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Emerging ENDS products and challenges in tobacco control toxicity research

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Abstract

Electronic nicotine delivery systems (ENDS) continue to rapidly evolve. Current products pose unique challenges and opportunities for researchers and regulators. This commentary aims to highlight research gaps, particularly in toxicity research, and provide guidance on priority research

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questions for the tobacco regulatory community. Disposable flavoured ENDS have become the most popular device class among youth and may contain higher nicotine levels than JUUL devices. They also exhibit enhanced harmful and potentially harmful constituents production, contain elevated levels of synthetic coolants and pose environmental concerns. Synthetic nicotine and flavour capsules are innovations that have recently enabled the circumvention of Food and Drug Administration oversight. Coil-less ENDS offer the promise of delivering fewer toxicants due to the absence of heating coils, but initial studies show that these products exhibit similar toxicological profiles compared with JUULs. Each of these topic areas requires further research to understand and mitigate their impact on human health, especially their risks to young users.

INTRODUCTION

Assessing the public health risks of electronic nicotine delivery systems (ENDS) is a significant current priority and challenge. At present, the complexity of the field is exacerbated by several issues. These include the marketing of vaping products containing synthetic nicotine[1] and the finding of thousands more unknown compounds in ENDS aerosols[2] than previously considered. The relevance of several recently introduced products to the authority of the US Food and Drug Administration (FDA) Center for Tobacco Products (CTP), as well as to international regulatory agencies, is either unknown or unclear. The need for evidence to aid the FDA CTP towards regulating ENDS was the impetus behind creating a working group focused on ENDS toxicity comprising researchers from diverse backgrounds and different institutions to collaborate on this manuscript. The purpose of this commentary is to identify emerging challenges in the field of ENDS toxicity research and to promote relevant strategies and directions for the tobacco control research community.

Tobacco-related diseases have a decades-long latency period. Due to the relatively recent emergence of ENDS in the market, there is a lack of long-term public health data on their use. However, a recent meta-analysis of epidemiological studies showed a direct relationship between ENDS use and asthma and chronic obstructive pulmonary disease,[3] while an associated convergent analysis of laboratory studies found correlations of ENDS e-liquid and aerosol exposure with oxidative stress, susceptibility to infection, altered gene expression and inflammation.[3] As ENDS continue to evolve, it is unclear to what extent changes in these products might or might not confound the understanding of their long-term health effects. Challenges related to ongoing changes in product characteristics are encountered more frequently in the study of ENDS compared with cigarettes, where nicotine content and cigarette size, for example, are more similar across brands.

The characteristic health risks of ENDS toxicity cannot be readily extrapolated based on the relatively fewer numbers or levels of toxins compared with cigarette smoke.[4–6] In addition, ENDS contain compounds not otherwise present in combustible cigarettes, such as the solvents propylene glycol (PG) and glycerol, and flavourants that may pose unique health risks through continuous use. For example, traditional cigarettes have not been associated with the rapid-onset, life-threatening severe lung injury that is a hallmark of ‘e-cigarette or vaping use-associated lung injury’ (EVALI), which have been documented in counterfeit

tetrahydrocannabinol (THC) vaping products and in nicotine exclusive ENDS users since 2015.[7–10] Tissue injury associated with ENDS exposure is distinct from that caused by combustible cigarettes,[11] and while chronic smoking and chronic vaping both result in serum that lowers nitric oxide release from cultured endothelial cells,[12] only the serum from chronic vapers—not from chronic smokers—increases microvascular endothelial cell permeability over that of non-user serum.[13] In addition, ENDS alter the expression of more genes, and with distinctive patterns, compared with traditional cigarettes.[5] Free radical concentrations in ENDS are lower compared with cigarettes; however, the environmentally persistent free radicals (EPFRs) arising from ENDS afford greater hydroxyl radical yields per unit EPFR.[14] Reducing toxin exposure by using ENDS may thus not result in proportional harm reduction.[5] Dose–response relationships between smoking and cardiovascular disease are non-linear.[15] Cancer risk estimations among smokers switching to products with reduced toxicant exposure profiles are also non-linear.[16] These facts highlight the ongoing need for current evidence-based scientific data concerning ENDS and public health.[17 18] Below, we highlight currently salient concerns in the field of ENDS research among researchers and regulators that call for more investigation and potential regulatory actions.

