

Critical Gaps in the Scientific Basis for Electronic Cigarette Regulation

An American College of Chest Physicians Research Statement



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BACKGROUND: The 2009 Family Smoking Prevention and Tobacco Control Act granted the US Food and Drug Administration regulatory authority over tobacco products, extended to include electronic cigarettes (ECs) in 2016. Regulatory science informs potential market restrictions based on the population health standard. The American College of Chest Physicians (CHEST) Tobacco/Vaping Work Group is charged with prioritizing tobacco-related advocacy. To identify critical gaps in the science guiding EC regulation, we undertook a systematic exploration of existing evidence to develop future research recommendations.

METHODS: Fifteen CHEST Tobacco/Vaping Work Group members with relevant expertise in tobacco science, health policy, and methodology prioritized 12 candidate research areas and selected the 4 highest-ranked questions for review: accessibility limitations, nicotine delivery limits, non-cardiac/non-malignant risks, and flavorant impact on airway biology. A comprehensive literature search was conducted, and relevant studies were reviewed to develop recommendations through group consensus.

KEY FINDINGS AND RECOMMENDATIONS: While age-appropriate restrictions reduce uptake, alternative access channels limit their impact, necessitating pragmatic trials of various restrictions and enforcement methods. Limiting nicotine delivery may lead to compensatory behaviors and increased toxicant exposure, requiring pharmacokinetic assessments that account for substantive variations in user behavior. Associations between EC use and respiratory symptoms, mood disorders, attentional disturbances, and poor academic performance underscore the need for epidemiologic and mechanistic research into non-cardiac/non-malignant health risks. There is strong evidence that flavorant aerosols induce cytotoxicity in mammalian cells; however, their specific effects on humans remain insufficiently studied to inform product regulation.

CONCLUSIONS: Gaps in EC regulatory science hinder effective policy development. The panel recommends a focused research agenda addressing pragmatic trials of access restrictions, detailed evaluation of nicotine delivery limits, investigation of non-cardiac/non-malignant risks, and quantification of aerosol toxicity, with attention to diverse real-world use patterns to better inform regulation and protect public health.

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KEY WORDS: addiction; nicotine; regulation; smoking; smoking cessation; tobacco

Summary of Research Recommendations

To better characterize the anticipated population health impact of various accessibility limitations, the panel recommends:

1. **Pragmatic trials evaluating the feasibility and impact of systematic restrictions such as prescription-only access, pharmacy-only access, retailer licensing, etc., should be conducted to ascertain their potential to improve population health.**
2. **To amplify the effect of sales restrictions, pragmatic evaluations of various enforcement methods, including public announcements of non-compliance, “time-out” pauses in sales, fines, etc., should be conducted to define the circumstances in which specific strategies are most impactful.**
3. **Evidence supporting specific criteria guiding product promotional material placement should be urgently developed.**

To estimate the anticipated effects of limiting the amount of deliverable nicotine, the panel recommends:

4. **Because available EC devices are marked by significant variability in construction and technical specifications that directly affect user experience, future pharmacokinetic assessments should account for device characteristics and the interaction with user-defined topographic exposure patterns.**
5. **Estimating the impact of nicotine delivery limitations should be expansive, and include characterizations of propylene glycol, carbonyl, and other toxicant exposure.**
6. **Prospective observational studies to estimate exposure-by-time interactions should be performed and be sufficiently powered to evaluate variation by recognized social and biobehavioral phenotypes.**
7. **Because variations in nicotine delivery may influence the amount of aerosol consumed by the user, population health impact studies of reduced**

nicotine products should include known markers of cardiovascular stress, systemic inflammation, and carcinogenesis.

To understand the contribution of vaping to risk of non-cardiovascular, non-malignant conditions, the panel recommends:

8. **In light of potential associations between EC aerosol and the development/exacerbation of inflammation-mediated conditions such as interstitial lung disease and COPD, population-based research should pay increased attention to these conditions to inform regulatory decision making.**
9. **Future regulatory research should focus on clarifying the mechanisms of any identified causal relationships, interactions between vaping and important behavioral health risk factors, and long-term pragmatic implications of behavioral/cognitive effects of exposure.**
10. **Because dose-effect associations seem plausible, effort should be invested to identify user-controlled exposure patterns amplifying any deleterious effects of vaping. Particularly because device technology and nicotine chemistry are in rapid evolution, relationships between health impact and individual aerosol characteristics should be precisely defined.**

