Review Article

Health Risks and Concerns Associated with E-cigarettes (ECs) and Heated Tobacco Products (HTPs): A Comprehensive Review

Sombat Muengtaweepongsa

Introduction

E-cigarettes (ECs) and heated tobacco products (HTPs) are alternatives to traditional combustible cigarettes and operate on different principles. ECs, also known as electronic cigarettes or vapes, heat a liquid, often called e-liquid or vape juice, to produce an aerosol that users inhale. The e-liquid typically contains a base chemical such as propylene glycol (PG) or vegetable glycerin (VG), a carrier for nicotine, flavorings and other additives. When the liquid is heated, it vaporizes, creating an aerosol that users inhale into their lungs. ECs come in various forms and designs. Initially, cigar-like devices resembled traditional cigarettes in size and shape. These early models were often low-power and disposable. Additionally, small devices using high-concentration nicotine salt pods gained popularity, as did disposable ECs discarded after use.[1] On the other hand, HTPs heat specially designed sticks or cartridges of processed tobacco, usually at lower temperatures than traditional combustion. This process, called pyrolysis, releases the active compounds in the tobacco, which are then inhaled as an aerosol by the user.[2]

While ECs and HTPs are considered alternatives to smoking, they still carry potential health risks. The long-term effects of using these products are still being studied, and their use among certain populations worldwide, including Thailand, such as youth and non-smokers, is a concern.[3-5] According to the National Health and Nutrition Examination Survey (NHANES) data from 2013 to 2014, the prevalence of ECs/HTPs use among adolescents in the United States was reported to be 1.21%. It was estimated that this percentage represented around 236,000 U.S. adolescents.[6]

The typical ECs/HTPs liquid composition, consisting of various substances, are found in vaping aerosols. ECs/HTPs liquid, used to create the aerosol vapor in ECs/HTPs, consists of several components. The solvent carriers comprise the most liquid, usually propylene glycol (PG) and/or vegetable glycerin (VG). These solvents help create the aerosol when heated. In ECs/HTPs liquid, water is also found in smaller proportions (around 20%).[7] Flavoring substances are added to enhance the taste of the aerosol vapor and generally account for approximately 10% of the ECs/HTPs liquid composition. Nicotine, the addictive component of tobacco products, is typically included in ECs/HTPs liquid, albeit at varying concentrations. It's important to note that nicotine levels in ECs/HTPs liquid can vary widely depending on the product and user preferences. When ECs/HTPs liquid is heated and vaporized, it forms vaping-derived aerosols, which the user inhales. The aerosols contain the constituents of the ECs/HTPs liquid that may be concerning from a health perspective. These include

Faculty of Medicine, Thammasat University, Pathum Thani, 12121, Thailand

formaldehyde and acrolein, produced as byproducts of the heating process and can harm health.[8] Additionally, vaping-derived aerosols may contain trace amounts of potentially harmful substances, such as heavy metals (e.g., lead, cadmium), phenolic compounds and polycyclic aromatic hydrocarbons (PAHs). These substances can be present due to various factors, including the materials used in the ECs/HTPs device and the heating process.[9, 10]

Of the reported health risks, several cross-sectional studies of teenagers have found associations between ECs/HTPs use, increased risks of bronchospasm symptoms and asthma-related school absenteeism.[11, 12] These studies suggest that there may be a link between ECs/HTPs use and negative respiratory health outcomes in young people. Furthermore, similar associations between ECs/HTPs use and self-reported chronic respirational disorders have been described in adults.[13] This indicates that the potential respiratory risks associated with ECs/HTPs may extend beyond the adolescent population. When it comes to clinical trials specifically focusing on the respiratory changes resulting from ECs/HTPs exposure, the results have been mixed. Some early studies have not found impaired pulmonary outcomes.[14,15] However, latter studies reported significant lung damage following ECs/HTPs use.[16, 17]

Significant concern has arisen due to the increased incidence of a condition known as ECs or vaping product use-associated lung injury (EVALI). EVALI is a severe lung injury recognized as a nationwide outbreak in the United States. This outbreak has raised significant alarm about the potential acute respiratory risks of ECs/HTPs use. [18]

