10-2022

Ethyl Maltol, Vanillin, Corylone and other Conventional Confectionery-related Flavour Chemicals Dominate in Some E-cigarette Liquids Labelled 'tobacco' flavoured

Esther E. Omaiye
University of California Riverside

Wentai Luo
Portland State University, wentai@pdx.edu

Kevin J. McWhirter
Portland State University, kevin.mcwhirter@pdx.edu

James F. Pankow
Portland State University, pankowj@pdx.edu

Prue Talbot
University of California, Riverside

Citation Details

Omaiye, E. E., Luo, W., McWhirter, K. J., Pankow, J. F., & Talbot, P. (2022). Ethyl maltol, vanillin, corylone and other conventional confectionery-related flavour chemicals dominate in some e-cigarette liquids labelled 'tobacco'flavoured. Tobacco control, 31(Suppl 3), s238-s244.

OPEN ACCESS

Ethyl maltol, vanillin, corylone and other conventional confectionery-related flavour chemicals dominate in some e-cigarette liquids labelled 'tobacco' flavoured

Esther E Omaiye,[1] Wentai Luo,[2] Kevin J McWhirter,[2] James F Pankow,[2] Prue Talbot [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tc-2022-057484).

[1]Department of Molecular, Cell and Systems Biology, University of California Riverside, Riverside, California, USA
[2]Department of Civil and Environmental Engineering, Portland State University, Portland, Oregon, USA

Correspondence to
Dr Prue Talbot, Department of Molecular, Cell and Systems Biology, University of California Riverside, Riverside, CA 92521, USA; talbot@ucr.edu

Received 21 April 2022
Accepted 14 July 2022

ABSTRACT

Background The increased popularity of electronic cigarettes (e-cigarettes) has been linked to the abundance of flavoured products that are attractive to adolescents and young adults. In the last decade, e-cigarette designs have evolved through four generations that include modifications in battery power, e-cigarette liquid (e-liquid) reservoirs and atomiser units. E-liquids have likewise evolved in terms of solvent use/ratios, concentration and number of flavour chemicals, use of nicotine salts and acids, the recent increased use of synthetic cooling agents and the introduction of synthetic nicotine. Our current objective was to evaluate and compare the evolving composition of tobacco-flavoured e-liquids over the last 10 years.

Methods Our extensive database of flavour chemicals in e-liquids was used to identify trends and changes in flavour chemical composition and concentrations.

Results Tobacco-flavoured products purchased in 2010 and 2011 generally had very few flavour chemicals, and their concentrations were generally very low. In tobacco-flavoured refill fluids purchased in 2019 and Puff Bar Tobacco e-cigarettes, the total number and concentration of flavour chemicals were higher than expected. Products with total flavour chemicals >10 mg/mL contained one to five dominant flavour chemicals (>1 mg/mL). The most frequently used flavour chemicals in tobacco e-liquids were fruity and caramellic.

Conclusions There is a need for continuous surveillance of e-liquids, which are evolving in often subtle and harmful ways. Chemical constituents of tobacco flavours should be monitored as they clearly can be doctored by manufacturers to have a taste that would appeal to young users.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Little is known about the evolution of the use of flavour chemicals in electronic cigarette liquids (e-liquids), information that is critical to their regulation.
⇒ Historically, 'tobacco'-flavoured e-liquids have had few flavour chemicals at low concentrations.

WHAT THIS STUDY ADDS

⇒ There has been a recent stealth use of high concentrations of sweet and fruity confectionery-related flavour chemicals in 'tobacco-flavoured' e-liquids.
⇒ This change in tobacco e-liquid ingredients coincides with restrictions on the sale of sweet and fruity-flavoured products.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a need for continued surveillance of e-liquids, particularly tobacco flavoured, which may be manipulated to circumvent policies on flavour use.

INTRODUCTION

Understanding the compositions and toxicities of electronic cigarette (e-cigarette) liquids (e-liquids) is important in developing effective regulatory policies regarding vaping. However, e-liquid formulations continue to evolve rapidly, including the use of new ingredients expressly designed to circumvent regulatory law, such as synthetic nicotine[1 2] or the repurposing of synthetic coolants that Wilkinson Sword developed for topical use in shaving cream.[3–6] Flavour chemicals are particularly important since product flavours, such as fruit, candy and sweet, attract students and young adults who might otherwise not use e-cigarettes.[7–9] The rapid rise in JUUL's popularity[10] has prompted the enactment of flavour bans both locally and nationally,[11] with the Food and Drug Administration (FDA) issuing an enforcement policy to remove cartridge-based flavoured e-cigarettes (except for menthol and tobacco flavours) from the market.[12] JUUL withdrew its popular fruity and sweet flavours before the FDA enforcement policy, leaving only their 'Menthol' and 'Virginia Tobacco' flavours on the market. However, fruity and sweet flavours continue to be sold by companies, such as Puff, that market disposable products not covered by the FDA's enforcement policy on characterising flavours in cartridge-style e-cigarettes.[12] Some e-cigarettes (menthol and tobacco) manufactured by Vuse and Logic have been given FDA market authorisation based on data suggesting they are less harmful than tobacco cigarettes.[13] These flavours were probably authorised because they are less appealing to youth,[9] and they may help e-cigarette users with smoking cessation.[11 14]

Given the recent limitations on flavoured e-cigarette sales, our goal was to determine if an FDA-authorised flavour, specifically tobacco, was evolving in a way that would appeal to youth by incorporating sweet and fruity flavour chemicals. To accomplish this, we examined the flavour chemicals in tobacco-flavoured refill fluids over the last decade and in two popular pod-style e-cigarettes and determined if flavour chemical use has evolved

Check for updates

To cite: Omaiye EE, Luo W, McWhirter KJ, *et al*. *Tob Control* 2022;**31**:s238–s244.