To characterize the potential deleterious impact of flavorants on airway biology, the panel recommends:

11. **The regulatory research agenda should prioritize the precise quantification of potential toxicity among the individual components of EC aerosol, the potential synergistic effects of toxicant mixtures, and the interaction between toxicant delivery and the physical characteristics of the aerosol (eg, concentration, temperature, particle size, etc.).**
12. **Toxicity assessments should account for wide variations in user-defined exposure patterns. Variables**

ABBREVIATIONS: CHEST = American College of Chest Physicians; EC = electronic cigarette (aka e-cigarette); FDA = US Food and Drug Administration; ILD = interstitial lung disease

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such as exposure duration, inter-puff interval, and depth of inhalation/delivery have the potential to influence the severity and type of injury.

13. The potential population health benefit of ECs will depend on accurate placement of products on the proposed “continuum of risk.” To achieve this, researchers should strive to develop a validated risk scale that incorporates the complex data described above and presents the relative risk of individual EC products in language accessible to a lay audience.

Introduction

In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act in an effort to safeguard the public from the health consequences of tobacco use and in response to growing concerns over prior tobacco industry efforts to hide or downplay tobacco’s addictive and carcinogenic properties. The Act gave the US Food and Drug Administration (FDA) regulatory authority over the manufacture, distribution, and marketing of tobacco products, reissued restrictions on tobacco sales to youth, and required disclosure of tobacco product constituent ingredients.¹

Enacting the legislation proved to be complicated. In 2016, FDA issued its Final Deeming Rule extending the Center for Tobacco Products’ authority to include newer product types, including electronic cigarettes (ECs), vape pens, synthetic nicotine analogs, and other non-traditional forms.² The rule established a process for authorizing tobacco products for sale based on a “population health standard” that considers product health risks, carcinogenicity, and benefits to the population as a whole, including both individuals who use ECs and those who do not.^{3,4} The Act requires that risk modification claims, including product

designations as mild or light, be guided by risk-benefit calculations supported by scientific evidence.⁵

From this perspective, the traditional biomedical focus on basic and applied research may not provide FDA insights with the degree of specificity required for market-restricting decisions. Consequently, the field of regulatory science has evolved as a distinct, multidisciplinary endeavor, with core domains that align more closely with the population health standard and the FDA’s legal responsibilities.^{6,7} While some emerging products may prove to be valuable to public health, methods for estimating future health risks generally rely on animal models and weak assumptions regarding the relationship between toxicant concentrations and the genesis of disease.⁸ Given the tobacco industry’s history of harm denial and opacity, manufacturer claims should be independently evaluated through human exposure studies before being accepted as “verified” and used to direct regulatory action.^{9,10}

The American College of CHEST Physician’s (CHEST’s) overarching mission inherently includes a strong commitment to preventing tobacco use initiation and advocating for policies that improve research funding and access to cessation services. In pursuit of these objectives, CHEST empaneled a multidisciplinary group of experts and tasked them with identifying important gaps in existing EC regulatory science relevant to the most pressing questions of population health significance. To minimize the impact of preconceptions on recommendations, the panel used an evidence-based, systematic approach to explore the existing evidence, identify population health implications of potential regulations, and stimulate discussion regarding the scientific approach to gap closure.

Study Design and Methods

Expert Panel Composition

The chair (F. T. L.) was appointed by CHEST to lead a panel of expert representatives from a variety of fields including pulmonary medicine, tobacco treatment, regulatory science, health policy and advocacy. The final panel consisted of the chair, 14 panelists, and a methodologist (J. M. I.). All panelists were reviewed for conflicts of interest, with potential conflicts of interest managed by disclosure.