Increasing evidence suggests a potential link between using ECs/HTPs and adverse effects on cardiovascular health. Several studies have indicated an association between ECs use and an increased risk of cardiovascular diseases, including myocardial infarction.[19] Numerous studies have focused on investigating the acute effects of ECs/HTPs on vascular function using different biomarkers. These biomarkers include flow-mediated dilation, circulating endothelial progenitor cells, pulse wave velocity and others. The findings from these studies have provided evidence indicating that ECs/HTPs use can cause vascular harm. The observed transient abnormalities in these biomarkers may be attributed to the pharmacological effects of nicotine. Nicotine is a vasoactive substance found in ECs/HTPs aerosols and it can constrict blood vessels and affect endothelial function, thereby impairing vascular health. The presence of nicotine in ECs/HTPs aerosols has been associated with hemodynamic instabilities following acute exposure, such as increased pulse rate, elevated blood pressure and cardiac sympathetic activation. These findings suggest that the adverse cardiovascular effects associated with its use, such as changes in vascular function and hemodynamics, may be influenced by the presence of nicotine. Nicotine, an addictive substance, is known to have various physiological effects on the cardiovascular system. Its stimulant properties can lead to increased pulse rate and blood pressure and activation of the sympathetic nervous system, which controls the body's "fight or flight" response.[20, 21]

ECs/HTPs in traditional smoking cessation

Many ECs/HTPs advertising campaigns claim that they can help individuals quit smoking. However, the effectiveness of ECs/HTPs as a smoking cessation tool is a topic of ongoing debate and research. While some studies have found that ECs/HTPs with nicotine can help manage withdrawal symptoms during quit attempts, it is important to note that this does not automatically translate into long-term smoking cessation success.[22] Quitting smoking is a complex process involving more than managing withdrawal symptoms. It often requires a structured plan, behavioral support and a comprehensive approach to address addiction's psychological and social aspects.[23]

Moreover, research has shown a tendency toward dual use of ECs/HTPs and conventional cigarettes rather than complete substitution or cessation of smoking. This means many individuals who start using ECs/HTPs continue to smoke traditional cigarettes alongside ECs use. A cross-sectional study using The National Health and Nutrition Examination Survey (NHANES) database of the US population from 2015 to 2018 showed that dual smoking was the highest among the smoking population at 61%, while the ECs and traditional were 10 and 30%, respectively.[24]

It is crucial to consider that scientific understanding of ECs/HTPs and their efficacy as smoking cessation tools is evolving. While some studies suggest potential benefits in certain contexts, others have raised concerns about the long-term health effects and the impact of ECs/HTPs on overall smoking behaviors.

ECs/HTPs as a risk of stroke

The Behavioral Risk Factor Surveillance System (BRFSS), an annual survey conducted by the Centers for Disease Control and Prevention (CDC) to collect data on various health-related behaviors and chronic conditions among adults in the United States, reported that ECs/HTPs use leads to increased risk of not only myocardial infarction but also stroke.[25]

The experimental animal study showed that acrolein in ECs/HTPs products could trigger NOX-2 -driven oxidative stress in the cerebrovascular system, leading to inflammation. This implies a potential mechanism through which ECs/HTPs use, specifically the presence of acrolein, may contribute to cerebrovascular diseases.[26]

The NHANES cross-sectional study from 2015 to 2018 showed that individuals who use ECs/HTPs have 1.15 times higher odds of having a stroke history than traditional smokers. Similarly, individuals who use both ECs/HTPs and traditional cigarettes (dual smokers) have 1.14 times higher odds of having a stroke history than traditional smokers.[24] Another cross-sectional study using the NHANES database during a similar period showed that current ECs/HTPs use is associated with elevated triglycerides and reduced HDL-cholesterol. Moreover, former ECs/HTPs use is associated with elevated fasting glucose, reduced HDL-cholesterol and elevated blood pressure. Also, dual users have higher odds of having metabolic syndrome than never-smokers. They also have elevated triglycerides and reduced HDL-cholesterol compared to never-smokers. Furthermore, dual users are likelier to have metabolic syndrome and reduced HDL-cholesterol than exclusive traditional cigarette users.[27]