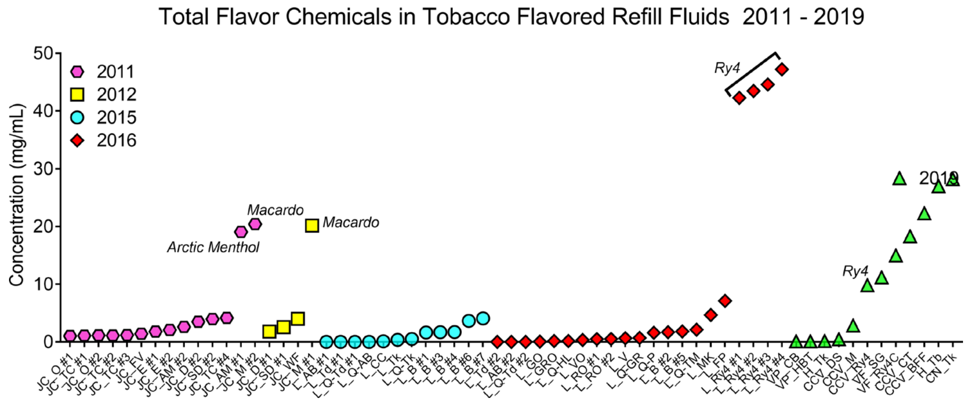


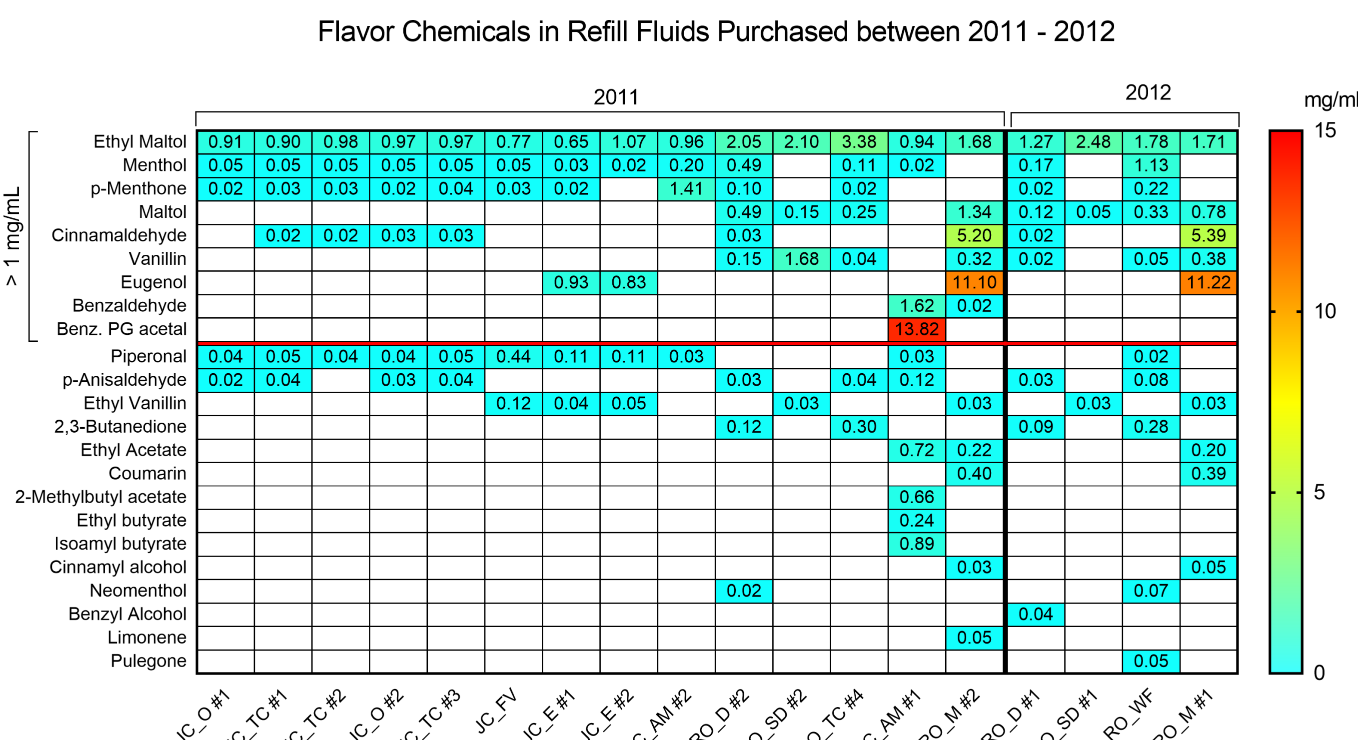
Figure 1 The total concentration of flavour chemicals in tobacco-flavoured refill fluids purchased between 2011 and 2019. The *y*-axis shows concentrations in mg/mL, and the *x*-axis is ordered by increasing concentrations from left to right within each year. Codes represent products as described in online supplemental table S1. While total concentrations ranged from 0 to 47 mg/mL, most tobacco-flavoured refill fluids had low total concentrations of flavour chemicals until 2019, when over 54% of the products analysed had concentrations >10 mg/mL.

in a manner that could increase the popularity of tobacco-flavoured products, especially among young consumers.

