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Full Length Article

Monoamine oxidase inhibitory activity of flavoured e-cigarette liquids

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ABSTRACT

Background and aims: Monoamine oxidase inhibitors have been hypothesised to be important in tobacco dependence, reinforcing the brain's response to nicotine by delaying the degradation of neurotransmitters by monoamine oxidases.

The development of electronic cigarettes has provided an alternative nicotine delivery system, which is widely viewed as less toxic than tobacco smoke. However, significant data gaps remain. This paper reports the results of measurements of monoamine oxidase inhibitory activity in a small sample of commercially available, flavoured e-liquids.

Methods: Twelve e-liquids were tested for monoamine oxidase inhibitory activity, using the kynuramine assay and monoamine oxidase enzymes (human, recombinant). Control samples of carrier liquids, propylene glycol and glycerol, and nicotine were also tested.

Results: Four e-liquids contained high levels of inhibitory activity, four more were moderately inhibitory. The remaining four e-liquids were mildly inhibitory, while the carrier liquids, and nicotine were inactive at relevant concentrations. The active compounds in the e-liquids were subsequently identified as vanillin and ethyl vanillin.

Under some conditions of use, the sampled e-liquids with the highest concentrations of monoamine oxidase inhibitory activity have the potential to expose consumers to physiologically significant levels of MAO inhibitory activity.

Conclusions: While only a small sample of e-liquids was tested, the findings suggest that some flavours have pharmacological actions, with potential to enhance the response to nicotine or to other drugs. The public health implications of these preliminary findings on addiction and smoking cessation warrant exploration and further research.

1. Introduction

Electronic cigarettes (i.e., e-cigarettes) comprise a group of products called electronic nicotine delivery systems (ENDS) which are provoking wide public health interest due to their widespread use among youth and their potential for use as nicotine replacement therapies for stopping or reducing smoking (Royal College of Physicians, 2016; Zhu et al., 2017).

This use of e-cigarettes, commonly called vaping, is a relatively recent phenomenon, largely uncontrolled through product safety regulations, with significant scientific data gaps that pose regulatory and safety challenges (Benowitz and Goniewicz, 2013; Green et al., 2018; US Department of Health and Human Services, 2016). While some of the initial concerns around e-cigarettes (e.g. cancer and cardiovascular risk) have not been verified by emerging evidence (Abrams et al., 2018; Britton et al., 2016; Warner and Mendez, 2018), uncertainties remain, particularly around pulmonary toxicity and addictive properties.

One significant concern centres around the potential for flavouring compounds either to cause harm in and of themselves (Barrington-Trimis et al., 2014; Behar et al., 2014; Cho and Paik., 2016; Egilman and Schilling, 2014; Kylystov and Samburova, 2017; Morgan et al., 2012), or to increase the attractiveness and addictiveness of e-cigarettes (Tierney et al., 2016; Villanti et al., 2017). Most flavouring compounds have been tested for acute oral toxicity, but their toxicity or pharmacology by inhalation is currently unknown. Further, there is concern about flavours that are targeted at younger users (King et al., 2014). Concerns around the nicotine uptake potential of e-cigarettes for current adult non-smokers and youth remain, and consensus among

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scientists as to the overall public health impact has not been reached (Green et al., 2018).

There is general consensus that nicotine is the main addictive agent in tobacco. However, recent evidence suggests that some other chemical constituents of tobacco smoke modulate the brain's response to nicotine, making it more addictive than it would be on its own (Brennan et al., 2013, 2015; Costello et al., 2014). One of the primary candidates to cause such an effect are the monoamine oxidase (MAO) inhibitors. These compounds are found in tobacco smoke (Fowler et al., 2003; Hogg, 2016; Smith et al., 2015). MAO inhibition is not caused by nicotine (Fowler et al., 2003), yet smokers have profoundly inhibited MAO-A and MAO-B in the brain and in the body, recovering only after weeks or months of abstinence (Fowler et al., 2003, 2005). MAO inhibitors modulate nicotine self-administration in rats, reinforcing the hypothesis that MAO inhibitors in tobacco smoke enhance smokers' addictive response to nicotine (Smith et al., 2015, 2016; Villegier et al., 2007).

In contrast to tobacco, e-cigarettes provide nicotine without most of the other components of tobacco smoke. The assumption, therefore, is that they will provide nicotine without MAO inhibitors and other iniquitous or harmful compounds normally associated with tobacco smoke. In accordance with this expectation, limited emerging evidence suggests that e-cigarettes may not be as addictive as tobacco (Liu et al., 2017; Truman et al., 2018). However, the MAO inhibiting activity of flavouring chemicals in electronic cigarettes has generally not been studied.

