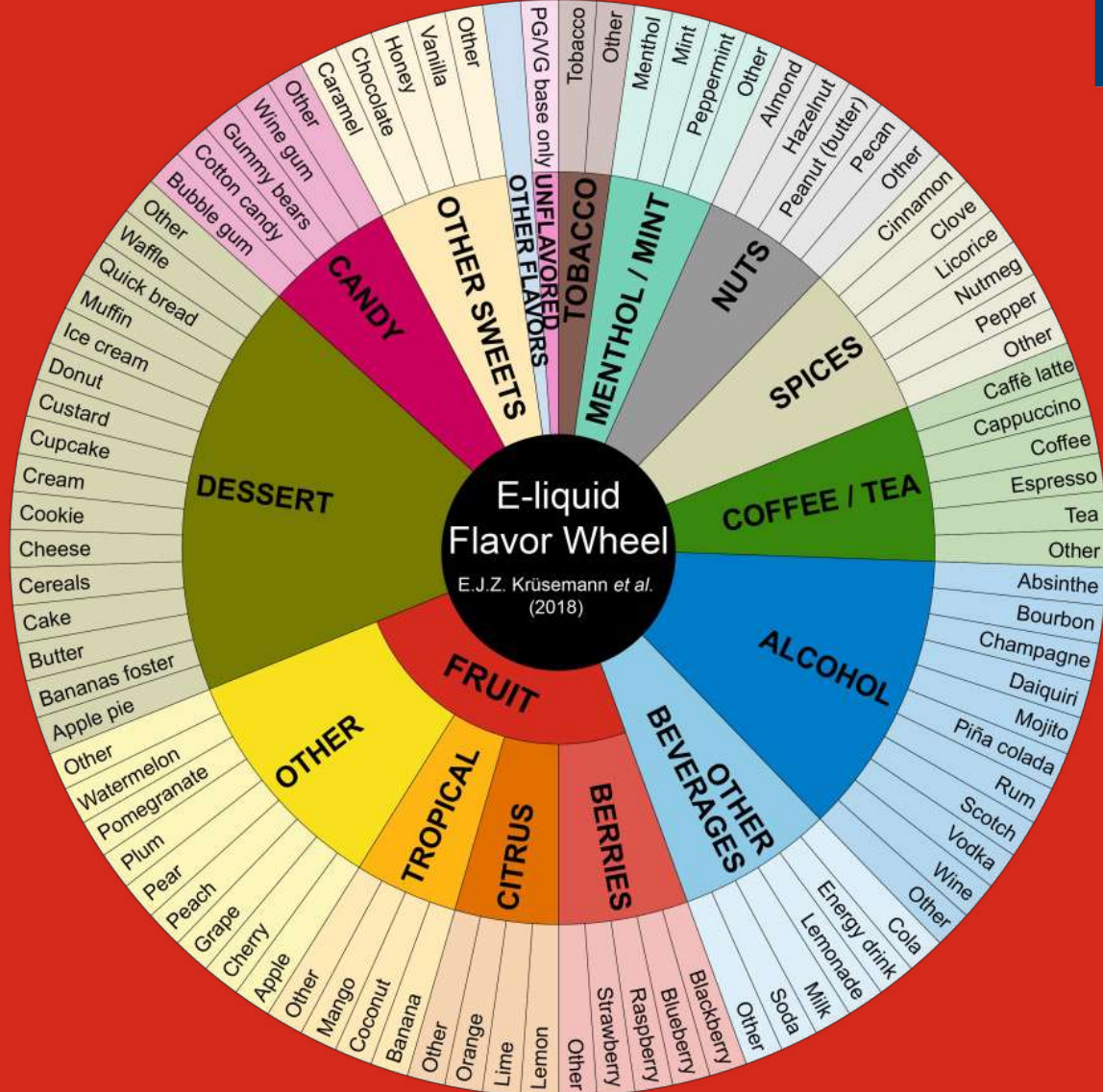




National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*



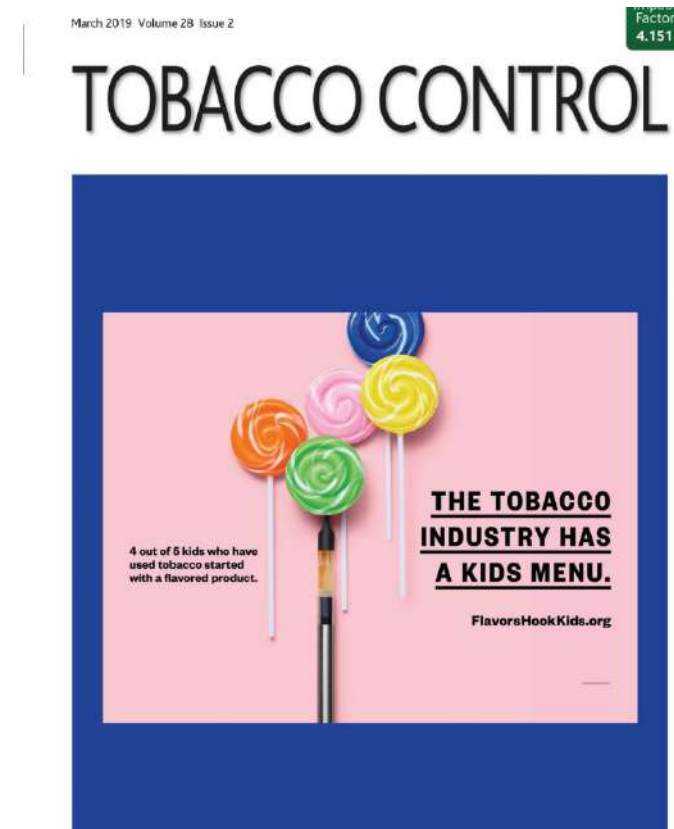
# Flavours and flavourings in e-cigarettes

Reinskje Talhout  
Center for Health Protection  
RIVM, Bilthoven, The Netherlands



# Flavours in tobacco and related products

- > Increase attractiveness
- > Make tobacco use smoother
- > Reduce harm perception
- > Popular among youth
- > Facilitate tobacco initiation



*Tobacco Control, March 2022 - Volume 28 - Issue 2*



# Scheer Opinion on electronic cigarettes

## Weak evidence:

- for the support of electronic cigarettes' effectiveness in **helping smokers to quit**

## Weak to moderate evidence:

- on **smoking reduction**

## Moderate evidence:

- that electronic cigarettes are a **gateway** to smoking for young people

## Strong evidence:

- that **nicotine** in e-liquids is implicated in the development of **addiction**
- that **flavours** have a relevant contribution for **attractiveness of use** and initiation