METHODS

During the past 10 years, we have identified, quantified and toxicologically evaluated >200 chemicals in e-liquids in many hundreds of products purchased in the USA and worldwide.[6 15–24] This work has been consolidated in the UCR/PSU Electronic Cigarette Data Collection, a unique and extensive knowledge base on flavour chemicals, acids, consequent reaction products, and metals found in e-liquids and aerosols. We have previously used this knowledge base to publish on the unusually high concentrations of flavour chemicals used in many e-liquids,[23] and the sudden market presence of the 'Wilkinson Sword' coolants WS-3 and WS-23 in Puff brand e-cigarettes.[6] The current study compared the number and concentrations of flavour chemicals in 63 tobacco-flavoured e-cigarette refill fluids purchased between 2011 and 2019 and 2 popular disposable/pod-style e-cigarettes (JUUL and Puff). Specifically, the flavour chemical concentrations in each tobacco-flavoured product were extracted from the Electronic Cigarette Data Collection and compared across products and time of purchase.

The refill fluids were selected from two libraries: a convenience library purchased online[17 18] and worldwide library of one brand of refill fluids that included samples purchased in the USA, Great Britain, Nigeria and China.[24] The JUUL and Puff tobacco products were included due to their popularity among young adults and adolescents.[25–28]



	JC_O #1	JC_TC #1	JC_TC #2	JC_O #2	JC_TC #3	JC_FV	JC_E #1	JC_E #2	JC_AM #2	RO_D #2	RO_SD #2	RO_TC #4	JC_AM #1	RO_M #2	RO_D #1	RO_SD #1	RO_WF	RO_M #1
Ethyl Maltol	0.91	0.90	0.98	0.97	0.97	0.77	0.65	1.07	0.96	2.05	2.10	3.38	0.94	1.68	1.27	2.48	1.78	1.71
Menthol	0.05	0.05	0.05	0.05	0.05	0.05	0.03	0.02	0.20	0.49		0.11	0.02		0.17		1.13	
p-Menthone	0.02	0.03	0.03	0.02	0.04	0.03	0.02		1.41	0.10		0.02			0.02		0.22	
Maltol										0.49	0.15	0.25		1.34	0.12	0.05	0.33	0.78
Cinnamaldehyde		0.02	0.02	0.03	0.03					0.03				5.20	0.02			5.39
Vanillin										0.15	1.68	0.04		0.32	0.02		0.05	0.38
Eugenol							0.93	0.83						11.10				11.22
Benzaldehyde													1.62	0.02				
Benz. PG acetal													13.82					
Piperonal	0.04	0.05	0.04	0.04	0.05	0.44	0.11	0.11	0.03				0.03				0.02	
p-Anisaldehyde	0.02	0.04		0.03	0.04					0.03		0.04	0.12		0.03		0.08	
Ethyl Vanillin						0.12	0.04	0.05			0.03			0.03		0.03		0.03
2,3-Butanedione										0.12		0.30			0.09		0.28	
Ethyl Acetate													0.72	0.22				0.20
Coumarin														0.40				0.39
2-Methylbutyl acetate													0.66					
Ethyl butyrate													0.24					
Isoamyl butyrate													0.89					
Cinnamyl alcohol														0.03				0.05
Neomenthol										0.02							0.07	
Benzyl Alcohol															0.04			
Limonene														0.05				
Pulegone																	0.05	

Figure 2 Heat map showing individual flavour chemicals in refill fluids purchased in 2011 and 2012. The *y*-axis shows flavour chemicals ordered by high versus low concentrations, and the *x*-axis represents product codes as described in online supplemental table S1. Most flavour chemicals were present in low concentrations.