This study was conducted to determine the MAO inhibitory activity of a variety of e-liquids, which typically contain tobacco-derived nicotine and flavours, to better inform our understanding of how e-liquid content may impact consumers. In this pilot project, we tested the MAO inhibitory activity of twelve e-liquids, along with the carrier liquid components and nicotine. We also separately measured the MAO inhibitory activity of vanillin and ethyl vanillin, following their identification as compounds of interest.

2. Methods

2.1. The e-liquids tested in this study

Table 1 presents twelve e-liquids available at the time of this study, which represent different brands, flavours, stated nicotine content, and stated mixtures of propylene glycol (PG) and vegetable glycerine (VG).

2.2. Analysis of e-liquid MAO inhibitory activity

The e-liquids, with a variety of flavors and stated nicotine contents, were purchased from normal commercial outlets in California, USA. Each e-liquid was diluted 1/10 in 500 mM phosphate buffer pH 7.3. Cloudiness that formed on mixing was allowed to resolve overnight, and the diluted samples were analyzed for MAO inhibitory activity against human recombinant MAO-A and MAO-B (available from Sigma Aldridge) using an established method (Truman et al., 2017). This assay relies on hydrolysis of kynuramine to 4-hydroxyquinoline, which is fluorescent (Ex 320, Em 380) under alkaline conditions. Intrinsic fluorescence of the e-liquids was also checked, so that any background fluorescence could be accounted for during calculation of the degree of inhibition observed. Each diluted e-liquid was tested at up to 10 μL per 100 μL total reaction volume (equivalent to adding 10 μL of undiluted e-liquid in 1 mL of reaction mix). Carrier liquids, diluted 1/10 in 500 mM phosphate buffer, and the buffer itself, served as negative controls. Harman, a known MAO inhibitor, at 50 μM final concentration was used as the positive control. All MAO inhibition assays were performed at Massey University, in triplicate, and repeated at least once.

Concentration-response curves were produced for some e-liquids, and could be fitted using a standard inhibition model (four parameter, variable slope fit of log concentration vs fluorescence). The amounts of e-liquid causing half-maximal inhibition (IC_{50} s) are expressed in μL undiluted e-liquid/mL, where 10 μL/mL was the maximum concentration tested. Curve fitting was performed using Prism (Graphpad software, San Diego, CA).

2.3. Analysis of e-liquids for identification of compounds responsible

Four e-liquids, spanning the range of MAO inhibitory activity found, were analysed by gas chromatography/mass spectrometry (GC/MS) in full scan mode, at Centers for Disease Control. Compound identity was determined using probability based matching (> 95% identity) using mass spectral database searches against the NIST 11 Mass Spectral Database (National Institute of Standards and Technology; Gaithersburg, MD). The candidate peaks, identified in e-liquids with higher MAO inhibitory activity, were vanillin and ethyl vanillin (discussed further in the Results Section). A dilution series for these two compounds was prepared by CDC, ranging from approx. 0.1 to 20.1 mg/mL and using propylene glycol as diluent, and was express shipped at ambient temperature to Massey University for MAO inhibitory activity testing. Upon receipt, MAO inhibitory activity testing was performed on these two dilution series.

2.4. Statistical methods

The association between the presence of nicotine or the candidate MAO inhibitors with the monoamine oxidase inhibitory activity of the e-liquids was tested using Spearman's correlation (Prism).

Table 1
The e-liquids chosen for testing.

E-liquid No.	Brand Name	Product Name/ Flavour	Nicotine (mg/mL)	PG/VG Content (%)
1	Beard	No. 64 (Blue raspberry)	3	70% VG
2	Beard	No. 64 (Blue raspberry)	12	70% VG
3	Everest	Cured Kentucky Tobacco Leaf	0	n.a.
4	Everest	Black Honey Hookah Tobacco	18	n.a.
5	Vuse	Original	48	PG and VG
6	Vuse	Menthol	48	PG and VG
7	Njoy	Vanilla bean	15	50% PG / 50%VG
8	Njoy	Menthol	15	50% PG / 50%VG
9	Velvet Cloud	Vanilla custard	6	90%+ VG
10	Midas	Cinnamon Roll	12	60% VG
11	Boosted	B.O.V. (Tropical fruit medley)	0	60% VG
12	Boosted	B.O.V. (Tropical fruit medley)	18	60% VG

Notes: VG = vegetable glycerine; PG = propylene glycol.
% nicotine (w/v) converted to mg nicotine/ml e-liquid; n.a. = not available.