Another retrospective cross-sectional study based on the NHANES database from 2013 to 2018 showed that ECs/HTPs use is associated with higher odds of cerebrovascular disease or stroke when compared to other substance use disorders. According to the study, ECs/HTPs use is associated with an odds ratio of 2.03, suggesting that individuals who use ECs/HTPs have more than twice the odds of experiencing cerebrovascular disease or stroke compared to individuals with other substance use disorders.[28]

ECs/HTPs as brain toxicity

ECs and HTPs use remain a relatively recent phenomenon and scientific research often requires time to catch up with emerging trends and technologies. While awareness of the potential hazards associated with ECs and HTPs usage is growing, understanding its brain-toxic effects remains limited.[29] However, a few studies have specifically addressed the brain toxicity of ECs/HTPs, particularly in brain development. An animal study demonstrated that dams (mother mice) were exposed to ambient air and ECs/HTPs aerosols, with some aerosols containing nicotine and others without nicotine. The exposure occurred during and after pregnancy. Offspring from dams exposed to ECs/HTPs aerosols showed deficits in short-term memory compared to offspring exposed to ambient air. This suggests that maternal ECs/HTPs exposure negatively impacted the offspring's cognitive abilities. The study suggests that the observed memory deficits in the offspring were likely caused by nicotine, as the effect was stronger when compared to the group exposed to ECs/HTPs aerosols without nicotine. Interestingly, both groups exposed to ECs/HTPs aerosols, with and without nicotine, showed reduced anxiety levels, as observed in elevated plus maze tests. This implies that other constituents in ECs/HTPs aerosols might have brain-toxic effects related to anxiety regulation.[30]

Exposure to nicotine-free ECs/HTPs aerosols was found to increase global DNA methylation soon after birth significantly. This suggests that the aerosols, even without nicotine, impacted epigenetic modifications (chemical modifications to DNA) that can influence gene expression and cellular function. The study also indicates that the exposure affected histone acetyltransferases, enzymes involved in gene regulation. Additionally, changes were

observed within genes linked to neurological activity, suggesting potential effects on brain function and development.[31]

Numerous studies highlight the potential toxicity of solvent carriers, such as propylene glycol (PG) and vegetable glycerin (VG), in ECs/HTPs liquids. As mentioned earlier, solvent carriers, specifically PG and VG, make up a significant proportion (> 3/4) of the e-liquid used in e-cigarettes. These solvents are responsible for creating the aerosol when heated. When heated in an ECs device at temperatures ranging from 150 to 350 °C, both PG and VG undergo pyrolysis, producing mist or aerosol. This aerosol contains various toxic carbonyl compounds, including acrolein, acetaldehyde and formaldehyde.[32] The carbonyl compounds generated during vaping, particularly formaldehyde, are associated with neurotoxic effects. Formaldehyde is a known environmental neurotoxicant linked to neurodegeneration. At high voltages (e.g., 5V), formaldehyde can react with ECs/HTPs solvents to form potentially toxic formaldehyde hemiacetal.[33] Acrolein, another carbonyl compound found in ECs aerosols, is a common environmental pollutant known for its pro-inflammatory and pro-oxidative properties. It has been linked to neurodegeneration.[34] Acetaldehyde, also present in EC aerosols, has been shown to exhibit neurotoxic effects through mechanisms such as oxidative stress, calcium dyshomeostasis and activation of NMDA receptors.[35] Pyrolysis of solvent carriers in ECs/HTPs vapor can produce other hazardous compounds. For example, glycidol is considered a developmental neurotoxicant. Compounds like glyoxal and methylglyoxal also act as potent glycating agents that contribute to developing advanced glycation end-products (AGEs) linked to neurodegeneration.[36]