NEW ENDS PRODUCTS AND RESEARCH AGENDAS Disposable ENDS

On 2 January 2020, to address the US youth vaping epidemic, the FDA issued an enforcement policy that removed cartridge-based ENDS containing mint or fruit flavours, excluding menthol and tobacco from the market.[19] However, all disposable ENDS and open-system ENDS, regardless of their flavour contents, were exempt, which can be considered a loophole given the current developments.[19] The FDA's rationale was that the enforcement policy did not extend to the flavours that were the least popular among young people (ie, tobacco and menthol). It was also reasoned that while the FDA was reviewing applications to determine whether products should be authorised to stay on the market, the partial enforcement policy enabled much of the industry to remain intact while enabling adult ENDS users to have access to ENDS among those who are trying to quit smoking.

By July 2020, with the continued use of ENDS in the COVID-19 era exacerbating earlier concerns, the FDA directed the manufacturers of 10 brands of fruit-flavoured, disposable ENDS to remove their products from the market because they were appealing to youth.[20] Young people had apparently compensated for the removal of fruit-flavoured and mint-flavoured JUULs and other popular products by switching to flavoured disposables such as Puff Bar. Disposable ENDS usage increased from 2.4% in 2019 to 26.5% in 2020 among high school current ENDS users and from 3.3% in 2019 to 15.2% in 2020 among middle school current ENDS users.[21] The 2021 National Youth Tobacco Survey reported that the most popular disposable brand among US middle school and high school students was Puff Bar.[22]

Puff Bar copycat brands continue to be available. Most are similar in design to the JUUL devices, and to each other and appear to differ only in size and the maximum number of puffs each can deliver. Flavoured Puff Bars are also still being sold, but since the FDA's action against the company,[20] these appear to be counterfeits using the original name and

logo. A Premarket Tobacco Product Application (PMTA) submission to the FDA is needed to obtain a marketing order for these or other new tobacco products. The PMTA must include scientific data showing that a product is 'appropriate for the protection of public health'.[23] In February 2021, Puff Bar introduced a 'tobacco-free nicotine' (TFN, *vide infra*) to elude FDA jurisdiction, as the FDA, at the time, only regulated nicotine derived from tobacco. Table 1 summarises recent regulatory actions concerning flavoured ENDS, TFN products and the PMTA process.

Proposed research directions

1. Disposable flavoured ENDS nicotine salt levels are often higher than those of JUUL's (~59 mg/mL nicotine or ~40 mg in a JUUL pod), thereby ranking them among the highest nicotine-containing ENDS. There is a need for more studies addressing the identity of nicotine salts, which vary based on the counterion used to form the nicotine salt,[24] and how these various salts impact nicotine delivery, addiction and physiological effects.

2. The e-liquid and aerosol composition of flavourings derived from the disposable products, which are harmful and potentially harmful constituents (HPHCs, as identified by the FDA), is not yet clear and warrants investigation. HPHCs, especially from lower quality and copycat devices, are presumably present at relatively high levels due to poor wicking and heat transfer. Many of the manufacturers advertise high device lifetime puff numbers, and it is well known that heating quality can be compromised with increasing puff number, leading to higher HPHC emissions, especially metals.[25] This will lead to elevated HPHC exposure, especially towards the end of the device lifetime. Although there was a limited sampling of brands, an initial study indeed found consistently higher aerosol levels of HPHC and metal emissions from disposable devices compared with a JUUL pod mod.[26]

3. Chemical reactions leading to adduct formation between e-liquid constituents, such as between aldehydic flavourants and the e-liquid solvents PG and glycerol, are anticipated to occur within disposable ENDS e-liquid during storage conditions. These compounds need to be characterised, identified and quantified. For example, several aldehyde-solvent acetals have been shown to be more irritating and toxic than the parent aldehydic flavourants in studies of other ENDS e-liquids.[27 28]