*Scheer Opinion on electronic cigarettes, 2021*



# Attractiveness or product appeal



important in consumer's choice to use a specific product



target for discouraging unhealthy behavior and promoting healthy behavior



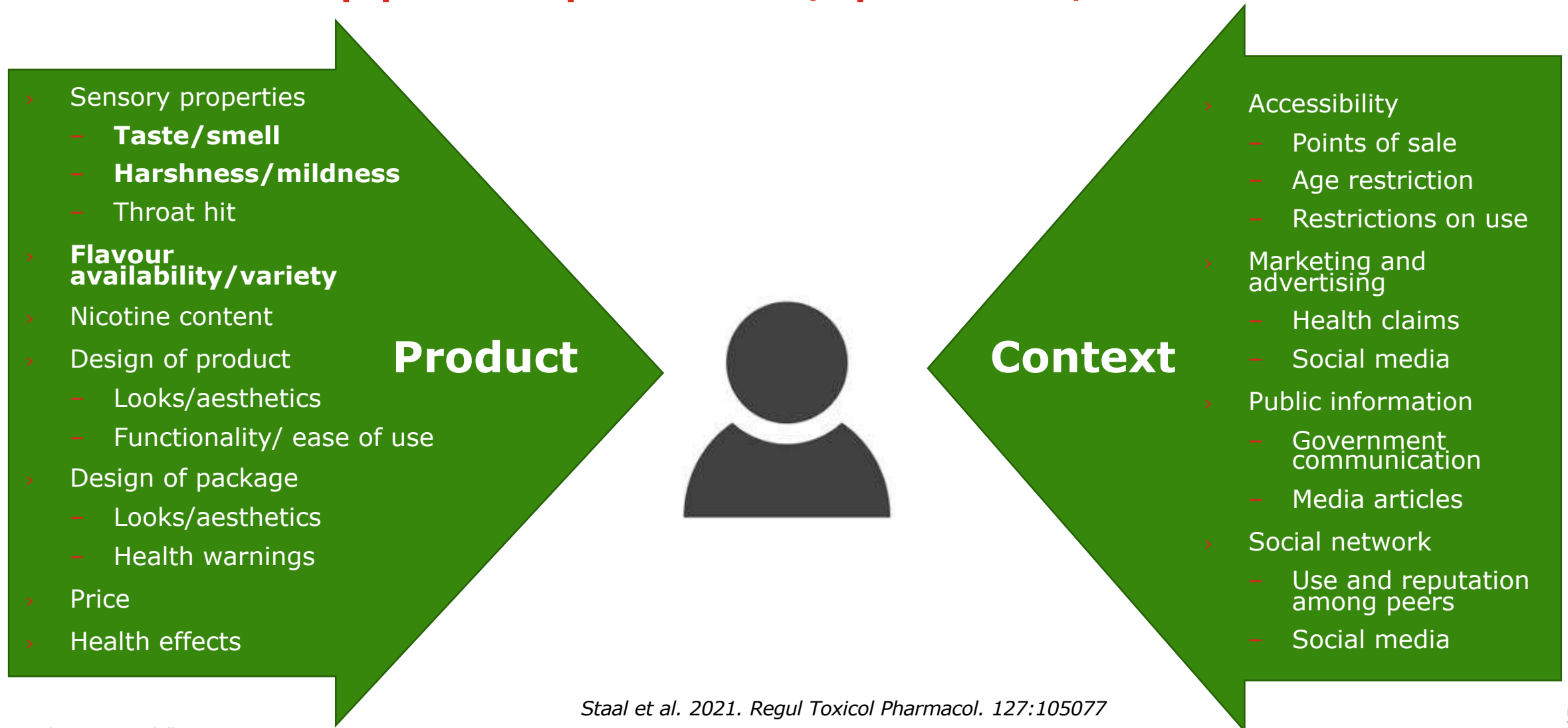
all factors that stimulate the start and continuation of use, such as marketing, **sensory properties**, design, price, perceived risks and benefits, and ease of use



influenced by the inherent characteristics of the product and situational factors, but also by consumer taste and preferences





# Product appeal: product, person, context



Staal et al. 2021. Regul Toxicol Pharmacol. 127:105077



# Flavour most attractive e-cigarette characteristic

					
 Attractiveness	Attractive characteristics e-cigarettes (%)	Non-users (n=407)	Smokers (n=138)	Dual users (n=122)	E-cig users (n=61)
	Variety of e-liquid flavours	10	30	34	69
	E-cigarette design	7	20	22	44
	Ability to adjust e-liquid nicotine levels	5	14	16	31
	Ability to adjust settings of device	4	11	12	25
	Variety of e-cigarette design	3	9	11	21
	Ability to do 'cloud chasing'	2	7	8	16
	Price	2	6	7	13



Romijnders/Krusemann et al. *IJERPH*. 2019;16(23)



# Need for categorisation of flavours

- A high variety of e-liquids is available: thousands of brands and hundreds of unique flavours
- For research and regulation, a common lexicon is needed





# Flavour wheels

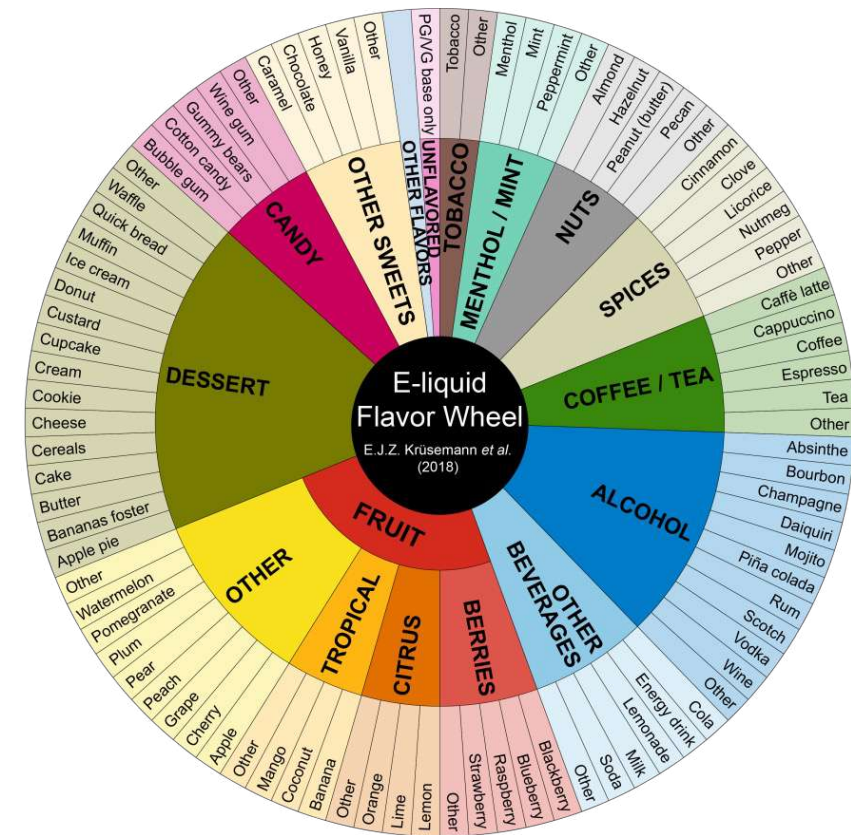
- › Flavour wheels used in food, alcohol, and fragrance industry
- › General and specific descriptors: main categories and subcategories





# E-liquid flavour wheel enables categorisation

- Systematic review e-liquid flavour scientific literature
  - Main categories: e-liquid flavour classifications
  - Subcategories: specific e-liquid flavours as examples of main categories
- 13 main categories (inner wheel)
- 90 subcategories (outer wheel)