Vitamin E acetate has been detected in most tetrahydrocannabinol (THC)-containing products and lung fluid samples from patients with EVALI.[37] This suggests a possible link between vitamin E acetate and the occurrence of this vaping-related illness. According to the U.S. Food and Drug Administration (FDA) reports, outbreak-associated THC products have been found to contain vitamin E acetate at an average concentration of 50%, ranging from 23% to 88%.[38] It is used as a solvent for THC due to its similar viscosity. Vitamin E acetate is commonly used in dietary supplements and cosmetics and when ingested, it has not been associated with adverse health outcomes. It is generally recognized as safe (GRAS) for ingestion. However, the safety profile of vitamin E acetate inhalation, particularly in aerosolized forms like those found in ECs/HTPs, is poorly understood. There is a lack of studies investigating the effects of inhaling aerosolized vitamin E acetate specifically. In animal studies conducted with rats, it has been observed that inhalation of vitamin E acetate did not have the same protective effect as vitamin E in attenuating the inflammatory response to bacterial lipopolysaccharide toxicity in the lungs. This suggests that there may be differences in the effects of vitamin E acetate when inhaled compared to other forms of vitamin E.[39] Additional research is necessary to examine the potential health effects of inhaling aerosolized vitamin E acetate and its lung and other organs toxicity. The safety and risks associated with its inhalation are still not well understood.

Flavorings are crucial in attracting ECs/HTPs users, including youth and individuals with little or no smoking experience. Flavored products are more likely to initiate vaping among these populations. A recent study suggests that popular flavor substances in ECs/HTPs may trigger a reward mechanism in mice, indicating their potential role in enhancing the pleasurable experience of vaping.[40] Flavorings in ECs/HTPs have become a major focus for regulatory authorities due to concerns raised by the outbreak of EVALI and fatal cases, particularly among young ECs/HTPs users. [41] This has prompted increased attention to regulating the availability and use of flavored products. Hundreds of flavor substances have been detected in e-liquids, with some in most commercial ECs/HTPs products. While flavorants used in food products are GRAS, their aerosolized and inhaled safety is often poorly understood. Most flavor substances have only been tested for safety through ingestion and chronic exposure and their potential risks when inhaled as aerosols are often unrecognized.[42] Multiple studies have suggested that the high number and concentration of flavor substances in e-liquids are critical for their cellular and brain toxicity[42, 43] However, no differences in neurobehavioral outcomes have been observed among various flavors in mice.[30] Currently,

research is lacking in addressing the brain toxicity of ECs/HTPs -derived flavoring substances.

Various organic compounds, including toluene, p,m-xylene, ethyl acetate, benzene, ethanol and methanol, have been found in e-liquids. Some of these compounds have been detected in e-liquids at levels exceeding established safety limits, indicating potential health risks associated with inhalation.[44] It's important to note that these organic compounds in e-liquids raise concerns about potential health risks, including brain toxic effects. Further research is needed to understand better the extent of exposure and the specific health implications of these compounds when inhaled through ECs/HTPs. Regulatory authorities and scientific communities continue to investigate and assess the safety of these substances in relation to ECs/HTPs use.

Several brain-toxic heavy metals, including arsenic (As), cadmium (Cd), lead (Pb), manganese (Mn), zinc (Zn), nickel (Ni), aluminum (Al), tin (Sn), chromium (Cr) and copper (Cu), have been found in ECs/HTPs vapors.[45] These metals primarily originate from components of the ECs/HTPs atomizer, such as the metallic coil, but may also be present in e-liquids. ECs-derived metals can contribute to an overall increase in the body's internal dose of these metals. Studies have demonstrated increased internal doses of chromium (Cr), nickel (Ni), cadmium (Cd) and lead (Pb) among its users.[46] ECs users have been found to have higher serum levels of selenium (Se), silver (Ag), vanadium (V), lanthanides and other rare earth elements.[47] Many metals detected in ECs/HTPs vapors exhibit brain-toxic properties when inhaled, indicating potential risks to the nervous system.[29]

All potential brain toxicity caused by e-cigarettes (ECs) and heated tobacco products (HTPs) is shown in Figure 1.