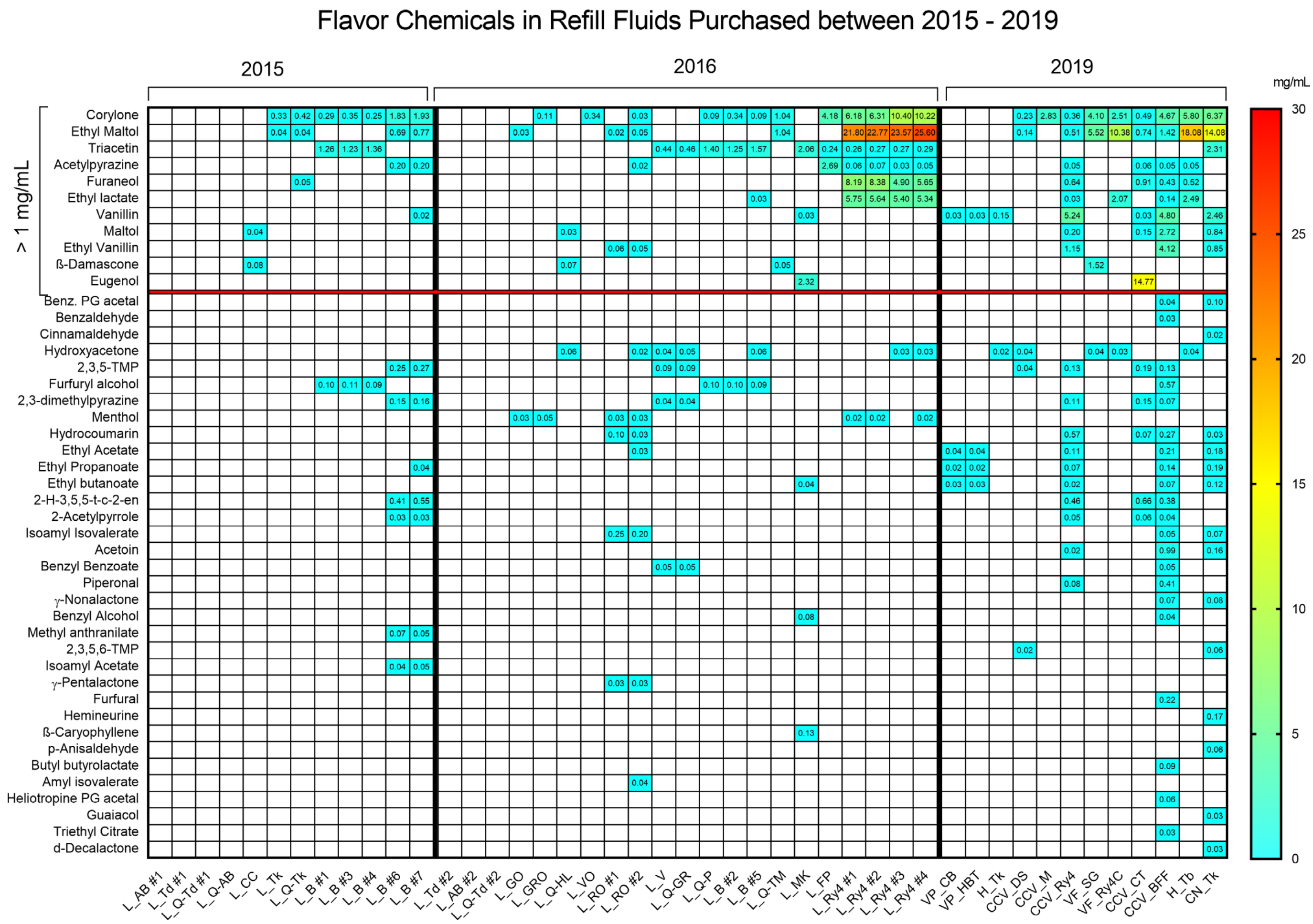


Figure 3 Heat map showing individual flavour chemicals in refill fluids purchased in 2015, 2016 and 2019. The *y*-axis shows flavour chemicals ordered by high versus low concentrations, and the *x*-axis represents product codes as described in online supplemental table S1. Most flavour chemicals were present in low concentrations. However, increases in the concentrations of several commonly used flavour chemicals are seen in products purchased in 2016 and 2019. 2-H-3,5,5-t-c-2-en, 2-Hydroxy-3,5,5-trimethyl-cyclohex-2-en; TMP, trimethylpyrazine.

RESULTS

Total concentrations of flavour chemicals in refill fluids

Flavour chemicals were identified and quantified in 63 tobacco-flavoured refill fluids purchased between 2011 and 2019 (online supplemental table S1). Figure 1 shows the total concentrations of the flavour chemicals in each product. Most (63%) of the refill fluids purchased before 2019 had low total concentrations of flavour chemicals (<2 mg/mL) and 84% were <5 mg/mL. There were six notable exceptions: (1) duplicate bottles of 'Marcado' purchased in 2011 and 2012 with ~20.3 mg/mL); (2) 'Arctic Menthol' purchased in 2011 with 19.1 mg/mL; and four LiQua 'RY4 Tobacco' products purchased in 2016 with 42.3–47.2 mg/mL. In contrast, of 13 products purchased in 2019, 54% had total flavour chemical concentrations >10 mg/mL.

Concentrations of individual flavour chemicals in refill fluids

The individual flavour chemicals used in tobacco-flavoured refill fluids purchased between 2011 and 2019 are shown in figures 2 and 3, in which blank cells indicate the chemical was not detected.[17 18 22 24] In the 2011–2012 group, duplicate bottles of 'Macardo' had elevated cinnamaldehyde and eugenol, while one 'Arctic Menthol' product with benzaldehyde (1.62 mg/mL) had a high concentration of benzaldehyde PG acetal (13.82 mg/mL) that may have formed at room temperature during storage.[29] All other products had low total concentrations of flavour chemicals (figure 2).

Figure 3 shows products purchased in 2015, 2016 and 2019. 'American Blend' flavours purchased in multiple countries in 2015 and 2016 had neither flavour chemicals nor nicotine. 'Traditional Tobacco' refill fluids contained one to four flavour chemicals below the limit of quantification. The absence of flavour chemicals is unusual and was not observed in the other flavour categories studied previously.[18 21 22] Most flavour chemicals were present at very low concentrations (<1 mg/mL). Nine flavour chemicals that were used mainly in products purchased in 2016 and 2019 had concentrations >2 mg/mL, and these included: ethyl maltol (sweet or caramel), cinnamaldehyde (cinnamon), benzaldehyde PG acetal (fruity), corylone (caramellic, maple), triacetin (fruity, creamy), furaneol (sweet, caramellic), ethyl lactate (sweet, fruity) and eugenol (spicy, clove).

Frequency of occurrence and odour description of flavour chemicals

The frequency with which 55 flavour chemicals were used in tobacco-flavoured refill fluids is shown in figure 4. The dominant flavour chemicals (>1 mg/mL in at least one product) are indicated by an asterisk. The five most frequently used flavour

