Preliminary investigative analysis of flavor compounds crossing blood-brain barrier using computational models

CENTER FOR TOBACCO PRODUCTS

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BACKGROUND

- Seizures have been reported for users of electronic nicotine delivery systems (ENDS), with many reports involving youth or young adults.
- Seizures are known potential side effects of nicotine toxicity and have been reported in the scientific literature in relation to intentional or accidental ingestion of e-liquids.[4]
- E-liquids and aerosols from ENDS contain many flavor compounds.[5]
- The blood-brain barrier blocks many deleterious compounds in the blood from entering the brain, but when harmful compounds cross the barrier, toxicity may occur.
- Flavor chemical ingredients, which have been previously reported to be found in popular ENDS refill liquids, were compared in terms of molecular structure and physiochemical properties to known neuroactive compounds in this study.

OBJECTIVES

- Apply computational modeling methods as non-testing screening tools to predict the potential of flavor compounds to penetrate the blood-brain barrier or flag for central nervous system (CNS) activity in order to prioritize compounds for further investigation, including potential *in vitro* or *in vivo* research.
- Screen flavor compounds in ENDS pods for potential CNS toxicity.

OVERVIEW

Data Mining & Compilation
Compounds from Published ENDS Pods Literature[5]
Neuroactive compounds data

Curate Data
Validate chemical structure, CASRNs, Name

Computational Platforms
Canvas/Maestro
ADMET Predictor

Predictive Computational Screening Models
Penetration of Blood-Brain Barrier
Structural Similarity
CNS Activity

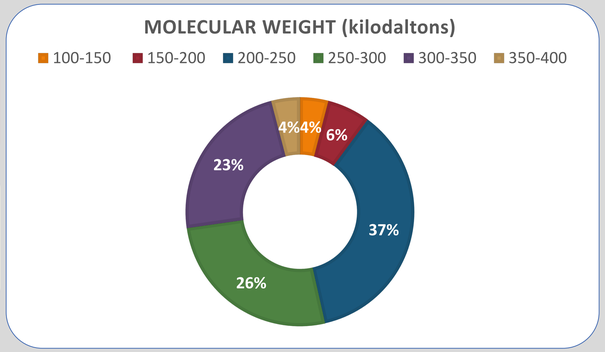
METHODS

- Conducted a literature search to determine flavor compounds documented in ENDS pods, compounds not known to be found in tobacco products but are known to be neuroactive as well as known compounds found in tobacco products (including nicotine).[3,5-6]
- In silico: Conducted chemical structure-based computational toxicology assessments using software's that are licensed to CTP-OS including Canvas (v4.1)/Maestro (v12.1) with QikProp and ADMET Predictor (v9.0) models to predict structural similarity, CNS activity and penetration potential to cross the blood-brain barrier.

Dataset of 70 Unique Compounds

37 Flavor Compounds in ENDS Pods

33 Neuroactive Compounds

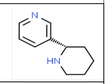


Flavor compounds in ENDS pods and neuroactive compounds were identified in the literature. Neuroactive compounds are known to affect the CNS in humans and rodents as well as known neuroactive amino acids. The blood-brain barrier has a size threshold of 400 kilodaltons that limits penetration potential.

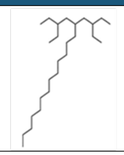
Summary Data of Flavor Compounds in ENDS Pods and Neuroactive Compounds

Filters	Minimum	Average	Maximum	Standard Deviation
Molecular weight	86.09	114.80	410.73	80.29
ALogP	-2.94	2.32	12.69	3.01
HBA	0	2.11	8	1.82
HBD	0	0.89	6	1.09
Aromatic rings	0	0.45	4	0.94
Tertiary amines or amides	0	0.25	3	0.79
Rotatable bonds	0	2.56	24	5.33

MW (<400kDa), lipophilicity (>0), high BBB prediction, CNS activity (+ value)

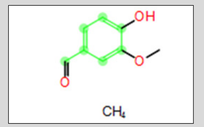
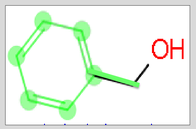
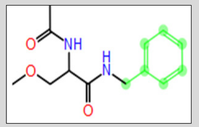
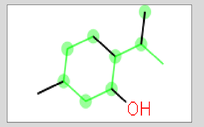
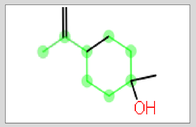
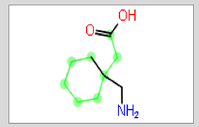
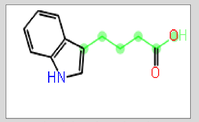
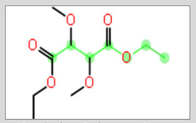
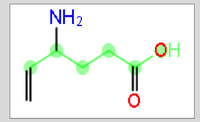
Aromatic ring and tertiary amine	Without aromatic ring with tertiary amine	
Neuroactive Compounds	Flavor Compounds and Other Ingredients in ENDS Pods[5]	
nicotine 	cis-beta-terpineol 	(S)-(-)- anabasine 
clobazam 	benzoic acid 	menthol 
chloropromazine 	benzyl alcohol 	menthol derivative 

CNS activity (+ value), high BBB coefficient, high [brain/blood]

heptacosane	3-ethyl-5-(2-ethylbutyl)octadecane 

Structural Motifs in ENDS Flavor Compounds Similar to Neuroactive Compounds

CASE EXAMPLES of COMMON SUBSTRUCTURES

Flavor Compounds in ENDS Pods		Neuroactive Compounds
 vanillin	 benzyl alcohol	 lacosamide
 menthol	 cis-beta-terpineol	 gabapentin
 methyl (3*R*)-3-hydroxy-4-[(2-methylpropan-2-yl)oxy]butanoate	 indole-3-butyric acid	 vigabatrin

SUMMARY and CONCLUSIONS

- This is the first known study to examine the utility of computational toxicology tools focused on comparing flavor compounds in ENDS pods and neuroactive compounds.
- All but one compound was less than 400 kilodaltons suggesting that the analyzed flavor compounds have low enough molecular weight to penetrate the blood-brain barrier.
- Lipophilicity is a common feature of flavor and neuroactive compounds due to the average LogP value, thus suggesting penetration potential of the blood-brain barrier.
- Interestingly, there are 12 flavor compounds that fit parameters to penetrate the blood-brain barrier while nicotine was the only compound found in ENDS pods that also fit the aromatic ring with tertiary amine criteria.
- There are structural motifs in ENDS flavor compounds that are similar to neuroactive compounds based off a computational analysis of common substructures.
- Most, if not all, filters examined in this study are for lipid-mediated free diffusion and do not take into account transporter-mediated potential which can be addressed with future studies.
- It is of interest to take advantage of computational models for early identification, signal detection and screening of potential CNS toxicity of flavor compounds in ENDS.
- Compounds predicted *in silico* to penetrate the blood-brain barrier with have high CNS activity can be scrutinized in research for potential toxicity.
- These *in silico* tools can help to prioritize compounds for further research.

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