Question Development

The panel employed a process of asynchronous iterative categorization to describe and analyze potential research themes and develop a comprehensive list of 12 important policy-relevant areas for exploration. Questions dealing primarily with clinical priorities, although important in a different context, were omitted from regulatory policy consideration. Topics were anonymously ranked by panelists using a 10-point priority scale, with the 4 highest-ranked questions selected for inclusion (Fig 1). All panel

Research Questions	Mean Priority Score
<i>High Priority Regulatory Questions</i>	
1. What is the anticipated population health impact of accessibility limitations?	8.25
2. What would be the anticipated effect of limiting the amount of nicotine deliverable through electronic devices like ECs?	8.25
3. What is the mechanistic contribution of ECs to non-cardiac and non-malignant health risks?	7.25
4. What is the specific impact of flavorant classes on airway biology?	7.13
<i>Other Considered Questions</i>	
Is there a better way to organize / describe “harm” in this context? How are contradictory effects of EC exposure incorporated into a global estimate of “harm?”	6.88
What is the relative addictive potential of various salts of nicotine used in these products?	6.38
What is the association, if any, between topography of EC aerosol exposure and markers of injury?	6.38
What are the core Advertising / Behavioral Economic principles that should guide dissemination of information aimed at maximizing public benefit?	6.38
How are e-cigarettes optimally integrated into existing pharmacologic / behavioral paradigms to achieve abstinence?	6.25
Are there intermediate markers of health effect that can serve as appropriate outcome measures for public health surveillance?	6.13
How does addictive liability change in response to differences in isomeric composition of synthetic nicotine solutions?	5.88
What are the anticipated Equity / Social Justice implications of e-cigarette product authorizations?	5.63

Figure 1 – Research questions assessed by systematic evidence review. Priority scores were derived using a 10-point scale, with values ranging from 1 = “Not at all a regulatory research priority” to 10 = “An exigent priority of immediate policy relevance.” Values represent average of all 15 respondent scores. Four highest scoring questions of 12 candidate topics included in the analysis. EC = electronic cigarette (aka e-cigarette).

members participated in the refinement and approval of the final questions.

Literature Search and Study Selection

A comprehensive search using MEDLINE via PubMed was performed to identify evidence informing the finalized questions. A combination of the National Library of Medicine’s Medical Subject Headings and key words pertaining to each question were used to refine the search (e-Appendix 1). The search was restricted to

studies in the English language and was initially completed in May 2023 and updated in February 2025.

Studies from the literature search were reviewed for relevance by panel members in 2 steps. Study titles and abstracts were first screened for potential relevance, and selected studies were then reviewed in full to determine if they were directly related to the question. Case reports, review articles, editorials, and expert opinion statements were excluded. Studies for which there was disagreement on inclusion underwent secondary review

by a designated panelist who made a final determination. Included studies were reviewed and summarized to form the basis of the recommendations.

Recommendation Drafting

Results from the literature search were distributed to 4 independent writing groups tasked with producing

draft study summaries. Draft results were discussed among panel members through email and video conferences, after which the panel drafted research recommendations through group consensus. All panel members had opportunity to provide comments and suggestions for each recommendation and approved the final form.

Results

Question 1: What is the anticipated population health impact of various accessibility limitations?

Evidence Summary

Twenty-two references related to this question were identified and summarized (e-Table 1). Evidence informing the regulatory utility of systematic restrictions including prescription-only accessibility or distributor licensing could not be identified. Data on the impact of other sales restrictions suggest that a complex set of interactions may lead to mixed outcomes.

While investigating EC marketing near schools, Giovenco et al¹¹ found that EC retailer density and advertising volume significantly affected the probability of student prior month EC use. Similarly, D'Angelo et al¹² found that, among tobacco-naïve youth, frequent access to convenience stores was associated with greater susceptibility to EC use.

Bateman et al¹³ attempted to document the proportion of tobacco outlets selling ECs prior to the legalization of EC sales in New Zealand and examined associations between point-of-sale marketing, outlet type, area-level deprivation, and proximity to secondary schools. They found most outlets were convenience stores located in otherwise high-deprivation areas. A significant number incorporated self-serve displays or placed ECs proximal to children's products. The extensive use of promotions to increase adult EC accessibility raised significant concerns over the potential for increasing youth exposure. Wagoner et al¹⁴ similarly found less than one-half of US retailers evaluated sold ECs exclusively behind the counter, suggesting easy youth access.

Research on the impact of Internet sales suggest they provide a significant alternative channel for use. Gaiha et al¹⁵ found that local restrictions on flavored ECs reduced retail access but led to increased purchases through online sources and surrogate purchasers. Gravely et al¹⁶ similarly observed that individuals who used ECs accessed desired flavors by shifting to online

purchases when federal flavor restrictions were implemented. Romm et al¹⁷ reported that federal flavor restrictions had limited impact; individuals accessed flavors by using tank-based ECs or devices not covered by regulations. Dove et al¹⁸ found that flavorant restrictions did not significantly reduce current or ever EC use among high school students but noted confounding by increased EC cannabis use after implementation. Hawkins et al¹⁹ found local restrictions on flavored tobacco products associated with decreased EC use among Massachusetts adolescents, suggesting that locally tailored policies can be effective.