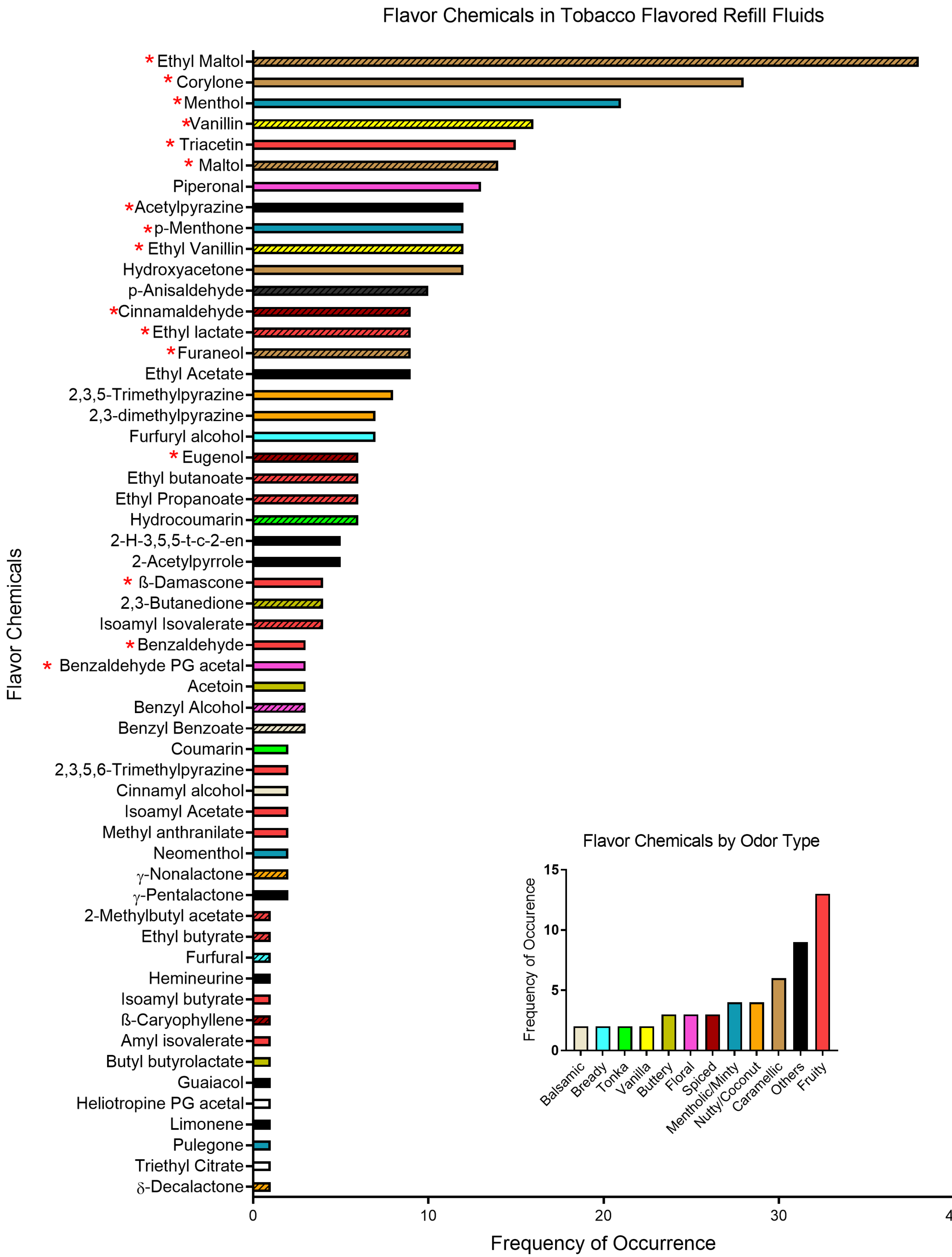


Figure 4 Frequency distribution for 55 flavour chemicals found in 63 tobacco-flavoured refill fluids. The *x*-axis is the number of products, and the *y*-axis is sorted according to decreasing frequency of their occurrence. Representative colour codes based on odour type are shown in the insert. Frequency ranged from 1 to 38, with the highest being ethyl maltol. The asterisks indicated chemicals found at >1 mg/mL in at least one product, and hatched bars indicate flavour chemicals that produce a sweet taste. 2-H-3,5,5-t-c-2-en, 2-Hydroxy-3,5,5-trimethyl-cyclohex-2-en.

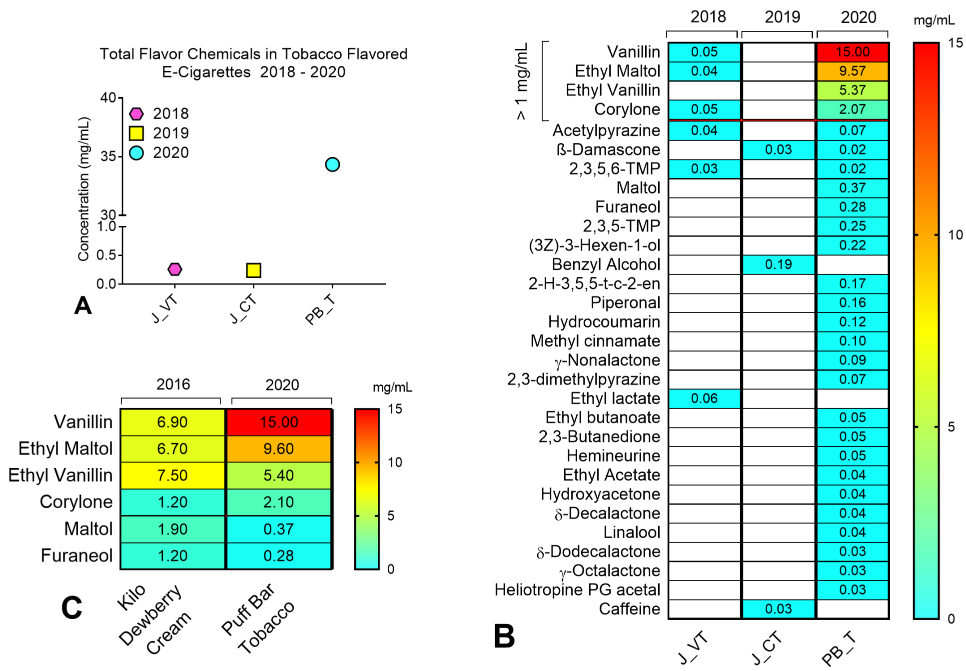


Figure 5 The total flavour chemical concentrations and individual chemicals in JUUL and Puff products. (A) Total flavour chemical concentrations in JUUL and Puff e-cigarettes. (B) Concentrations of individual flavour chemicals in JUUL and Puff e-cigarettes. (C) Dominant flavour chemicals in Kilo 'Dewberry Cream' and Puff Bar 'Tobacco.' The *y*-axis shows concentrations in mg/mL, and codes represent the products as described in online supplemental table S1. 2-H-3,5,5-t-c-2-en, 2-Hydroxy-3,5,5-trimethyl-cyclohex-2-en; e-cigarettes, electronic cigarettes; TMP, trimethylpyrazine.

chemicals were ethyl maltol (60%), corylone (44%), menthol (33%), vanillin (25%), maltol and triacetin (24%).