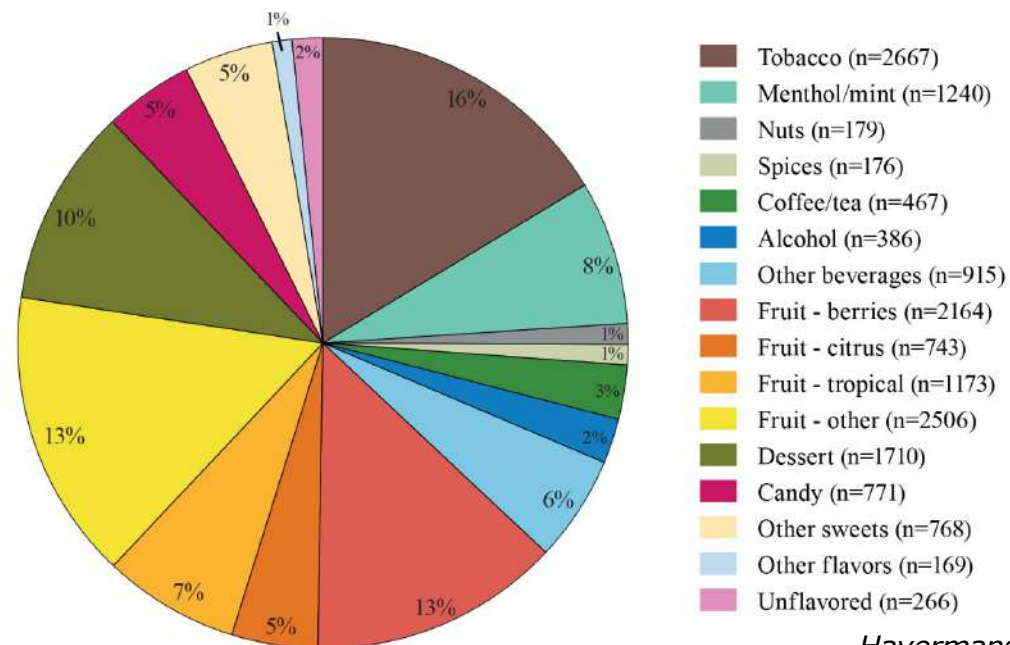


Krüsemann et al. *Nicotine Tob Res.* 2019;21(10):1310-1319



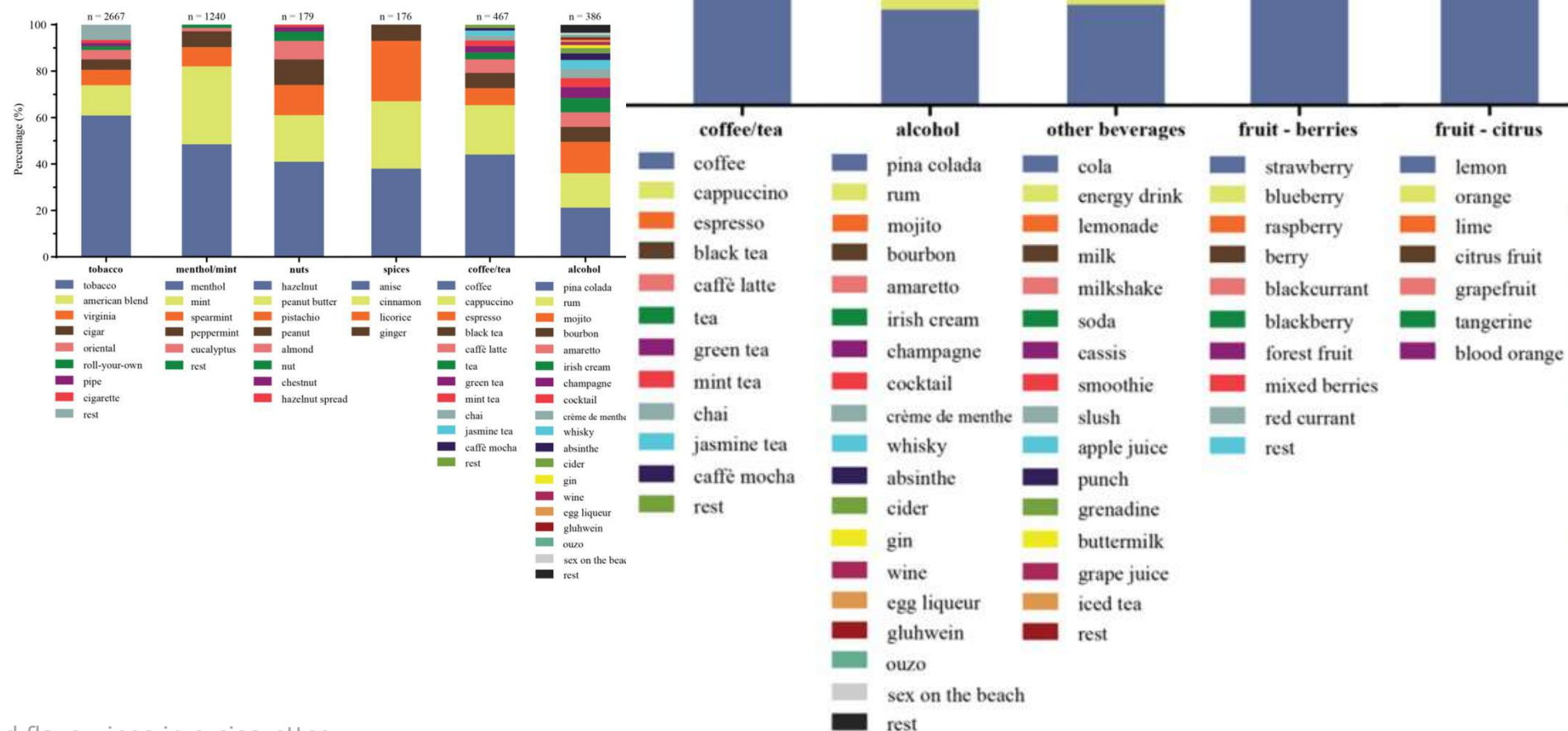
# Dutch e-liquid market in main flavour categories

- 19,266 e-liquids and 245 unique flavours
- Classified according to flavour wheel



*Havermans, Krüseman, et al. Tob Control 2021 Jan;30(1):57-62*

# Distribution over fla





# Flavouring ingredients in Dutch e-liquids

Top 10 most commonly reported flavorings mostly has sweet or fruit flavour

	<b>Flavoring ingredient</b>	<b>Prevalence (% of total e-liquids)</b>	<b>Median concentration (mg/10mL)</b>	<b>Flavor description</b>
<b>1</b>	Vanillin	35%	7.0	Sweet, powerful, creamy, vanilla-like
<b>2</b>	Ethyl maltol	32%	5.9	Sweet, fruity-caramellic, cotton candy
<b>3</b>	Ethyl butyrate	28%	3.6	Ethereal, fruity with buttery-pineapple-banana, ripe fruit & juicy notes
<b>4</b>	Ethyl acetate	23%	1.1	Ethereal, sharp, wine-brandy-like
<b>5</b>	Maltol	23%	1.3	Sweet, fruity, berry, strawberry, caramellic
<b>6</b>	Ethyl vanillin	19%	6.8	Intense, sweet, creamy, vanilla-like
<b>7</b>	Furaneol	19%	2.0	Fruity, caramelized, roasted, pineapple-strawberry
<b>8</b>	Methyl cyclopentenolone	18%	2.0	Very strong, caramellic-maple, lovage
<b>9</b>	$\gamma$ -Decalactone	18%	0.5	Coconut-peach
<b>10</b>	Cis-3-hexenol	18%	1.5	Strong, fresh, green, grassy