4. 'Cooling' ENDS flavours have been associated with greater nicotine vaping and frequency of ENDS use in high school students.[29] A recent report showed that JUUL partially substituted menthol with the synthetic cooling agent WS-3 in their European products, a compound with similar cooling properties as menthol but lacking a distinct odour.[30] Similarly, all available Puff Bar flavours, including both menthol/mint as well as those not labelled as 'cool'/'ice', have recently been reported to contain higher levels of the synthetic coolants WS-3 and WS-23 compared with JUUL.[31 32] Because WS-3 and WS-23 were initially developed for skin applications, little is known about their inhalation safety. A margin of exposure assessment—frequently used in risk assessment—showed that the

use of as little as half a Puff Bar (150 puffs according to Puff) per day could expose users to quantities of synthetic coolants that would be considered unsafe in food and raises concerns about health risks through chronic exposure.[32] In vitro studies on mammalian cells found that WS-23 may cause structural chromosomal aberrations (clastogenicity) in the presence of metabolic activation, suggesting the formation of a reactive metabolite of WS-23.[33] Moreover, WS-23 was found cytotoxic at concentrations 90 times lower than those found in the analysed e-liquids. It was concluded that switching from flavoured JUUL to Puff Bar would expose users to increased harm due to the higher levels of WS-23 as well as pulegone in mint/menthol Puff products.[31] More work is needed to better understand the health risks of inhaling cooling or 'ice'[34] flavoured ENDS, particularly in those disposable products containing relatively high levels of these synthetic coolants.

5. The rise in popularity of disposable ENDS will result in greater amounts of waste as, in contrast to JUUL and other pod mod devices, disposable devices cannot be recharged. While in pod mod devices, only the pod or cartridge is discarded after use, disposable devices must be discarded entirely, including the battery. As a result, increased amounts of plastic, nicotine salts, heavy metals, lead, mercury, flammable lithium ion batteries and other compounds may make their way into the environment. Unfortunately, no proper disposal system for ENDS waste is in place and accessible to vapers. This unintended consequence of the mentioned loophole in the legislation of flavoured pod mod devices which resulted in the rise in popularity of flavoured, disposable ENDS is a large and understudied urgent issue that has not been a priority area for the ENDS industry.[35 36]

6. Short-term and long-term health effects associated with the use of disposable flavoured ENDS remain largely unknown to users, investigators and regulatory agencies. Investigating the toxicity of disposable flavoured products is challenging, as there are multiple factors to be considered, including the specific ENDS device used, production consistency fluctuations especially in copycat devices, the flavour of the disposable product and the user's vaping topography which directly affects the user's vaping experience. These factors will also impact the physicochemical profile of the aerosol produced and result in a unique toxicity profile. There is a substantial knowledge gap for exclusive biomarkers of cardiopulmonary toxicity associated with long-term exposure to disposable flavoured ENDS.[37] Thus, harmonised studies using physiologically relevant in vitro and in vivo models to better understand the health outcomes from using these emerging ENDS devices are critically needed. This will help bridge the research gap associated with the correlation of in vitro toxicity data and in vivo biomarkers of toxicity.

ENDS containing synthetic nicotine

Following the FDA's ban of the sale of Puff Bars,[20] the manufacturer began selling disposable ENDS presumably containing synthetic, rather than tobacco-derived, nicotine.

The use of synthetic nicotine in commercial products was previously thought to be too cost-prohibitive to be practical. Puff Bar was not the first ENDS brand claiming to use synthetic nicotine. A few examples had been observed before 2018.[38] The company was using this strategy to evade FDA jurisdiction by not selling a tobacco-derived product. Other companies, such as BLVK, Cloud Nurdz and Syn Bar, have also recently begun selling disposable products containing synthetic nicotine.[39]

Some argue that synthetic nicotine is a cleaner and less harmful ingredient since it contains less accompanying toxicants extracted from plant material. However, the prevalent use by young people of these products that have high levels of nicotine salts and flavourings remains a significant concern. If the price of synthetic nicotine is no longer viewed as prohibitive, more brands may begin to use it, and it would be likely that its use becomes more widespread.[1] A 2018 article puts forth an argument for regulating synthetic nicotine-containing ENDS as medical devices.[38]