Based on odour type, flavour chemicals with a fruity or caramellic flavour were used most frequently. The 'Other' category in the insert includes flavour chemicals that appeared only once (popcorn, anisic, ethereal, woody, musty, herbal, meaty, phenolic and citrus). Based on odour/taste description information[30] (www.thegoodscentscompany.com), flavour chemicals used in tobacco-flavoured e-cigarette refill fluids are sweet (figure 4).

Fourth-generation pod-style e-cigarettes

Flavour chemicals were compared in JUUL and Puff e-cigarettes, two popular disposable/pod-style fourth-generation e-cigarettes (figure 5, online supplemental table S1). JUUL has marketed two tobacco flavours, 'Classic' and 'Virginia', containing very low levels of flavour chemicals (range=0.03–0.19 mg/mL). Total flavour chemical concentrations for both JUUL products were under 0.35 mg/mL, and the concentrations of the individual chemicals were, in most cases, ≤0.05 mg/mL (figure 5A,B). Different flavour chemicals were used in the 'Classic' versus 'Virginia Tobacco' products, suggesting these chemicals were added intentionally to create distinct tastes for each product.

In contrast, Puff 'Tobacco' had 27 different flavour chemicals with a total concentration of 34.3 mg/mL (figure 5A,B), which is higher than the other Puff products we evaluated.[3] Individual chemicals ranged in concentration from 0.03 to 15 mg/mL. Four flavour chemicals (vanillin, ethyl maltol, ethyl vanillin and corylone), which were the highest in concentrations (range=2.07–15 mg/mL), are typically used in sweet-flavoured e-cigarette products, such as Dewberry Cream (figure 5B).[21] For the dominant flavour chemicals found in both brands, the fold increase in Puff versus JUUL was 300 for vanillin, 239 for ethyl maltol and 41 for corylone. The total number of flavour chemicals used in Puff Bar 'Tobacco' was greater than 94% of the refill fluids. The vanillin and ethyl vanillin concentrations in Puff Bar Tobacco were higher than in other tobacco-flavoured refill fluids we have examined.[17 18 22 24] A comparison of dominant flavour chemicals in Puff Bar 'Tobacco' with previously evaluated Kilo 'Dewberry Cream'[21] revealed an identical flavour profile (figure 5C).

DISCUSSION

Our goal was to determine if flavour chemical use in tobacco-flavoured e-cigarette products has changed during the past 10 years as flavour restrictions have come into play. Our main finding is the recent inclusion of high concentrations of sweet and fruity flavour chemicals in products labelled 'tobacco', which historically have had few flavour chemicals at low concentrations.[17] This change coincides with the national public health concern regarding the rapid adoption of JUUL products by students and young adults attracted to these pod-style e-cigarettes with appealing flavours.[31] Surveys found that many young adults and students started JUULing because they found the flavours attractive.[32] In contrast, tobacco-flavoured pods are not generally attractive to young users,[33] which may be why recent FDA authorisations were granted for tobacco-flavoured e-cigarettes manufactured by Vuse and Logic.[13] The chemicals in high concentrations in recently manufactured tobacco-flavoured e-cigarettes were ethyl maltol, corylone, vanillin and ethyl vanillin. These chemicals were often found in our samples at concentrations much higher than in other consumer products, such as cosmetics and ingestibles.[23 34–36] As we have shown previously, these chemicals are totally absent in US commercial tobacco cigarettes[37]; therefore, their use is not to replicate tobacco cigarette flavour but appears to be to create a sweet flavour, attractive to a broad base of customers.

The flavour chemicals in Puff 'Tobacco' are remarkably similar to those in 'Dewberry Cream', a flavour popular with young e-cigarette users.[21] The Puff 'Tobacco'-flavoured e-liquid has a higher total concentration of flavour chemicals (~35 mg/mL) than Dewberry Cream (27 mg/mL), which had the highest total flavour chemical concentration in popular products purchased in southern California.[21] Concern has been raised previously about the safety of flavour chemicals when inhaled at these high concentrations.[23] Although these particular flavours are Generally Regarded As Safe by the Flavor Extract Manufacturers Association (FEMA) for ingestion, FEMA has not evaluated them for inhalation toxicity.[38] The concentrations at which these flavour chemicals are used in tobacco products exceed levels usually used in other consumer products.[23 34–36] We have shown that ethyl maltol produces cytotoxicity in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay[21] at concentrations lower than those in many of the products purchased in 2019, LiQua 'Ry4 Tobacco' and Puff e-cigarettes.