# Flavourings common for a category

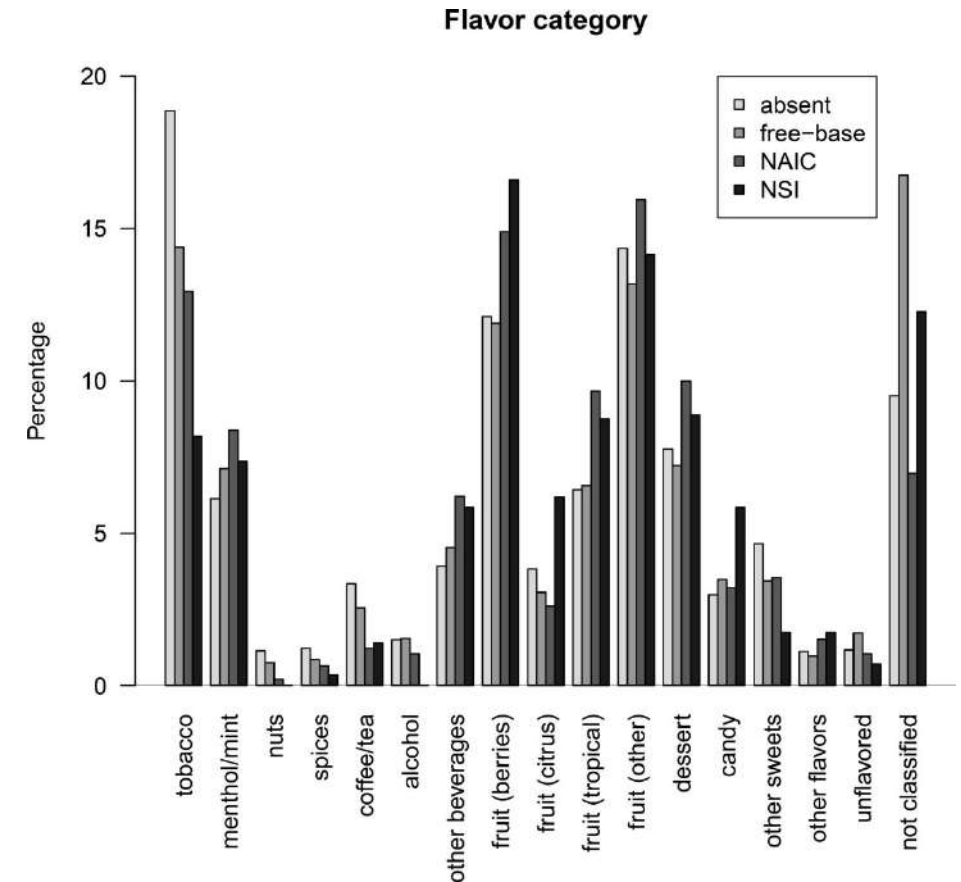
Highlighted = unique for top 5 of that category

	Tobacco	Mentho l/mint	Nuts	Spices	Coffee/ tea	Alcohol	Other beverag es	Fruit berries	Fruit citrus	Fruit tropical	Fruit other	Dessert	Candy	Other sweets	Unflavo red
1	Ethyl maltol (31%)	Sweet, fruity-caramellic, cotton candy											Ethyl maltol (39%)	Vanillin (61%)	Benzyl acetate (3%)
2	Methyl cyclopentenolone (30%)	Very strong, caramellic-maple, lovage											Propyl acetate (7%)	Ethyl maltol (38%)	Vanillin (3%)
3	Vanillin (26%)	Sweet, powerful, creamy, vanilla-like											Ethyl acetate (7%)	Ethyl vanillin (35%)	Ethyl maltol (2%)
4	2,3,5-Trimethylpyrazine (16%)	Nutty, baked potato, roasted peanut, cocoa, burnt notes											Vanillin (5%)	Maltol (26%)	Methyl cyclopentenolone (2%)
5	Furaneol (13%)	Fruity, caramelized, roasted, pineapple-strawberry											Ethyl acetate (55%)	Piperonal (24%)	N/A
				(12%)	(15%)	ate (19%)	(31%)	(30%)		(31%)		tenolone (49%)			



# Flavours and nicotine type

- > E-liquids with nicotine salts less often tobacco flavoured, more often had fruity or sweet flavours, than in free base liquids
- > Flavour ingredients in e-liquids with nicotine salts fourfold higher:
  - number (median n=17 vs. n=4)
  - concentration (median 31.0 vs. 7.4 mg/mL)
  - in NAIC-containing e-liquids, threefold higher (n=12, 21.5 mg/mL)

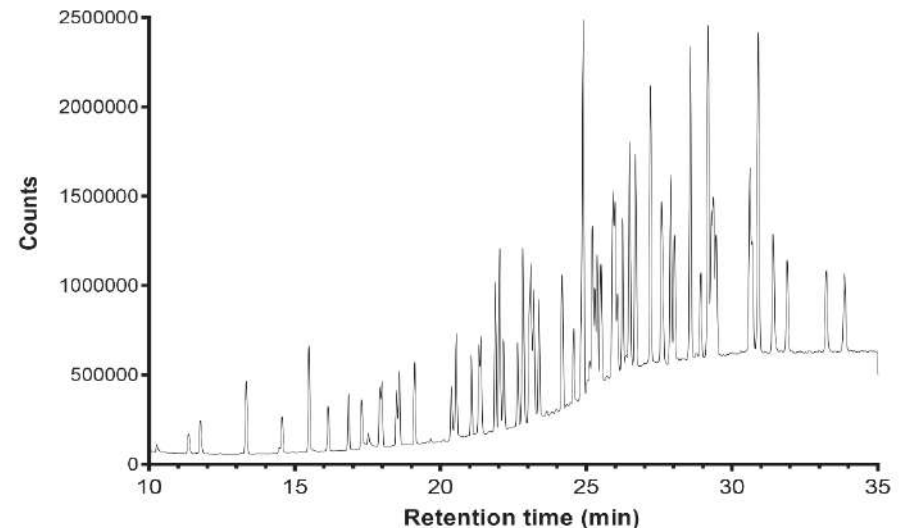


Jeroen L A Pennings et al. Tob Control  
doi:10.1136/tobaccocontrol-2021-056952



# GC-MS analysis e-liquid flavourings

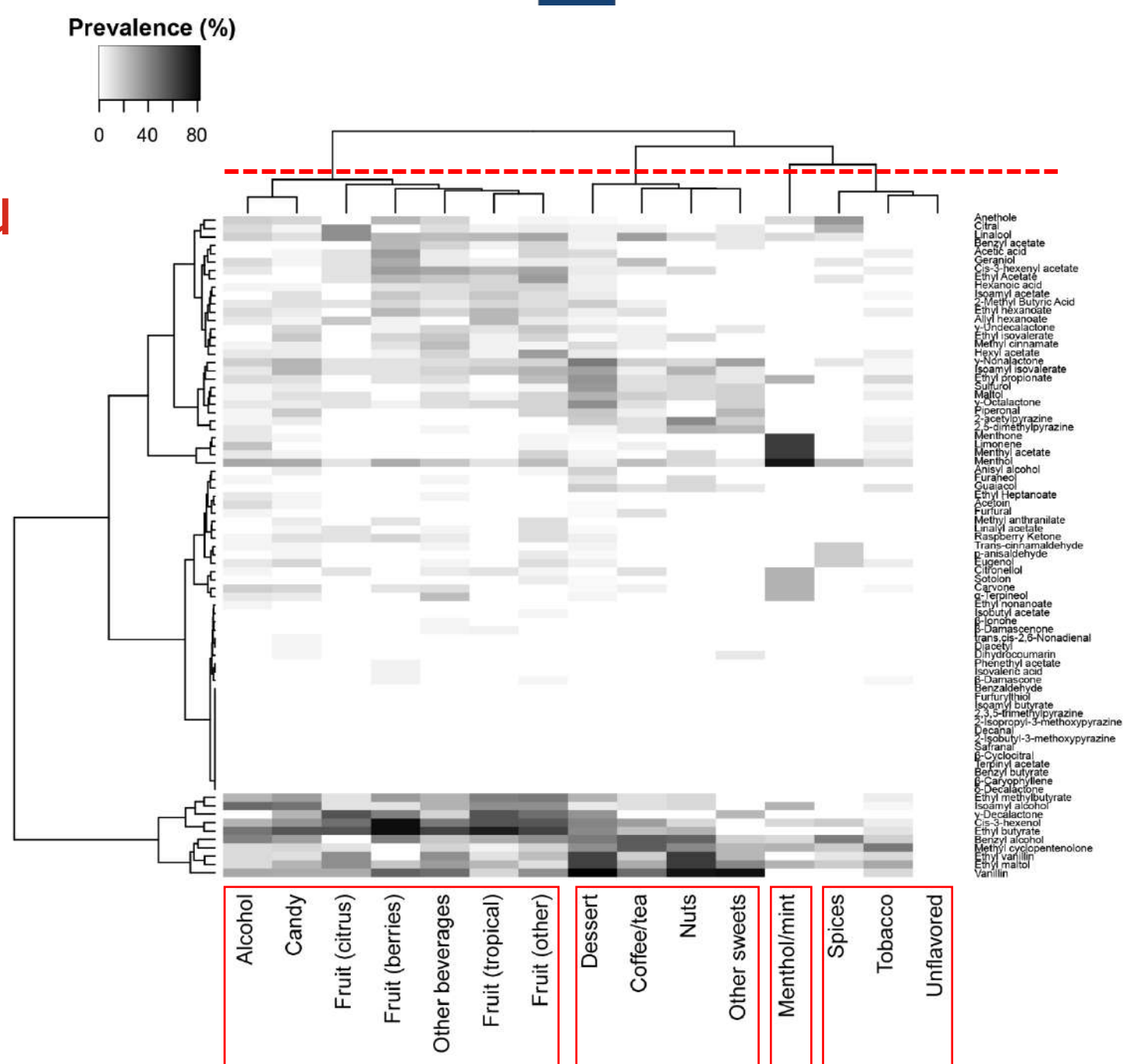
- 320 e-liquids with 204 unique flavours
- Targeted approach: 79 flavourings selected
  - Based on EU-CEG information
  - Based on pilot data
  - Based on literature