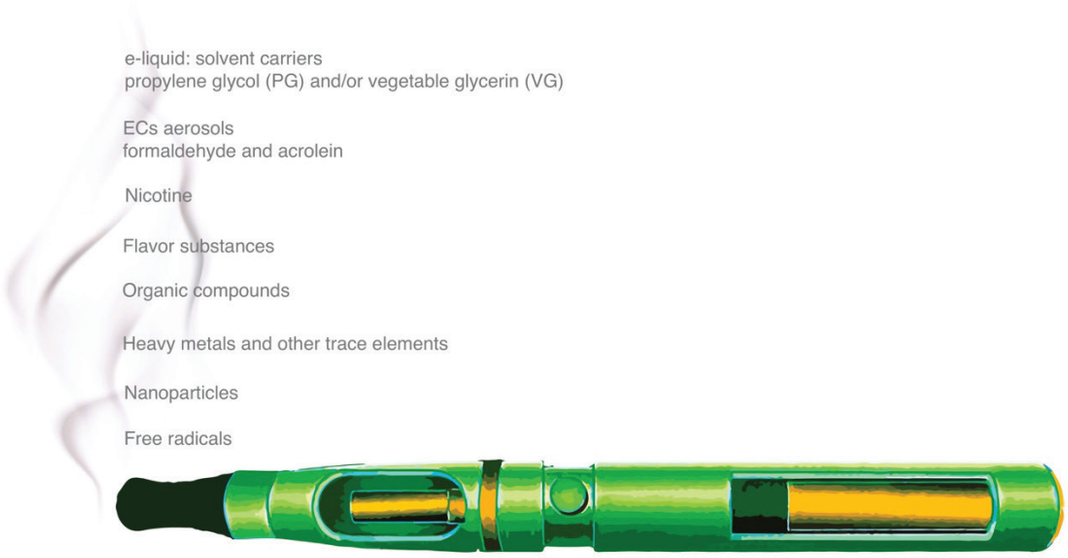

Figure 1 Potential brain toxicity caused by e-cigarettes (ECs) and heated tobacco products (HTPs)

Conclusions

E-cigarettes (ECs) and heated tobacco products (HTPs) are alternative products to traditional combustible cigarettes that operate on different principles. ECs heat a liquid to produce an aerosol, while HTPs heat specially designed sticks or cartridges of processed tobacco. Both ECs and HTPs carry potential health risks and the long-term effects of their use are still being studied. Concerns exist about their use among certain populations, including youth and non-smokers. ECs/HTPs liquid composition typically includes solvents (propylene

glycol and vegetable glycerin), flavorings, nicotine and other additives. Heating the liquid can produce aerosols containing potentially harmful substances such as formaldehyde, acrolein, heavy metals, phenolic compounds and polycyclic aromatic hydrocarbons (PAHs). Studies have found associations between ECs/HTPs use and increased risks of respiratory symptoms, asthma-related school absenteeism and chronic respiratory disorders in both adolescents and adults. However, results from clinical trials focusing on respiratory changes resulting from ECs exposure have been mixed. The e-cigarette or vaping product use-associated lung injury (EVALI) outbreak raised significant concerns about the acute respiratory risks of ECs/HTPs use. Evidence suggests a potential link between ECs/HTPs use and adverse effects on cardiovascular health, including an increased risk of cardiovascular diseases such as myocardial infarction. The presence of nicotine in ECs/HTPs aerosols can contribute to vascular harm and adverse cardiovascular effects. The effectiveness of ECs/HTPs as a smoking cessation tool is still debated and many individuals tend to engage in dual use, using both ECs/HTPs and traditional cigarettes. ECs/HTPs use has been associated with an increased risk of stroke and cerebrovascular diseases. Acrolein, a compound found in ECs/HTPs products, may trigger oxidative stress and inflammation in the cerebrovascular system. Research suggests that ECs and HTPs use may have brain-toxic effects, including cognitive deficits, epigenetic modifications and potential neurotoxicity related to solvent carriers, such as propylene glycol and vegetable glycerin. The safety and risks of inhaling aerosolized vitamin E acetate, a substance found in some ECs/HTPs products, are poorly understood. Flavorings significantly attract ECs/HTPs users, particularly youth, but their safety when inhaled as aerosols is often poorly understood. The high number and concentration of flavor substances in e-liquids may contribute to cellular and brain toxicity.