The inclusion of high levels of distinctly non-tobacco flavour chemicals in e-cigarette products labelled as 'tobacco' flavoured is not limited to Puff; the practice was also observed in a small number of refill fluids. The LiQua 'Ry4 Tobacco' refill fluids had a total flavour chemical concentration of ~45 mg/mL, mainly due to ethyl maltol (>22 mg/mL). The LiQua 'Ry4 Tobacco' products were among the most cytotoxic of any fluids we have tested in that line or other brands.[24] Other tobacco-flavoured refill fluids in the LiQua companies' product line did not have a high concentration of flavour chemicals. Ry4 refill fluids are generally blended to have vanilla and caramel accents, but in the case of LiQua Ry4, the concentrations of accent flavours were usually high.

Our data support the conclusion that e-liquids are evolving in a manner that appears to broaden their appeal to young users. More specifically, the changes in e-liquids that have occurred in the last 10 years appear to be designed to: (1) intensify the user experience (eg, using novel coolants),[4–6] (2) facilitate nicotine delivery (eg, using acids to allow inhalation of high nicotine levels,[39–41] and/or (3) appeal to a broader market that includes young vapers (eg, using fruity/sweet flavour chemicals in 'tobacco'-flavoured products (this study)). In an effort to comply with the FDA regulation of fruity and sweet-flavoured products that appeal to youth, JUUL reduced its product line and now sells only two flavours, 'Menthol' and 'Virginia Tobacco'. However, the FDA regulation on flavours did not include disposable pod-style e-cigarettes like Puff, which quickly filled the vacuum created by a reduction in JUUL flavours. Ironically, the limited availability of fruity/sweet JUUL products drove young users to an arguably more dangerous product with high nicotine concentrations, synthetic coolants and pulegone, a carcinogen.[6] Additionally, the Puff Bar tobacco-flavoured product with high concentrations of vanillin, ethyl maltol, ethyl vanillin and corylone is likely appealing to young people and may become a staple should other Puff flavours be removed from the market in the future.

Our data show that the chemical composition of e-cigarette liquids is evolving. High concentrations of sweet/fruity flavour chemicals have been used in recently manufactured 'tobacco' e-liquids, apparently to circumvent regulations on the use of flavour chemicals and to make 'tobacco' e-cigarettes attractive to young users. It is important for the FDA to identify and quantify flavour chemicals before authorising Premarket Tobacco Applications (PMTA) for two reasons. First, flavour chemicals are often used in e-liquids without safety data at concentrations much higher than those found in other consumer products.[6 23 24] Second, our data show that e-cigarette manufacturers are manipulating e-liquid formulations apparently to circumvent flavour chemical regulations. Once a product receives PMTA authorisation, periodical surveillance independent of the manufacturers would be needed to be certain that e-liquids are not modified in a way that would broaden their appeal. Going forward, it will be important to evaluate additional currently used products to determine if other manufacturers follow Puff's lead and use formulations in their tobacco-flavoured e-cigarettes/e-liquids that would be attractive to young users. While our study deals with the flavour chemicals in 'tobacco-flavoured' e-liquids, the e-liquids market likely has more than 15 000 distinct flavour names other than 'tobacco' on labels,[42] and these may also be evolving and should be studied in future work.

Contributors EEO and PT formed the conception and design of the study. WL, KJM and JFP performed the gas chromatography/mass spectrometry analysis. EEO and PT were involved in the data analysis and interpretation. EEO and PT drafted the manuscript. PT is the guarnator. All authors critically reviewed, edited and approved the final manuscript.

Funding Research reported in this publication was supported by grant R01ES029741-01 from the National Institute of Environmental Health Sciences, the Food and Drug Administration Center for Tobacco Products to PT and JFP, and the University of California's President's Dissertation Year Fellowship awarded to EEO.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

ORCID iD

Prue Talbot http://orcid.org/0000-0001-8833-0845

REFERENCES

1 Zettler PJ, Hemmerich N, Berman ML. Closing the regulatory gap for synthetic nicotine products. *Boston Coll Law Rev* 2018;59:1933–82.
2 Jordt S-E. Synthetic nicotine has arrived. *Tob Control* 2021. doi:10.1136/tobaccocontrol-2021-056626. [Epub ahead of print: 07 Sep 2021].
3 Leffingwell J, Rowsell D. Wilkinson sword cooling compounds: from the beginning to now. *Perfumer & Flavorist* 2014;39:34–43.
4 Erythropel HC, Anastas PT, Krishnan-Sarin S, *et al*. Differences in flavourant levels and synthetic coolant use between USA, EU and Canadian Juul products. *Tob Control* 2021;30:453–5.
5 Jabba SV, Erythropel HC, Torres DG, *et al*. Synthetic cooling agents in US-marketed e-cigarette refill liquids and popular disposable e-cigarettes: chemical analysis and risk assessment. *Nicotine Tob Res* 2022;24:1037–46.
6 Omaiye EE, Luo W, McWhirter KJ, *et al*. Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes. *Tob Control* 2022;31:e3–9.
7 Ambrose BK, Day HR, Rostron B, *et al*. Flavored tobacco product use among US youth aged 12-17 years, 2013-2014. *JAMA* 2015;314:1871–3.
8 Zare S, Nemati M, Zheng Y. A systematic review of consumer preference for e-cigarette attributes: flavor, nicotine strength, and type. *PLoS One* 2018;13:e0194145.
9 Goldenson NI, Leventhal AM, Simpson KA, *et al*. A review of the use and appeal of flavored electronic cigarettes. *Curr Addict Rep* 2019;6:98–113.
10 Williams R. The rise of disposable JUUL-type e-cigarette devices. *Tob Control* 2020;29:e134–5.
11 Erinoso O, Clegg Smith K, Iacobelli M, *et al*. Global review of tobacco product flavour policies. *Tob Control* 2021;30:373–9.