Table 2
MAO-A and MAO-B inhibition of the 12 tested e-liquid flavours, with calculated inhibitory concentrations at 50% (IC_{50}). Products are listed in ascending order of their respective MAO-A inhibitory activity.

	MAO-A Inhibition Ranking	Sample ID or E-Liquid No.	Maximal % MAO-A inhibition	Maximal % MAO-B inhibition	IC_{50} for MAO-A (µL/mL)[a]	IC_{50} for MAO-B (µL/mL)
Controls	–	Negative Control (PO_4 buffer)	0%	0%	na	na
	–	Negative Control (VG)	0%	0%	na	na
	–	Negative Control (PG)	0%	0%	na	na
	–	Nicotine, 30 uM	0%	0%	na	na
Low MAO Inhibitory Activity	1	Njoy menthol (8)	0%	24%	nd	nd
	1	Cured Kentucky Tobacco Leaf (3)	14%	24%	nd	nd
	2	Vuse original (5)	33%	28%	nd	nd
	2	Vuse menthol (6)	42%	42%	nd	nd
Moderate to High MAO Inhibitory Activity	3	Vanilla custard (9)	> 50%	> 50%	2.5	3.5
	3	Black Honey Hookah Tobacco (4)	> 50%	> 50%	2.2	4.5
	4	B.O.V. (tropical fruit medley) (12)	> 50%	> 50%	1.4	3.4
	4	B.O.V. (tropical fruit medley) (11)	> 50%	> 50%	1.1	1.9
	5	Blue raspberry (2)	> 50%	> 50%	0.82	1.0
	5	Blue raspberry (1)	> 50%	> 50%	0.81	1.3
	5	Cinnamon Roll (10)	> 50%	> 50%	0.70	1.3
	5	Vanilla bean (7)	> 50%	> 50%	0.50	1.7

[a] IC_{50} values were produced using a standard 4-parameter fit (Graphpad Prism). R^2 values ranged from 0.77 to 0.99. na = not applicable; nd = not determined.

3. Results

3.1. MAO-A and MAO-B inhibitory activity of the e-liquids

Repeatable results were generated for each of the samples. Under the concentrations used, the contribution of intrinsic fluorescence of the e-liquids was found to be minimal. Neither the buffer, the carrier liquids, nor the nicotine inhibited MAO-A or -B under the conditions used.

Of the e-liquids tested, four (e-liquid No. 3, 5, 6 and 8; see Table 2) contained only weak inhibitory activity, insufficient to allow estimation of an IC_{50} value. Results for these four samples are shown as a % inhibition of MAO enzymes when tested at 1% of total volume in the reaction mix.

The results for the remaining, more strongly inhibitory samples, are also shown in Table 2. For each of these samples, inhibition of more than 50% was observed and an IC_{50} value could be produced, expressed as the µL of undiluted sample per mL of reaction mix required to cause 50% inhibition of the enzyme.

3.2. Identification of vanillin and ethyl vanillin as monoamine oxidase inhibitors

Of the four e-liquids examined initially, two chromatographic peaks stood out as potentially causing the MAO inhibition. Candidate peaks were identified by mass spectrometry as vanillin (CAS # 121-33-5) and ethyl vanillin (CAS # 121-32-4). Comparison of retention times and mass spectra of standards matched with peaks found in the e-liquids.

MAO inhibition tests of propylene glycol (PG) solutions containing vanillin or ethyl vanillin across a concentration range of 0.1–20.1 mg/mL revealed almost identical concentration-response curves for MAO-A inhibition, for each component (Fig. 1A).

Both vanillin and ethyl vanillin were clear MAO-A inhibitors with half maximal inhibition reached when each compound was present at approximately 2.5 µg/mL (17 µM and 15 µM respectively). In comparison, the IC_{50} for harman, the known MAO inhibitor found in tobacco, is 0.31 µM, under the same test conditions. Similar, but less potent inhibition, was seen when vanillin and ethyl vanillin were each tested for inhibition of MAO-B (Fig. 1B).

Typical concentration-response curves for two strongly inhibitory e-liquids (no. 7 and 10) one slightly inhibitory e-liquid (no.6) and one marginally inhibitory e-liquid (no. 3) are shown in Fig. 2 for comparison.