Research Recommendations

While well-designed, age-appropriate restrictions on access to ECs may have the intended effect of reducing uptake, the moderating effects of concurrent social phenomena and ubiquitous alternative channels for access limit their population health impact. Promoting multidisciplinary teams of researchers is warranted to more fully understand available levers for managing this complex social milieu and protecting public health.

1. Pragmatic trials evaluating the feasibility and impact of systematic restrictions such as prescription-only access, pharmacy-only access, retailer licensing, etc., should be conducted to ascertain their potential to improve population health.
2. To amplify the effect of sales restrictions, pragmatic evaluations of various enforcement methods, including public announcements of non-compliance, "time-out" pauses in sales, fines, etc. should be conducted to define the circumstances in which specific strategies are most impactful.
3. Evidence supporting specific criteria guiding product promotional material placement should be urgently developed.

Question 2: What would the anticipated effect be of limiting the amount of nicotine deliverable through electronic devices like ECs?

Evidence Summary

Six studies were identified directly addressing this question. One study was excluded from the analysis due to direct tobacco industry involvement and high risk of bias. Of the remaining 5 studies, 3 used cross-over design variations in small groups of participants and 1 used an Internet-based survey (e-Table 2).

Hajek et al²⁰ conducted a study of nicotine content's relationship to product appeal. Tested products included 6 first-generation "cig-a-like" ECs and 2 refillable tank products with nicotine concentrations closely standardized at 20 mg/mL. Pharmacokinetic parameters included maximum nicotine plasma levels, time to reach maximum level, and total nicotine delivery over 30 minutes. The majority of ECs had a time to reach maximum level of 6 minutes, and all effectively reduced the urge to smoke, with refillable ECs delivering higher nicotine levels with fewer puffs. Tank products initially showed a stronger decrease in craving, but after adjusting for multiple comparisons the difference was no longer significant. EC appeal ratings were more influenced by factors like draw resistance, mouthpiece comfort, and reduction in urge to smoke than by nicotine delivery.

Higgins et al²¹ evaluated whether variations in dependence severity influenced the response to cigarettes with reduced nicotine content. Across various measures, reducing nicotine content consistently decreased the relative reinforcing effects of smoking, regardless of dependence severity. There was minimal evidence to suggest that more severely nicotine-dependent people experienced significant withdrawal after using reduced nicotine cigarettes. While some differences in craving were noted based on dependence severity, there was no acute indication of compensatory smoking behavior among people highly addicted to nicotine.

Earlier studies²² showed that participants using low nicotine concentration (6 mg/mL) devices had significantly lower plasma nicotine levels compared to those using high nicotine concentration (24 mg/mL) devices but compensated by significantly increasing puff frequency, puff duration, and total e-liquid volume consumed. Using a smoking machine programmed to replicate the low nicotine puffing topography observed in prior studies, Kosmider et al²³ found that low nicotine aerosols contained higher levels of formaldehyde, acetaldehyde, and acetone than aerosols

generated by puffing patterns observed with high nicotine concentration products.

Phillips-Waller et al²⁴ investigated the pharmacokinetic profile of Juul EU (20 mg/mL nicotine) when used ad-lib by individuals experienced with EC use. Comparators included Juul US (59 mg/mL nicotine), own-brand cigarettes, and other ECs. Juul EU delivered nicotine at slower rates and lower levels than Juul US and cigarettes, while Juul US relieved smoking urges better and delivered more total nicotine than Juul EU. Smets et al²⁵ similarly uncovered compensatory behaviors while exploring historical and regional differences in vaping patterns among convenience affinity groups from the Netherlands and Belgium. The 2 groups exhibited variations in vaping behaviors, particularly in technical aspects such as coil resistance, wattage, and e-liquid consumption. Despite similarities in total weekly nicotine consumption, Belgian participants reported using larger volumes of e-liquid with lower nicotine concentration.