12 United States Food and Drug Administration. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint, 2020. Available: https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children [Accessed 27 June 2022].
13 United States Food and Drug Administration. Premarket tobacco product marketing granted orders, 2022. Available: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders [Accessed 27 June 2022].
14 Hartmann-Boyce J, McRobbie H, Butler AR. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2021;2021:CD010216.
15 Bahl V, Lin S, Xu N, *et al*. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol* 2012;34:529–37.
16 Behar RZ, Davis B, Bahl V, *et al*. Commentary in response to the letter from Farsalinos et al. regarding our publication entitled: "identification of toxicants in cinnamon-flavored electronic cigarette refill fluids". *Toxicol In Vitro* 2014;28:1521–2.
17 Behar RZ, Luo W, Lin SC, *et al*. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob Control* 2016;25:ii94–102.
18 Behar RZ, Luo W, McWhirter KJ, *et al*. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. *Sci Rep* 2018;8:8288.
19 Tierney PA, Karpinski CD, Brown JE, *et al*. Flavour chemicals in electronic cigarette fluids. *Tob Control* 2016;25:e10–15.
20 Behar RZ, Wang Y, Talbot P. Comparing the cytotoxicity of electronic cigarette fluids, aerosols and solvents. *Tob Control* 2018;27:325–33.
21 Hua M, Omaiye EE, Luo W, *et al*. Identification of cytotoxic flavor chemicals in Top-Selling electronic cigarette refill fluids. *Sci Rep* 2019;9:2782.
22 Omaiye EE, McWhirter KJ, Luo W, *et al*. High-nicotine electronic cigarette products: toxicity of JUUL fluids and aerosols correlates strongly with nicotine and some flavor chemical concentrations. *Chem Res Toxicol* 2019;32:1058–69.
23 Omaiye EE, McWhirter KJ, Luo W, *et al*. High concentrations of flavor chemicals are present in electronic cigarette refill fluids. *Sci Rep* 2019;9:2468.
24 Omaiye EE, Luo W, McWhirter KJ, *et al*. Electronic cigarette refill fluids sold worldwide: flavor chemical composition, toxicity, and hazard analysis. *Chem Res Toxicol* 2020;33:2972–87.
25 Wang TW, Neff LJ, Park-Lee E, *et al*. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1310–2.
26 Wang TW, Gentzke AS, Neff LJ, *et al*. Disposable E-Cigarette Use among U.S. Youth - An Emerging Public Health Challenge. *N Engl J Med* 2021;384:1573–6.
27 Miech R, Leventhal A, Johnston L, *et al*. Trends in use and perceptions of nicotine Vaping among US youth from 2017 to 2020. *JAMA Pediatr* 2021;175:185.
28 Park-Lee E, Ren C, Sawdey MD, *et al*. Notes from the field: E-Cigarette use among middle and high school students - National Youth Tobacco Survey, United States, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1387–9.
29 Erythropel HC, Jabba SV, DeWinter TM, *et al*. Formation of flavorant-propylene glycol adducts with novel toxicological properties in chemically unstable e-cigarette liquids. *Nicotine Tob Res* 2019;21:1248–58.
30 The Good Scents Company Information System. Providing information for the flavor, fragrance, food and cosmetic industries. Available: http://thegoodscentscompany.com/ [Accessed 27 June 2022].
31 Walley SC, Wilson KM, Winickoff JP, *et al*. A public health crisis: electronic cigarettes, Vape, and JUUL. *Pediatrics* 2019;143:e20182741.
32 Hamberger ES, Halpern-Felsher B. Vaping in adolescents: epidemiology and respiratory harm. *Curr Opin Pediatr* 2020;32:378–83.
33 Nguyen N, McKelvey K, Halpern-Felsher B. Popular flavors used in alternative tobacco products among young adults. *J Adolesc Health* 2019;65:306–8.
34 Oser BL, Ford RA. Recent Progress in the Consideration of Flavoring Ingredients Under the Food Additives Amendment [online] Femaflavor.org. In: *Reprinted from Food Technology*, 1977: 65–74. 10.GRAS Substances (3477-3525).pdf
35 Cohen SM, Eisenbrand G, Fukushima S. Gras flavoring substances 29, 2020. Available: https://www.femaflavor.org/sites/default/files/2020-03/GRAS%2029.pdf [Accessed 27 June 2022].
36 Hall RL, Oser BL. Recent progress in the consideration of flavor ingredients under the food additives amendment. 3. GRAS substances. *Food Technology* 1965;19 (2, Part 2):151–97.
37 Pankow JF, Luo W, McWhirter KJ, *et al*. 'Menthol-Plus': a major category of cigarette found among 'concept' descriptor cigarettes from Mexico. *Tob Control* 2022;31:e18–24.
38 Hallagan J. The safety assessment and regulatory authority to use flavors: focus on A. e-cigarettes, 2014. Available: http://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes [Accessed 27 Jun 2022].
39 Pankow JF, Kim K, McWhirter KJ, *et al*. Benzene formation in electronic cigarettes. *PLoS One* 2017;12:e0173055.
40 Duell AK, Pankow JF, Peyton DH. Free-Base Nicotine Determination in Electronic Cigarette Liquids by ^{1}H NMR Spectroscopy. *Chem Res Toxicol* 2018;31:431–4.
41 Leventhal AM, Madden DR, Peraza N, *et al*. Effect of exposure to e-cigarettes with salt vs free-base nicotine on the appeal and sensory experience of vaping: a randomized clinical trial. *JAMA Netw Open* 2021;4:e2032757.
42 Hsu G, Sun JY, Zhu S-H. Evolution of electronic cigarette brands from 2013-2014 to 2016-2017: analysis of brand websites. *J Med Internet Res* 2018;20:e80.