References

1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. *Med J Aust.* 2023; 218: 267-275. 20230320. DOI: 10.5694/mja2.51890.
2. E-Cigarettes & HTPs, https://tobaccoatlas.org/challenges/e-cigarettes-htps/ (accessed June 7th, 2023).
3. Bhatt JM, Ramphul M and Bush A. An update on controversies in e-cigarettes. *Paediatric Respiratory Reviews.* 2020; 36: 75-86. DOI: https://doi.org/10.1016/j.prrv.2020.09.003.
4. Kasemsap C. E-cigarettes as Environmental, Safety, Laws and Economic Dimensions in Thailand. *KASEM BUNDIT JOURNAL.* 2018; 19: 92-107.
5. Onmoy P, Buarueang A, Paponngam C, et al. Factors Associated with Electronic Cigarette Smoking Behaviors of Adolescents in Uttaradit Province, Thailand. *Journal of Health Science.* 2022; 31: 197-205.
6. Jaber RM, Mirbolouk M, Defilippis AP, et al. Electronic Cigarette Use Prevalence, Associated Factors, and Pattern by Cigarette Smoking Status in the United States From NHANES (National Health and Nutrition Examination Survey) 2013-2014. *Journal of the American Heart Association.* 2018; 7. DOI: 10.1161/jaha.117.008178.
7. Tayyarah R and Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. *Regulatory Toxicology and Pharmacology.* 2014; 70: 704-710. DOI: https://doi.org/10.1016/j.yrtph.2014.10.010.
8. Offermann FJ. Chemical emissions from e-cigarettes: Direct and indirect (passive) exposures. *Building and Environment.* 2015; 93: 101-105. DOI: https://doi.org/10.1016/j.buildenv.2015.03.012.
9. Kaisar MA, Prasad S, Liles T, et al. A decade of e-cigarettes: Limited research & unresolved safety concerns. *Toxicology.* 2016; 365: 67-75. DOI: 10.1016/j.tox.2016.07.020.