The US FDA is now authorised to regulate vaping products that contain laboratory-manufactured nicotine. On 15 March 2022, the US Congress passed and signed into law provisions in the Federal Omnibus Spending Bill, expanding the FDA's authority to regulate tobacco-derived nicotine (TDN) in vaping products to include nicotine manufactured in laboratories (synthetic nicotine).[40]

Proposed research directions

1. Studies enabling the testing of products for synthetic versus tobacco nicotine, such as the determination of the enantiomeric excess of the synthetic enantiomers, are needed for validating industry claims that they are not using TDN.[41–43] However, the distinction between synthetic and TDN has become more challenging, as new laboratory syntheses of enantiomerically pure nicotine have recently been patented.[1] Methods addressing the challenge of distinguishing synthetic from natural nicotine[1] are currently needed as long as more manufacturers will choose to market ENDS containing synthetic nicotine to promote reduced harm perceptions.[39]

2. For synthetic products containing both nicotine enantiomers,[42] an issue is that human exposure to (*R*)-(+)-nicotine has been relatively minimal to date, since it is present in tobacco at levels of just 0.1%–1.2%. In addition, it has proved challenging to purify. Any toxicological impact differing from the naturally more abundant (*S*)-(−)-nicotine has therefore not been extensively studied to date. However, prior studies show that (*R*)-(+)-nicotine can exhibit different bioactivity compared with TDN, which contains mostly (*S*)-(−)-nicotine.[44] Research focusing on the toxicology of (*R*)-(+)-nicotine and/or the racemic nicotine mixture is relatively limited.

3. Animal and human studies are warranted to assess differential levels of synthetic nicotine versus TDN biomarkers in biological matrices, including tissues, blood and urine. Measuring metabolites of the two types of nicotine is important for quantifying the associated health risks related to nicotine consumption.[45]

4. In contrast to TDN being bitter, one manufacturer of a synthetic nicotine product claims that it is virtually tasteless and odourless, thereby improving e-liquid flavour, and devoid of many of the residual impurities that TDN contains.[46–48] While studies are needed to determine whether the adverse health effects of synthetic nicotine are different from those of TDN, claims of improved taste may entice early initiation of nicotine consumption and possibly addiction in young people.[39] Studies are needed to confirm such claims, determine differential addiction levels of its use compared with TDN and collect survey data on perceived harm and perceived benefits of synthetic nicotine use, particularly among young vapers.

The re-emergence of flavour capsules

A relatively new product that enables users to evade FDA flavour bans are flavour enhancers, the best known brand being ‘Puff Krush’. They are compatible with JUUL and other pod mods of similar dimensions. Users simply snap them onto the top of the device and crush the internal flavour-containing capsule to contact the aerosol with the flavour molecules during use. In other words, this enables users to add a host of otherwise currently banned flavours to JUUL and other closed pod mods that are otherwise compliant with current regulations (ie, no flavourings beyond tobacco and menthol). Interestingly, the ‘crushing’ experience was similarly used in older Camel cigarettes to deliver menthol flavour via crushing a capsule.[49] The Camel marketers had found that the crushing action appealed to younger smokers.[50] Since Puff Krush is used in conjunction with tobacco products, they are subject to regulation by FDA CTP.[49]

Proposed research directions

1. The contents, purity, identities and doses of flavour molecules, as well as any other compounds added to the aerosol via the capsules, are not clear.[51] It is likely that the flavouring compounds remain largely chemically intact during vaping since they are not heated along with the e-liquid, though this remains to be shown. Also, adsorbing of the flavourants on a surface of the freshly formed micron or submicron-sized particles (due to high surface to volume ratio of those particles) may lead to significant enhancement of the flavourings on the surface of the particles, thereby increasing appeal of these tobacco products to youth.

2. Typically, flavourings promote the production of free radicals and elevated levels of HPHCs during vaping.[52] However, individual ENDS flavourants induce toxicity in the respiratory tract, cardiovascular and circulatory systems, and in the skeletal system and skin.[53] A recent literature review found >65 specific flavourings associated with these outcomes, with cinnamaldehyde the most frequently reported as cytotoxic, followed by vanillin, menthol, ethyl maltol, ethyl vanillin, benzaldehyde and linalool.[53] It is not known currently how the use of the capsules, which deliver flavourings to heated aerosols, affects particle sizing, flavouring dosing and health risks.