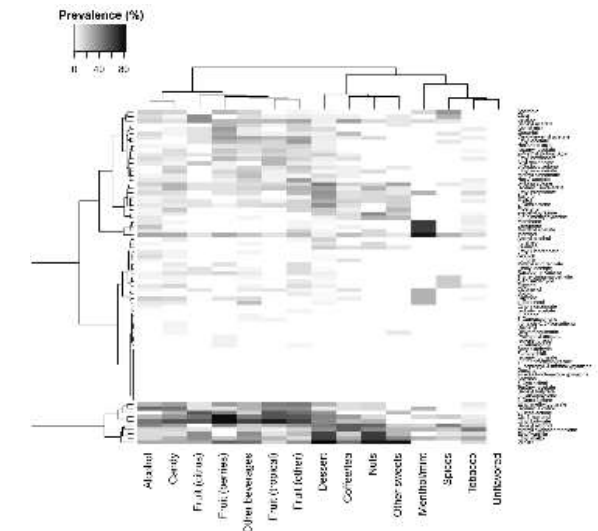
# Flavou

# ory





# Four clusters of flavour categories



## Fresh/sweet



- Ethyl butyrate (ethereal, fruity flavor)
- Cis-3-hexenol (fresh, green flavor)
- $\gamma$ -decalactone (coconut-peach flavor)
- Isoamyl alcohol (breathtaking, alcoholic flavor)

## Warm/sweet



- Vanillin & ethyl vanillin (creamy, vanilla flavor)
- Ethyl maltol (sweet, fruity-caramellic flavor)
- Methyl cyclopentenolone (strong caramellic-maple flavor)

## Fresh/cooling



- Menthol (minty, cooling sensation)
- Menthyl acetate (minty, cooling sensation)
- Limonene (fresh orange citrus flavor)
- Menthone (minty-herbaceous flavor)

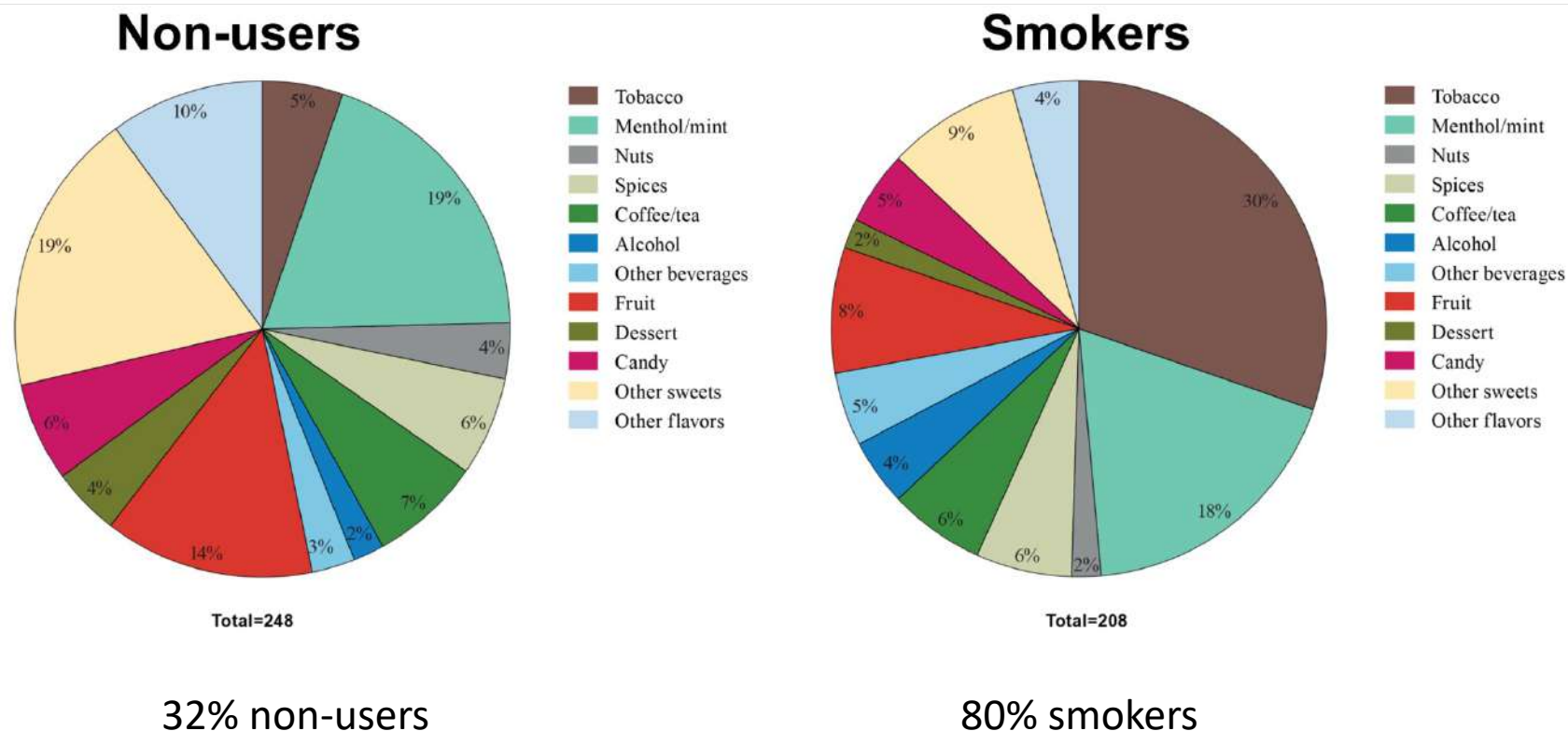
## Non-sweet



- overall low flavoring prevalence, particularly regarding the flavorings that characterize the other clusters