10. Sleiman M, Logue JM, Montesinos VN, et al. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. *Environmental Science & Technology*. 2016; 50: 9644-9651. DOI: 10.1021/acs.est.6b01741.
11. Cho JH and Paik SY. Association between Electronic Cigarette Use and Asthma among High School Students in South Korea. *PLOS ONE*. 2016; 11: e0151022. DOI: 10.1371/journal.pone.0151022.
12. Kotoulas S-C, Katsaounou P, Riha R, et al. Electronic Cigarettes and Asthma: What Do We Know So Far? *Journal of Personalized Medicine*. 2021; 11: 723. DOI: 10.3390/jpm11080723.
13. Perez MF, Atuegwu NC, Mead EL, et al. Adult E-Cigarettes Use Associated with a Self-Reported Diagnosis of COPD. *International Journal of Environmental Research and Public Health*. 2019; 16: 3938. DOI: 10.3390/ijerph16203938.
14. Polosa R, Cibella F, Caponnetto P, et al. Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. *Scientific Reports*. 2017; 7. DOI: 10.1038/s41598-017-14043-2.
15. Boulay M-È, Henry C, Bossé Y, et al. Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. *Respiratory Research*. 2017; 18. DOI: 10.1186/s12931-017-0518-9.
16. Chaumont M, Borne Pvd, Bernard A, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 2019; 316: L705-L719. DOI: 10.1152/ajplung.00492.2018.
17. Meo SA, Ansary MA, Barayan FR, et al. Electronic cigarettes: impact on lung function and fractional exhaled nitric oxide among healthy adults. A*merican Journal of Men's health*. 2019; 13: 1557988318806073.
18. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products, https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html (accessed June 8th, 2023).
19. Fernandez de Bobadilla J, Dalmau R and Salto E. Cardiologists and electronic cigarettes. *Rev Esp Cardiol (Engl Ed)*. 2015; 68: 286-289. 20141230. DOI: 10.1016/j.rec.2014.08.014.
20. Carnevale R, Sciarretta S, Violi F, et al. Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. *Chest*. 2016; 150: 606-612. DOI: https://doi.org/10.1016/j.chest.2016.04.012.
21. Chatterjee S, Caporale A, Tao JQ, et al. Acute e-cig inhalation impacts vascular health: a study in smoking naïve subjects. *American Journal of Physiology-Heart and Circulatory Physiology*. 2021; 320: H144-H158. DOI: 10.1152/ajpheart.00628.2020.
22. Bullen C, McRobbie H, Thornley S, et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco Control*. 2010; 19: 98-103. DOI: 10.1136/tc.2009.031567.
23. Wattanaruangkowit P, Muengtaweepongsa S, Kengganpanich M, et al. The Effects of Foot Reflexology for Smoking Cessation on Brain Activities with Functional Magnetic Resonance Imaging (fMRI): A Pilot Study. *Evidence-Based Complementary and Alternative Medicine*. 2022; 2022: 1727479. DOI: 10.1155/2022/1727479.
24. Patel U, Patel N, Khurana M, et al. Effect Comparison of E-Cigarette and Traditional Smoking and Association with Stroke—A Cross-Sectional Study of NHANES. *Neurology International*. 2022; 14: 441-452. DOI: 10.3390/neurolint14020037.
25. Ndunda PM and Muutu TM. Abstract 9: Electronic Cigarette Use is Associated With a Higher Risk of Stroke. *Stroke*. 2019; 50: A9-A9. DOI: doi:10.1161/str.50.suppl_1.9.
26. Kuntic M, Oelze M, Steven S, et al. Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase

(NOX-2). *European Heart Journal.* 2019; 41: 2472-2483. DOI: 10.1093/eurheartj/ehz772.