Table 3 lists the e-liquids in order of decreasing MAO-A inhibitory activity, along with their flavour and nicotine content. The first column shows the degree of MAO inhibitory activity, where higher numbers denote stronger inhibitory activity. Where the numbers are the same, the inhibitory activity was not significantly different.

Once vanillin and ethyl vanillin had been identified as MAO inhibitors we then tested each of the e-liquids for the relative amounts of each of the two inhibitors. All e-liquids with high MAO inhibitory generally contained both of these compounds. Some of the e-liquids with lower MAO inhibition only contained lower levels of ethyl vanillin or neither compound.

Relative peak areas of vanillin and ethyl vanillin in each e-liquid are shown in the Supplementary Figure.

Six products classified with high MAO inhibition in Table 2, including vanilla bean (7), cinnamon roll (10), blue raspberry (1, 2) tropical-fruit medley (11, 12) contained vanillin and ethyl vanillin. Two e-liquids with moderate inhibition also contained both vanillin and ethyl vanillin; vanilla custard (9) and Black Honey Hookah Tobacco (4) that contained ethyl vanillin with relatively lower levels of vanillin. Four products with low MAO inhibition (Table 2), included the menthol, original and tobacco-flavoured e-liquids which generally lacked or contained extremely low levels of vanillin. Njoy Menthol (8) contained extremely low levels of both compounds. Vuse 0riginal (5) and Menthol (6) contained very low levels of ethyl vanillin. Cured Kentucky Tobacco Leaf (3) and lacked both vanillin and ethyl vanillin.

The ranked MAO inhibitory activity (Tables 2 and 3) corresponded well with the relative vanillin content (rs (Spearman) = 0.92) but less well with the relative ethyl vanillin content (rs (Spearman) = 0.87). However the correlation was greatest when the relative peak areas for vanillin and ethyl vanillin for each e-liquid were added (rs (Spearman) = 0.975; $p < 0.0001$).

Vanillin, ethyl vanillin, and the e-liquids inhibited MAO-A slightly more than MAO-B (Figs. 1 and 2).

4. Discussion

Results of this study show unequivocally that some e-liquids contain

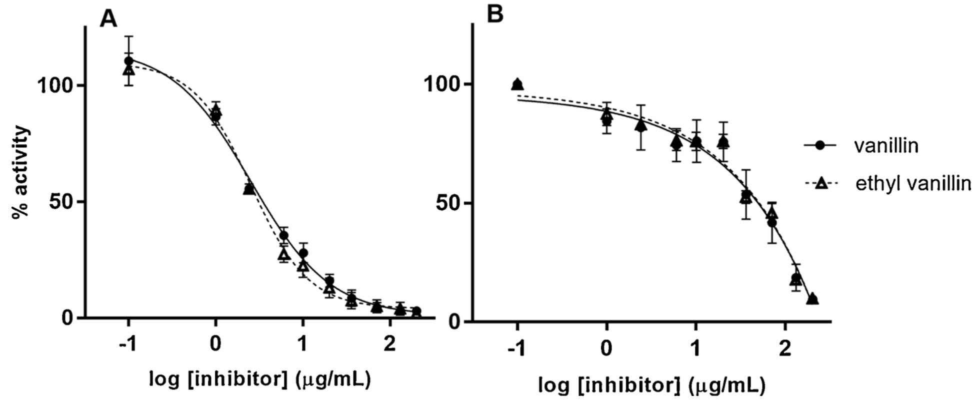

Fig. 1. Concentration: response curve for inhibition of A: MAO-A and B: MAO-B by vanillin and ethyl vanillin (μg or μL/mL in reaction mix). Points are shown as ± S.E.M.

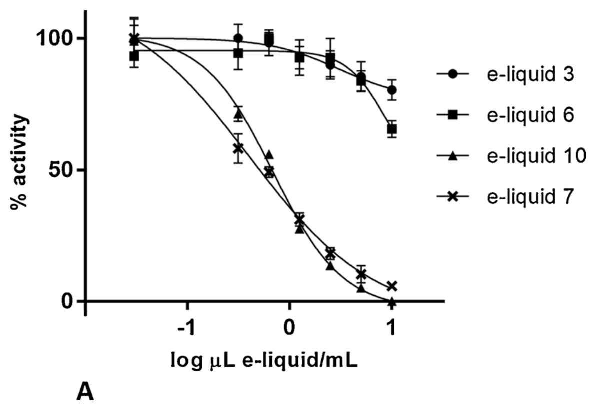

Fig. 2. A: Concentration: response curve for inhibition of MAO-A by four e-liquids (μL undiluted e-liquid/mL reaction mix). Points are shown as ± S.E.M. **B**: Concentration: response curve for inhibition of MAO-B by four e-liquids (μL undiluted e-liquid/mL reaction mix). Points are shown as ± S.E.M.