3. The potential for using these or related custom ‘add-ons’ to deliver substances such as illegal drugs needs to be investigated. Data showing the prevalence of

capsule-based products, along with studies showing their impact on appeal to youth, are needed.[54]

4. In general, the majority of current data on ENDS flavouring toxicology have been derived from in vitro studies.[55–58] There is a significant need to standardise methods for exposing cells to ENDS e-liquids and aerosols to decrease interlaboratory variability.[53] Alternative flavour delivery products such as Puff Krush add to these challenges.

Coil-less ENDS

In addition to the relatively well-characterised ingredients of pure e-liquids (PG, vegetable glycerine (VG), nicotine, nicotine acidifiers and flavourants), a wide range of chemical reaction products are present in the aerosol, both as a result of slow reactions during storage (eg, Maillard reaction and acetal formation) and of acute production at the heating coil during use.[59 60] The heating coil material and temperature can catalyse the breakdown of PG and VG, and can itself shed toxic metals into the aerosol.[61–63] A relatively new approach is to produce aerosols via an ultrasonically vibrating membrane as opposed to a heating coil. While the vibration heats up the liquid to some extent (~75°C under airflow conditions according to early experiments with the USONICIG Zip[64]), the increased temperature does not approach the relatively high temperatures at a heating coil. The companies that produce such devices (figure 1) have an interesting marketing angle that asserts that conventional vaping is potentially harmful due to the reactions at the coil, so their ultrasonic devices are harm reduction products. Such claims need to be validated.

Proposed research directions

1. These products have not been heavily studied. However, while the assertion of fewer chemical reaction products is reasonable to expect, the aerosol generated from the USONICIG Zip has been shown to impair vascular endothelial function in rats comparably to impairment by JUUL, previous generation freebase nicotine ENDS and tobacco cigarettes,[64] indicating that claimed reduction of HPHCs does not necessarily reduce the risk of some of the adverse effects of vaping and smoking. Further related research is warranted.

2. In addition to HPHC production, another issue to consider when investigating these devices is their efficiency in delivering nicotine relative to other ENDS and cigarettes.

3. Studies addressing the prevalence and usage patterns concerning these new products are lacking.

REGULATORY GUIDANCE AND RESEARCH DIRECTIONS

The dynamic nature of the current ENDS regulatory environment is challenging for tobacco control researchers working to support the mission of the FDA CTP.[65] Recently, the TFN issue was settled by affording the FDA regulatory authority over all nicotine-containing products. However, other challenges remain. For example, how can researchers best address challenges, such as occurred during the EVALI outbreak, that necessitate an

urgent investigation of ENDS products containing scheduled or other substances outside the jurisdiction of the FDA CTP? THC-containing ENDS were used by patients with EVALI; however, federal law restricts the investigation of THC.

CONCLUSION

This is an eventful time in tobacco control research. Several current ENDS products are exhibiting concerning trends in heightened (1) youth appeal (flavour capsules, disposables), (2) nicotine and cooling flavour content (disposables), (3) environmental hazard and burden (disposables), and (4) evasion of regulatory oversight (synthetic nicotine until recently and flavour capsules). Other products, such as coil-less devices, are marketed for reducing toxicant exposure, but studies to date indicate a toxicological profile similar to other (heating coil-containing) ENDS and to cigarettes. The products described herein are popular with young users, amplifying the current need for research.

This focused special communication is limited in scope. There are additional issues meriting further consideration that need to be addressed in the context of the emerging products described herein. For example, user behaviour and how it changes from device to device impacting toxicant exposure, factors modulating particle size distributions,[66] interlaboratory reproducibility of findings, the correlation of laboratory studies to realistic usage, the significance of secondhand and thirdhand smoke and the development of standardised laboratory methods[67] are relevant issues.[68] As the FDA continues to aggressively regulate tobacco products through the PMTA pathway and approves new ENDS to enter the market, tobacco researchers need to be vigilant and conduct research that supports regulatory actions to protect public health.