27. Cai J and Bidulescu A. Associations between e-cigarette use or dual use of e-cigarette and combustible cigarette and metabolic syndrome: Results from the National Health and Nutrition Examination Survey (NHANES). A*nn Epidemiol.* 2023 20230516. DOI: 10.1016/j.annepidem.2023.05.009.
28. Chelikam N, Mohammad Z, Tavrawala K, et al. Prevalence of Cerebrovascular Accidents Among the US Population With Substance Use Disorders: A Nationwide Study. *Cureus.* 2022. DOI: 10.7759/cureus.31826.
29. Ruszkiewicz JA, Zhang Z, Gonçalves FM, et al. Neurotoxicity of e-cigarettes. *Food and Chemical Toxicology.* 2020; 138: 111245. DOI: https://doi.org/10.1016/j.fct.2020.111245.
30. Nguyen T, Li GE, Chen H, et al. Maternal E-Cigarette Exposure Results in Cognitive and Epigenetic Alterations in Offspring in a Mouse Model. *Chemical Research in Toxicology.* 2018; 31: 601-611. DOI: 10.1021/acs.chemrestox.8b00084.
31. Nguyen T, Li GE, Chen H, et al. Neurological Effects in the Offspring After Switching From Tobacco Cigarettes to E-Cigarettes During Pregnancy in a Mouse Model. *Toxicological Sciences.* 2019; 172: 191-200. DOI: 10.1093/toxsci/kfz194.
32. Rubinstein ML, Delucchi K, Benowitz NL, et al. Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes. *Pediatrics.* 2018; 141. DOI: 10.1542/peds.2017-3557.
33. Salamanca JC, Munhenzva I, Escobedo JO, et al. Formaldehyde Hemiacetal Sampling, Recovery, and Quantification from Electronic Cigarette Aerosols. *Scientific Reports.* 2017; 7. DOI: 10.1038/s41598-017-11499-0.
34. Wang Y-T, Lin H-C, Zhao W-Z, et al. Acrolein acts as a neurotoxin in the nigrostriatal dopaminergic system of rat: involvement of α-synuclein aggregation and programmed cell death. *Scientific Reports.* 2017; 7: 45741. DOI: 10.1038/srep45741.
35. Cui J, Liu Y, Chang X, et al. Acetaldehyde Induces Neurotoxicity In Vitro via Oxidative Stress- and Ca(2+) Imbalance-Mediated Endoplasmic Reticulum Stress. *Oxid Med Cell Longev.* 2019; 2019: 2593742. 20190109. DOI: 10.1155/2019/2593742.
36. Wetzels S, Vanmierlo T, Scheijen JLJM, et al. Methylglyoxal-Derived Advanced Glycation Endproducts Accumulate in Multiple Sclerosis Lesions. *Frontiers in Immunology. 2019; 10. Original Research.* DOI: 10.3389/fimmu.2019.00855.
37. Moritz ED, Zapata LB, Lekiachvili A, et al. Update: Characteristics of Patients in a National Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injuries - United States, October 2019. *MMWR Morb Mortal Wkly Rep.* 2019; 68: 985-989. 20191101. DOI: 10.15585/mmwr.mm6843e1.
38. Lung Injuries Associated with Use of Vaping Products, https://www.fda.gov/news-events/public-health-focus/lung-injuries-associated-use-vaping-products#Analysis (accessed June 13, 2023).
39. Hybertson BM, Chung JH, Fini MA, et al. AEROSOL-ADMINISTERED α-TOCOPHEROL ATTENUATES LUNG INFLAMMATION IN RATS GIVEN LIPOPOLYSACCHARIDE INTRATRACHEALLY. *Experimental Lung Research.* 2005; 31: 283-294. DOI: 10.1080/01902140590918560.
40. Avelar AJ, Akers AT, Baumgard ZJ, et al. Why flavored vape products may be attractive: Green apple tobacco flavor elicits reward-related behavior, upregulates nAChRs on VTA dopamine neurons, and alters midbrain dopamine and GABA neuron function. *Neuropharmacology.* 2019; 158: 107729. DOI: https://doi.org/10.1016/j.neuropharm.2019.107729.
41. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Final Report. *New England Journal of Medicine.* 2020; 382: 903-916. DOI: 10.1056/nejmoa1911614.
42. Hua M, Omaiye EE, Luo W, et al. Identification of Cytotoxic Flavor Chemicals in Top-Selling Electronic Cigarette Refill Fluids. *Scientific Reports.* 2019; 9. Article. DOI: 10.1038/s41598-019-38978-w.

43. Behar RZ, Luo W, McWhirter KJ, et al. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. *Scientific Reports*. 2018; 8. DOI: 10.1038/s41598-018-25575-6.
44. Lim H-H and Shin H-S. Determination of volatile organic compounds including alcohols in refill fluids and cartridges of electronic cigarettes by headspace solid-phase micro extraction and gas chromatography-mass spectrometry. *Analytical and Bioanalytical Chemistry*. 2017; 409: 1247-1256. DOI: 10.1007/s00216-016-0049-0.
45. Zhao D, Navas-Acien A, Ilievski V, et al. Metal concentrations in electronic cigarette aerosol: Effect of open-system and closed-system devices and power settings. *Environmental Research*. 2019; 174: 125-134. DOI: 10.1016/j.envres.2019.04.003.
46. Jain RB. Concentrations of cadmium, lead, and mercury in blood among US cigarettes, cigars, electronic cigarettes, and dual cigarette-e-cigarette users. *Environmental Pollution*. 2019; 251: 970-974. DOI: https://doi.org/10.1016/j.envpol.2019.05.041.
47. Badea M, Luzardo OP, González-Antuña A, et al. Body burden of toxic metals and rare earth elements in non-smokers, cigarette smokers and electronic cigarette users. *Environmental Research*. 2018; 166: 269-275. DOI: https://doi.org/10.1016/j.envres.2018.06.007.