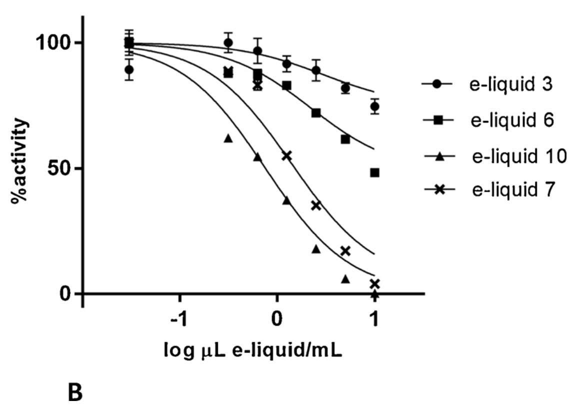

Fig. 2. (*continued*)

MAO-A and MAO-B inhibitory activity and identifies two widely-used e-liquid flavouring components, vanillin and ethyl vanillin (Hutzler et al., 2014) as MAO inhibitors.

The inhibition seen bore no relationship to the nicotine concentration, but was clearly related to the amount of vanillin and ethyl vanillin present. To the best of our knowledge, vanillin is not a recognized inhibitor of MAO enzymes, but is a product of the deamination of vanillylamine (4-hydroxy-3-methoxy-benzylamine) by monoamine oxidase enzymes (Gupta and Steiner, 1985) and might be expected to interact with the enzymes and compete with substrate for the active site.

Neither vanillin nor ethyl vanillin was detected in e-liquid 3 (Cured Kentucky Leaf flavour) but this sample did contain some inhibitory activity, possibly a result of the inhibitors that are in tobacco being carried over with the tobacco flavouring, or from other unidentified additives. However, inhibitory activity was highest in non-tobacco flavours.

Table 3
A comparison of the MAO-A inhibitory activity and nicotine content of twelve e-liquids.

Relative MAO-A inhibitory activity	Flavour (E-Liquid No.)	Stated nicotine conc. (mg/mL)
5	Vanilla bean (7)	15
5	Cinnamon Roll (10)	12
5	Blue raspberry (1)	3
5	Blue raspberry (2)	12
4	Tropical fruit medley (11)	0
4	Tropical fruit medley (12)	18
3	Black Honey Hookah Tobacco (4)	18
3	Vanilla custard (9)	6
2	Menthol (6)	48
2	Original (5)	48
1	Cured Kentucky Tobacco Leaf (3)	0
1	Menthol (8)	15

There was no correlation between inhibitory activity and stated nicotine content (rs (Spearman) = - 0.221; p = 0.485).

There was no indication that the carrier liquids affected the results obtained here. Ethanol is present in some e-liquids, and is capable of affecting enzyme activity once it reaches concentrations greater than 1% in the final reaction mix (20–30% inhibition at 4% ethanol). Since all of the e-liquids were measured at a maximum concentration of 1% in the reaction mix, any ethanol present in the e-liquids is unlikely to have affected the results. pH can also affect enzyme activity, and we did find that it was important to increase the buffer strength in order to obtain reliable results.

Erythropel et al. (2018) have recently shown that flavour compounds are commonly converted to propylene glycol acetals in e-liquids. Our methods would have detected the parent compounds only, and the MAOI activity of the acetal derivatives is unknown.

Vanillin and ethyl vanillin are common ingredients of e-liquids (Hutzler et al., 2014). The addition of popular flavours introduced by the manufacturers may enhance enjoyment of e-cigarettes but may also may result in MAO inhibition, as suggested in this study. The correlation between the inhibitory activity and the presence of vanillin and ethyl vanillin was robust, and all of the activity seen in the e-liquids, other than a small contribution most likely to be from tobacco flavours, could be explained by the presence of vanillin and ethyl vanillin. It remains possible that other flavourings could have made a contribution to the activity seen.