Research Recommendations

Contradictory signals currently limit our ability to make firm conclusions about the potential impact of compensatory behavior on EC aerosol and toxicant exposure. Much of the available information is laboratory-derived and may not adequately account for potential moderating effects of real-world use patterns. Outcomes generally focus on nicotine levels produced by standardized puffing protocols, rather than directly assessing *in vivo* measures of overall toxicity necessary for predicting impact on population health.

4. Because available EC devices are marked by significant variability in construction and technical specifications that directly affect user experience, future pharmacokinetic assessments should account for device characteristics and the interaction with user-defined topographic exposure patterns.
5. Estimating the impact of nicotine delivery limitations should be expansive, and include characterizations of propylene glycol, carbonyl, and other toxicant exposure.
6. Prospective observational studies to estimate exposure-by-time interactions should be performed and be sufficiently powered to evaluate variation by recognized social and biobehavioral phenotypes.²⁶
7. Because variations in nicotine delivery may influence the amount of aerosol consumed by the

individual, population health impact studies of reduced nicotine products should include known markers of cardiovascular stress, systemic inflammation, and carcinogenesis.

Question 3: What is the mechanistic contribution of ECs to non-cardiac and non-malignant health risks?

Evidence Summary

The current EC regulatory stance has been properly derived from a significant corpus of available biochemical observations and well-designed epidemiologic associations. To explore gaps in the knowledge base, our search sought to identify articles that represented a potential significant challenge to the current understanding. Twenty-one articles were identified addressing this complex question (e-Table 3). No direct mechanistic evidence was identified within the parameters of our search. However, several important associations were observed providing insight into the potential non-cardiovascular/non-malignant risks of EC use.

Respiratory Health: Varella et al²⁷ identified an association between EC use and clinically significant respiratory symptoms, including cough, phlegm, or dyspnea when compared to individuals who have never used ECs. This association was independent of reported pre-existing asthma or COPD diagnoses. The prevalence of self-reported diagnosis of COPD, emphysema, or chronic bronchitis was significantly higher among individuals with current and former EC use than individuals who have never used ECs, even after stratifying for combustible cigarette use.²⁸

Behavioral Health: Several studies identified a significant association between symptoms of depression or anxiety and current or ever EC use. For example, Wiernik et al²⁹ described a dose-dependent trend, with symptom severity related to concentration of nicotine employed. Similarly, Obisesan et al³⁰ identified an association between current and former EC use and a reported diagnosis of depression, with individuals with daily use more likely to report depression than individuals with occasional use. Highlighting the phenomenological complexity of the issue, Saeed et al³¹ also identified an association between a self-reported diagnosis of depression and current EC use, while noting a significant interaction between EC use and marital/employment status and marijuana use.

Observational studies among vulnerable subgroups further support this association. For example, Adzrago et al³² confirmed higher rates of current and former EC use among Black individuals from sexual minority groups. Among Black heterosexual individuals, those with anxiety/depression symptoms were more likely to use ECs than those without. Antwi et al³³ reported that cancer survivors similarly characterized as having current or former EC use had a higher likelihood of clinical depression than individuals who had never used ECs. While comparing college students with a history of non-suicidal self-injury to those without, Striley et al³⁴ reported a relationship between last-12 month self-injury and use of ECs, including dual use and cannabis-based devices. Data from the Korea Youth Risk Behavior Survey suggested that asthmatic adolescents with EC experience were more likely to report current alcohol or combustible tobacco use, unhappier self-perception, increased stress, depressed moods, and frequent suicidal ideation/suicide attempts compared to their non-using peers.³⁵

Culbreth et al³⁶ identified an association between dual use (ie, combustible and non-combustible forms) and self-reported diagnosis of depression and child maltreatment. Among participants in a crowd-sourced electronic survey of adults aged 18-25 years, a plurality of EC-using respondents used more than 2 forms of nicotine delivery products, and reported higher rates of depression and anxiety symptoms than those who used ECs alone.³⁷ Respondents who reported using ECs more frequently than other tobacco products had greater odds of depression or anxiety symptoms.