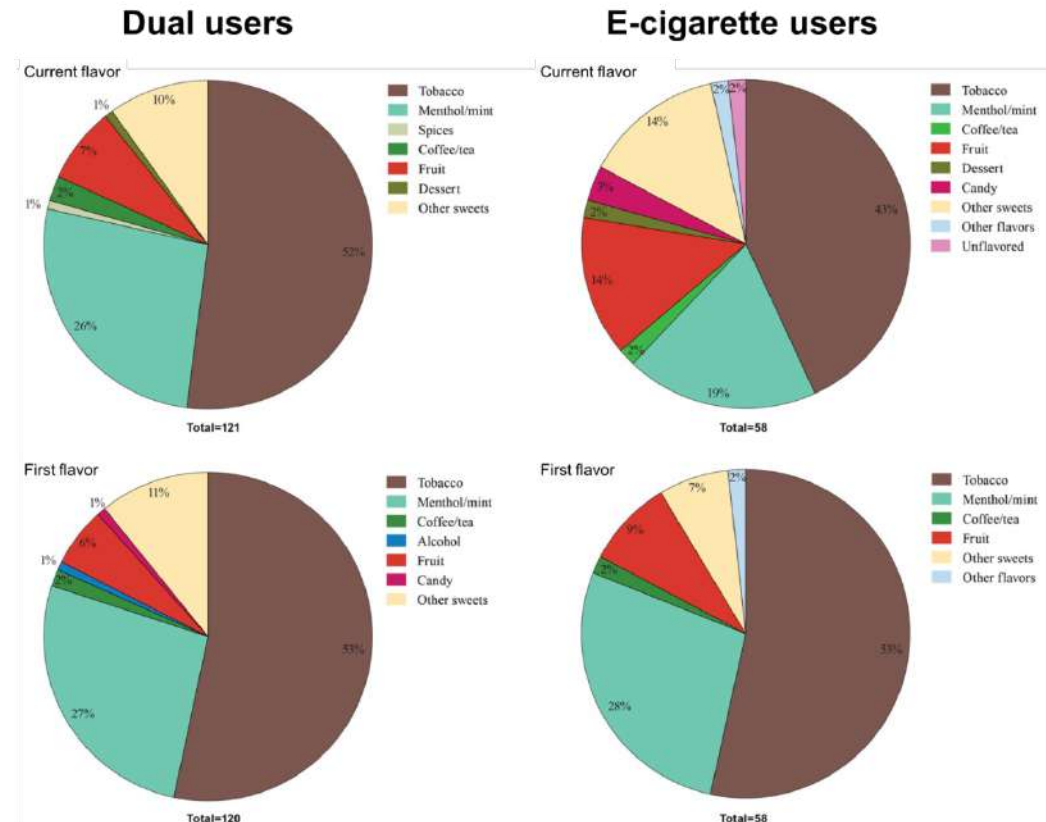
# Flavour preferences non-users and smokers



Romijnders/Krusemann et al. *IJERPH*. 2019;16(23)



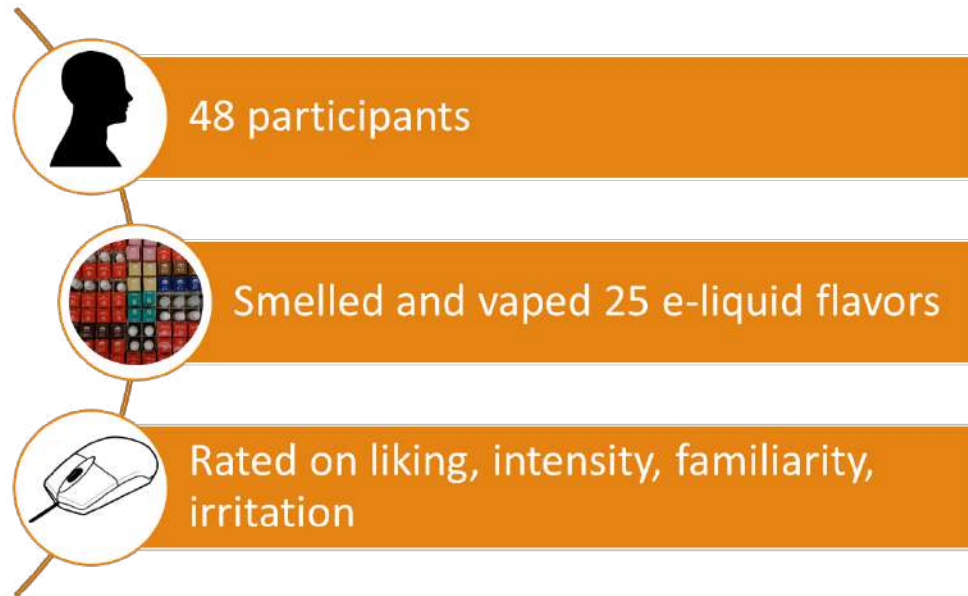
# Flavour preferences dual and e-cigarette users





# Correlation between smelling and vaping e-liquids?

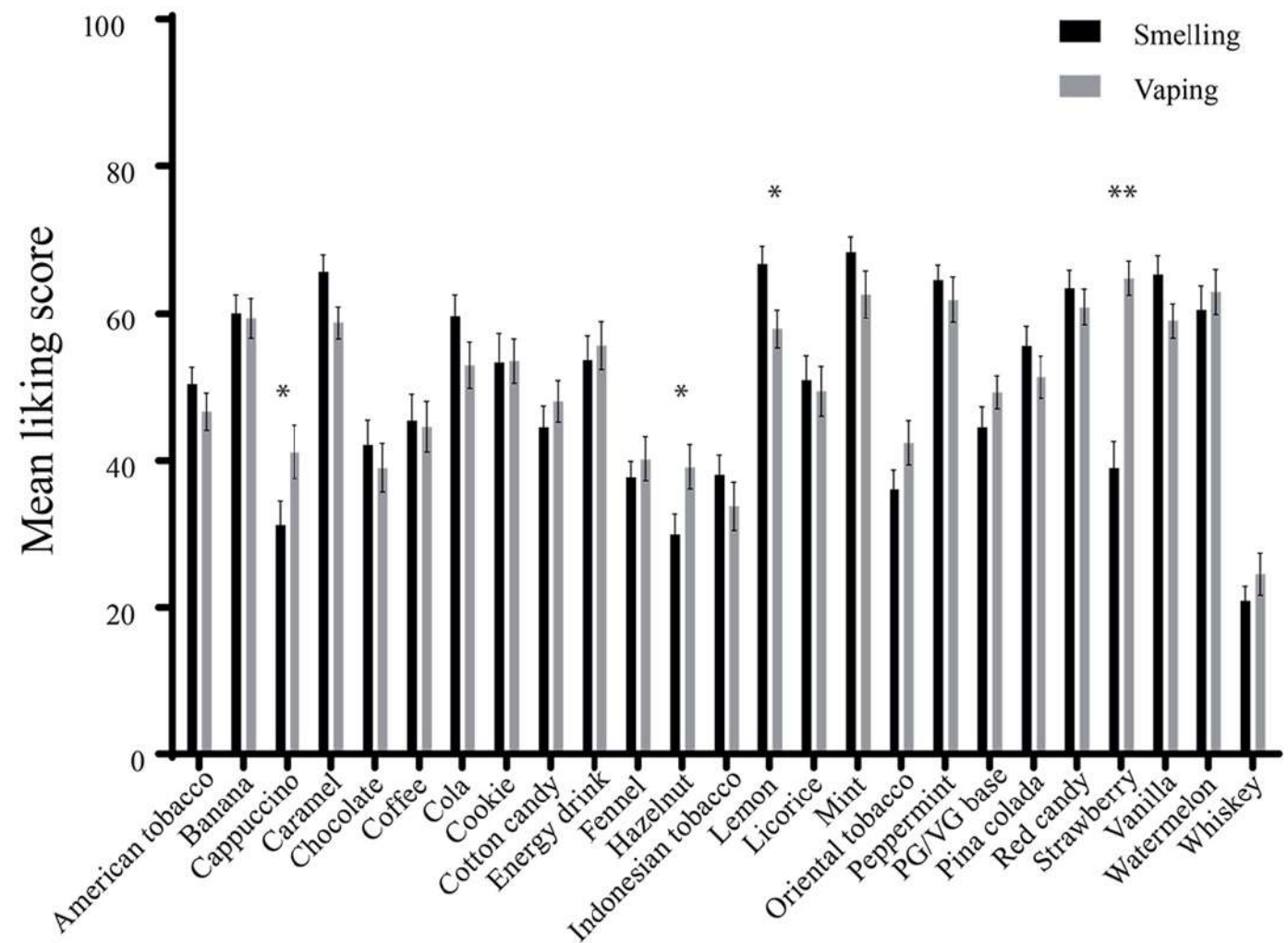
- Smelling studies easier and wider applicable than vaping studies