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What this paper adds

- A major challenge in the field of electronic nicotine delivery systems (ENDS) research is the ongoing introduction of a wide array of unique products. Moreover, a current trend includes the development of products, such as synthetic nicotine and flavour capsules, that have been recently used to circumvent Food and Drug Administration regulatory authority.
- Disposable flavoured products are currently prevalent, especially among young vapers. However, they have been found to contain some of the highest levels of nicotine and synthetic coolants present in commercial ENDS. Their popularity also poses a heightened risk to the environment. Coil-less ENDS have been recently designed to help mitigate the production of harmful and potentially harmful constituent emissions; however, in the limited independent studies to date, they have shown toxicological profiles similar to those of other ENDS as well as to traditional cigarettes.
- There is a dearth of evidence-based scientific data concerning the emerging ENDS products. Fundamental chemical characterisation and toxicological studies are currently needed, considering the prevalence of youth usage, industry marketing claims of enhanced safety, environmental concerns and complex regulatory challenges associated with many of the emerging ENDS products.

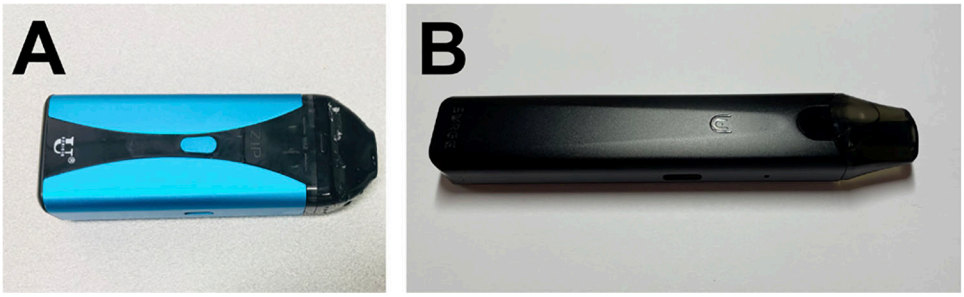

Figure 1.
Ultrasonic vaping devices. (A) USONICIG Zip, with a refillable pod. (B) Surge Vapor device, with disposable pod. Photographs by Poonam Rao (A) and Jordan Naughton (B), University of California, San Francisco.

Table 1

Regulatory actions involving ENDS flavour bans and TFN

Date	Action	Comment
2 January 2020	FDA announces an enforcement policy on flavoured cartridge-based e-cigarettes.	Cartridge-based e-cigarettes containing mint or fruit flavours are banned. Menthol and tobacco flavours are still permitted. Disposable e-cigarettes are also exempt from these restrictions.
20 July 2020	FDA sends warning letters to manufacturers of flavoured disposable e-cigarettes.	Ten companies, including the manufacturers of Puff Bar, are warned to remove their flavoured disposable e-cigarettes and youth-appealing e-liquid products from the market since they do not have the required premarket authorisation.
9 September 2021	FDA has completed actions on 93% of the >6.5 million 'deemed' new products submitted for PMTA evaluation.	By this date, marketing denial orders (MDO) for >946 000 flavoured ENDS products are issued because the applications lacked sufficient evidence of benefit to adult smokers.
12 October 2021	FDA authorises the first new tobacco products for marketing through the PMTA pathway.	Authorisation is granted to RJ Reynolds (RJR) Vapor for its Vuse Solo closed ENDS device and accompanying tobacco-flavoured e-liquid pods.
15 March 2022	Legislation is enacted to clarify that the FDA has regulatory authority over tobacco products containing nicotine from any source.	Establishments involved in the manufacture, preparation, compounding or processing of non-tobacco nicotine (eg, synthetic nicotine) products must register with the FDA and submit a PMTA by 14 May 2022 to obtain authorisation to market their products.
24 March 2022	The FDA authorises several tobacco-flavoured ENDS products via the PMTA process.	Authorisation was given to Logic Technology Development (Logic) for products associated with the Logic Vapeleaf, Logic Power and Logic Pro brands, including devices.
26 April 2022	The FDA issues additional marketing approval for other tobacco-flavoured products.	Specific products authorised include NJOY Ace closed e-cigarette and three accompanying tobacco-flavoured e-liquid pods.

ENDS, electronic nicotine delivery systems; FDA, Food and Drug Administration; PMTA, Premarket Tobacco Product Application; TFN, tobacco-free nicotine.