From the MAO inhibition, we estimated the amount of vanillin compounds (the sum of vanillin plus ethyl vanillin) present in the most strongly inhibitory e-liquid (No 7, vanilla bean, IC_{50} 0.5 μL/mL) at approximately 5 mg/mL, by comparison of the IC_{50} of vanillin and ethyl vanillin (both 2.5 mg/mL) and the IC_{50} of this e-liquid.

Given the proposed link between MAO inhibition and tobacco dependence, there are significant potential consequences of the presence of MAO inhibitors in e-liquids. If the amount of inhibitory activity seen is sufficient to produce a physiological effect, this could create a situation where some e-cigarette flavour combinations are more reinforcing and thus more addictive than others, and this could be subject to manipulation either by the ENDS users, in searching for a more satisfying experience, or by the manufacturers.

The question remains as to whether this activity is sufficient to have a measurable physiological effect during ENDS use. In tobacco smoking, physiological plasma concentrations of nicotine of around 0.2 μM are observed (Benowitz, 2009; Lewis et al., 2012) making it is possible to calculate the expected concentration of a known inhibitor in tobacco smoke (given reasonable assumptions as to its uptake and metabolism in the body) once nicotine has reached that physiological concentration (Truman et al., 2017). However, in e-liquids, there is no association between nicotine level and MAO inhibition. Although, nicotine concentration varies widely amount e-liquid brands, specific concentration of flavor components, for a given flavor/brand combination, is expected to stay constant. Thus, ENDS users, using zero nicotine or low nicotine concentration e-liquids, may intake a larger volume of e-liquid aerosol over a short time-frame, with correspondingly greater MAO inhibition, without experiencing any effects from nicotine. ENDS users using high nicotine concentrations, on the other hand, tend to use less e-liquid (Dawkins et al., 2018; Truman et al., 2018) and would be expected to experience less MAO inhibition for a similar flavour formulation.

Whether any overt inhibition of MAO-A and -B occurs as a result of consuming e-liquids containing this amount of MAO inhibitory activity would depend on the amount of e-liquid being used, the uptake of the inhibitor, its half-life and its distribution in the body. The amount of inhibitory activity seen in the most MAO inhibitory e-liquid was approximately half of that measured in tobacco smoke, per mg of nicotine (Truman et al., 2017) if the e-liquid contained nicotine at 2 mg/mL (the lowest nicotine concentration commonly sold). By analogy with tobacco smoking, then, it is possible that the amount of MAO inhibitory activity that ENDS users experience could have a physiological effect under real conditions of ENDS use. It is possible that other products, not included in this small sample, may contain even higher concentrations of vanillin or ethyl vanillin and possible other active ingredients.

MAO inhibition could be determined experimentally. As a first approximation, the results reported here suggest that if vanillin or ethyl vanillin were able to reach 1 μg/mL in the body, inhibition of MAO enzymes would be measurable and at 10 μg/mL substantial inhibition would be observed. Thus, it may be possible to infer an inhibitory effect on MAO enzymes by measurement of vanillin concentrations in the blood after ENDS use, particularly if short-term, peak concentrations of the inhibitors reach the enzyme systems.

After smoking, MAO-B activity in platelets in smokers was found to be inhibited (Rommelspacher et al., 2002). A research group has similarly reported a significant reduction in rat brain MAO activity in vitro on treatment with physiologically relevant amounts of a tobacco smoke preparation (Costello et al., 2014). Thus, it may be possible to directly test the effect of vanillin and ethyl vanillin by measuring changes in platelet MAO activity from volunteer subjects using e-cigarettes, or in rat brains after administration of vanillin/ethyl vanillin.

It will be important to determine whether strong MAO inhibitory activity is as common in e-liquids as this small study indicates, and to find out whether ENDS users do, in practice, experience measurable MAO inhibition when they use these products. A survey of a wider range of e-liquids, using a quantitative analytical method, is needed to determine the prevalence and concentrations of vanillin and ethyl vanillin in commonly available e-liquids. Other flavorants could prove to be MAO inhibitors also.

These results suggest that some flavouring compounds in e-liquids may strengthen dependence or addiction to the drugs that they may contain. Further research is needed to better understand the public health implications of MAO inhibition for addiction and cessation aspects of ENDS use.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, or the U.S. Department of Health and Human Services.

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Declaration of Competing Interest

P Truman was a member of the New Zealand Ministry of Health Technical Advisory Group on e-cigarette regulation (2017–2018).

The authors have no other conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2019.09.010.

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