*Krüsemann et al. Nicotine & Tobacco Research. 2020;22(5): 798–805*



# Liking scores of smelling and vaping





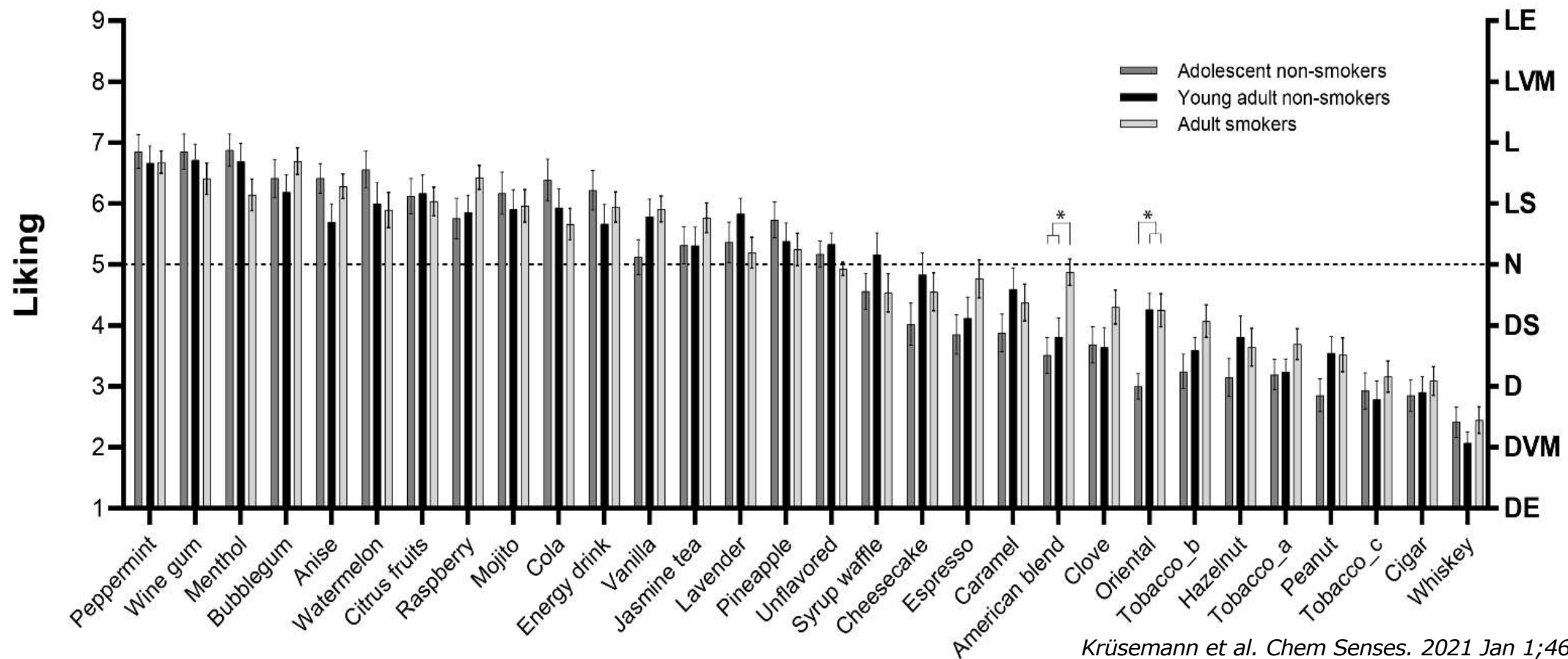
## Yes, strong correlation

- > No differences between smokers and non-smokers
- > So: smelling studies with non-users and youth

Variable	Correlation coefficient between smelling and vaping
	Between the mean scores of all flavors (n= 25)
Liking	0.84
Intensity	0.82
Familiarity	0.84
Irritation	0.73



# E-liquid smelling by smokers and non-smokers



Krüsemann et al. Chem Senses. 2021 Jan 1;46:bjab009





# Implications for regulators

Flavours most attractive product characteristic among all groups

Many different types of flavours available, mostly sweet

Both smokers and non-smokers like sweet and minty flavours better than tobacco

No magic flavour liked by smokers and not liked by non-smokers

Banning flavours will make them less attractive for both smokers and non-smokers





# Impact of Flavour Restricting Policies on Non-Cigarette Tobacco Products

- > Editorial
- > Optimal regulations pertaining to flavour policies would provide balance between increasing effectiveness of intended consequences (to reduce use among youth) while minimising unintended consequences among adult users.





# Regulation of flavours in e-liquids in NL

- › To protect youth, Dutch government bans e-liquids with flavours other than tobacco
- › Opposition Esigbond (e-cigarette manufacturers) and Acvoda (Action Committee for Vapours)
- › Twenty-four experts advise a rethink – The Counterfactual (clivebates.com)
- › Per January 1<sup>st</sup> 2023

*RIVM reports 2021-0074 and 2022-0050  
Pennings et al. 2023, Tobacco Control*



# Exhaustive list of allowed flavourings

Worldwide, countries implemented bans for e-liquid flavours

Methods to implement such a ban in practice are mostly lacking

Government decided: exhaustive list of allowed flavourings

- No sensory panel, as costly and other cons
- List of allowed flavourings is clearer for manufacturers



## RIVM approach

A list of flavouring additives in e-liquids that will only enable the production of e-liquids with a tobacco flavour

Several criteria to exclude flavouring additives that are not tobacco-related, or are harmful for health

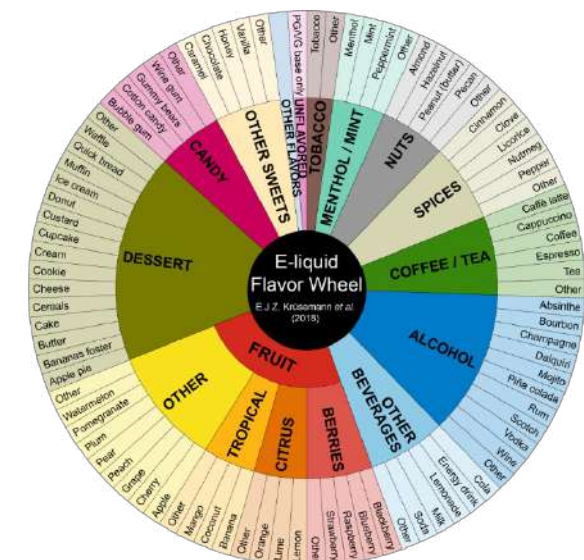
Applied these criteria to ingredient data for all e-liquids notified by manufacturers for the Dutch market just before flavour ban was announced



# Distribution of e-liquids across flavour categories

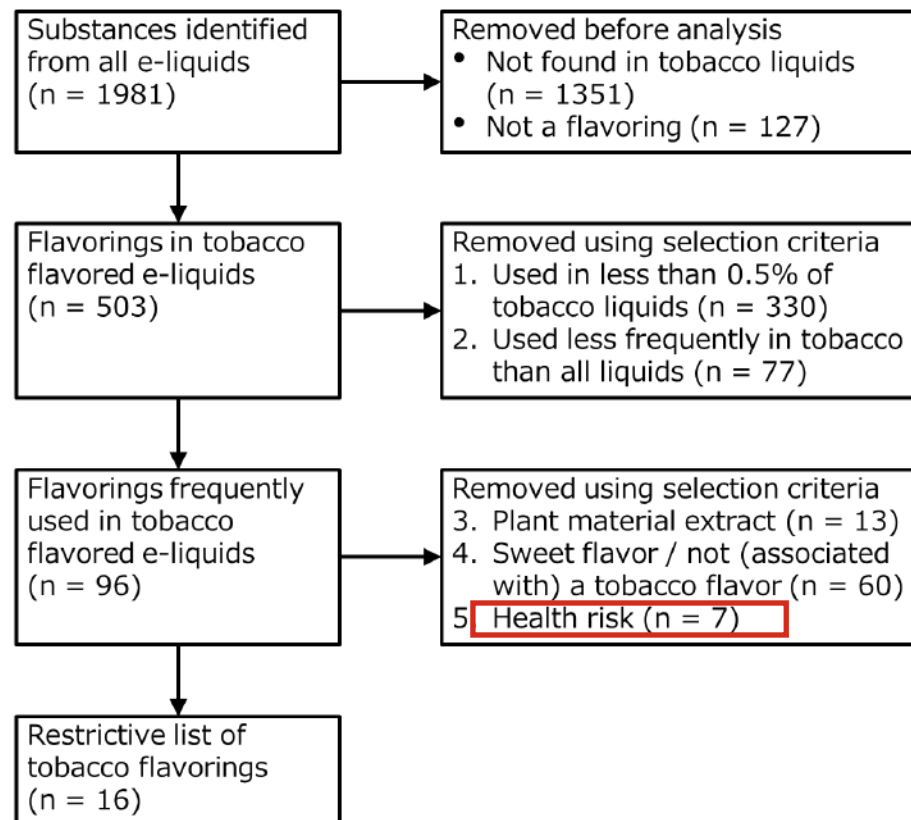
Category	total number	% total
tobacco (without sec. flavour)	<b>3,366</b>	11.8
tobacco (with sec. flavour)	855	3.0
menthol/mint	2,001	7.0
nuts	215	0.8
spices	259	0.9
coffee/tea	706	2.5
alcohol	419	1.5
other beverages	1,313	4.6
fruit (berries)	3,510	12.3
fruit (citrus)	920	3.2
fruit (tropical)	1,946	6.8
fruit (other)	3,904	13.7
dessert	2,212	7.7
candy	991	3.5
other sweets	1,036	3.6
other flavors	303	1.1
unflavoured	459	1.6
unclassifiable	4,141	14.5
total	<b>28,556</b>	100.0

EU-CEG data on e-liquids categorised according to flavour wheel





# Flowchart of selection criteria



16 out of 503  
flavourings present in  
original set of tobacco  
liquids

But...

23% of tobacco  
liquids could remain



# Health effects of the 23 flavourings

Concentrations  
in liquid from  
EU-CEG

Exposure  
scenario relevant  
for e-liquid use

Toxicity data  
from literature  
and databases

Inhalation toxicity data available for 3 compounds

2 potentially carcinogenic

1 can cause allergies



Oral toxicity data available for 4 compounds

3 could cause health risks

1 is an irritant for the lungs



Remaining 16 substances

insufficient information to assess their health risk for use in e-cigarettes



# RIVM recommendations for regulation

TPD 20.3.e: only ingredients are used in the nicotine-containing liquid that do not pose a risk to human health in heated or unheated form

- 2 carcinogenic substances and the substance that can causes allergies not permitted
- 3 substances that are harmful at high concentrations and the irritating substance not permitted

Two options proposed for the 16 compounds with unknown health effects

- Prohibit these substances from a precautionary principle
- Allow use of these substances in e-liquids to keep the product available for smokers to help them quit smoking





# Proposal for a list of allowed flavourings

CAS number	Flavouring name	Flavour description	Association to tobacco
35044-68-9	beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and tobacco	Tobacco-like flavor
23726-91-2	(E)-beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and tobacco	Tobacco-like flavor
23726-92-3	(Z)-beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and tobacco	Tobacco-like flavor
23696-85-7	Damascenone	Fruity-floral with apple-plum-raisin-prune, tea, rose, tobacco notes	Tobacco-like flavor
23726-93-4	(E)-beta-Damascenone	Fruity-floral with apple-plum-raisin-prune, tea, rose, tobacco notes	Tobacco-like flavor
1125-21-9	Ketoisophorone	Tobacco like, hay-straw, tea notes, honey	Tobacco-like flavor
4883-60-7	2-Hydroxy-3,5,5-trimethyl-2-cyclohexenone	Sweet, musty tea, caramelic odor; musty, tea, nutty, tobacco taste	Tobacco-like flavor
536-78-7	3-Ethylpyridine	Strong tobacco, roasted, nutty, smoky notes odor; tobacco-like flavor	Tobacco-like flavor
350-03-8	3-Acetylpyridine	Strong, burnt roasted, nutty, cigar tobacco like	Tobacco-like flavor
91-10-1	2,6-Dimethoxyphenol	Phenolic-woody-medicinal, smoky odor; a tarry, spicy, smoky (bacon) taste	Attribute of tobacco aroma
67-47-0	5-(Hydroxymethyl)-2-furfural	Herbaceous winey hay-like odor, sweet herbaceous hay & tobacco-like taste	Tobacco-like flavor
591-12-8	alpha-Angelica lactone	Sweet, bread, molasses, coumarin, tobacco odor; nut-like taste	Tobacco-like flavor
503-74-2	Isovaleric acid	Very sour, 'sweaty', cheesy, odor; fruity on dilution	Attribute of tobacco aroma
1139-30-6	(-)-Caryophyllene oxide	Dry, woody, faint cedar, tobacco like notes	Tobacco-like flavor
3738-00-9	Ambroxide	Intense velvety ambergris notes	Present in tobacco smoke
564-20-5	(3aR)-(+)-Sclareolide	Cedary; impact compound of certain tobaccos; fish & berry flavor improver	Tobacco-like flavor



# Ban of e-liquids other than tobacco flavour

- Per January 1<sup>st</sup> 2023
- Possible unintended consequences?
  - DIY flavouring addition
  - less attractive as smoking cessation tool
  - decreased ENDS use
  - increased cigarette use
  - increased use of illicit markets



# Learn from history... flavour accessories

- Flavour accessories can impart a menthol flavor on tobacco



- Sold separately they are not covered by the TPD
- 13% of respondents had started using such products (Euromonitor data, 2020)



# Ceterum censeo

Cigarette product regulation  
should not be forgotten  
Many options are available

Design

Filter ventilation

Flavourings

Sugars

Compounds that facilitate inhalation

Non-addictive nicotine levels (VLNC)

*Senator Cato Maior (234-149 BC)*



Questions?