Substance Use, Attention, and Academic

Performance: Within a cohort of undergraduate and graduate student respondents, Grant et al³⁸ identified an association between EC use and problematic alcohol and illicit substance use. Within this same sample, individuals who used ECs reported higher rates of posttraumatic stress disorder, attention deficit disorder, poor self-esteem, and greater impulsivity scores. Similarly, Kaplan et al³⁹ found adolescent individuals with cigarette, EC, and dual use had higher rates of parentally reported diagnosed attention-deficit/hyperactivity disorder than individuals with no use. Current dual use was likewise associated with higher rates of depression, binge and heavy drinking, with an 8-fold increase in odds of marijuana use compared with cigarette-only and nonuse.⁴⁰ Individuals who used ECs had higher impulsivity scores and were more likely to have ever used illegal drugs than individuals who had

never used ECs.⁴¹ These differences persisted among individuals with EC use who never used combustible cigarettes, but not among individuals who used ECs who did use combustible cigarettes. In an adjusted model of high school student behaviors, Dearfield et al⁴² identified an association between initiation of either ECs or combustible cigarettes with significantly lower 1-year academic performance.

Research Recommendations

Laboratory evidence has raised concerns over plausible mechanistic links between EC aerosol's ability to promote oxidative stress and the risk for inflammation-mediated diseases such as interstitial lung disease (ILD) and COPD,⁴³⁻⁴⁵ hemodynamic^{46,47} and vascular dysregulation,⁴⁸⁻⁵⁰ and atherosclerotic disease.^{51,52} Although much is known about the epidemiologic overlap of smoking and mental health,⁵³ a similarly important link between vaping and the development of mood disorders, attentional disturbances, and poor academic performance is less well-developed. Until the mechanisms underlying these associations are clarified, regulatory science objectives should assume EC aerosols have their own unique toxicologic profile, potentially distinct from that of tobacco smoke. Given the nature of the available science, common assumptions regarding the confounding role of risk-taking personalities or need for self-medication are insufficiently rigorous when considering risk for EC initiation.

8. In light of potential associations between EC aerosol and the development/exacerbation of inflammation-mediated conditions such as ILD and COPD, population-based research should pay increased attention to these conditions to inform regulatory decision making.
9. Future regulatory research should focus on clarifying the mechanisms of any identified causal relationships, interactions between vaping and important behavioral health risk factors, and long-term pragmatic implications of behavioral/cognitive effects of exposure.
10. Because dose-effect associations seem plausible, effort should be invested to identify user-controlled exposure patterns amplifying any deleterious effects of vaping. Particularly because device technology and nicotine chemistry are in rapid evolution, relationships between health impact and individual aerosol characteristics should be precisely defined.

Question 4: What is the specific impact of flavorant classes on airway biology?

Evidence Summary

Seven published articles were identified addressing the complex impact of specific flavorants, particularly tobacco and menthol, on airway biology (e-Table 4). Of these, 6 were performed *in vitro* on human cell or murine tissue preparations. A variety of measures were used to characterize impact on biology, including physical indicators such as fibroblast and bronchial epithelial cell cytotoxicity, contractile responsiveness to methacholine and ciliary beating, as well as biochemical signals such as impairment of mitochondrial oxidative phosphorylation and glycolysis.

In a study of human bronchial epithelial cells derived from patients with COPD, O'Farrell et al⁵⁴ were able to demonstrate clinically significant molecular and cellular damage resulting from exposure to tobacco and menthol flavored EC aerosols, comparable to the effects noted following combustible smoke exposure. Both Sundar et al⁵⁵ and Tommasi et al⁵⁶ demonstrated DNA damage to oral epithelial cells, which was dose dependent and correlated with available flavorants, including menthol. Behar et al⁵⁷ identified a relationship between the presence of multiple flavorants and fibroblast cytotoxicity, with menthol and cinnamaldehyde being the most toxic. Flavorant concentration and the voltage used to deliver the aerosol, a surrogate indicator of aerosol temperature, also affected toxicity. Morris et al⁵⁸ confirmed a similar effect on lung epithelial cells and macrophages. Herbert et al⁵⁹ were able to identify intrabronchial epithelial exfoliation within murine lung specimens exposed to menthol-containing aerosol condensates. In addition, they documented impaired contractile responsiveness following exposure to methacholine.

ACE2 and TMPRSS2 are proteins that facilitate entry of the SARS-CoV-2 virus into cells.⁶⁰ EC aerosol is known to increase their expression and potentially increase susceptibility to SARS-CoV-2 infection.⁶¹ Hamon et al⁶² addressed the question of how ACE2 and TMPRSS2 regulation is affected by EC aerosol constituents. When epithelial cells were exposed to either cigarette smoke or nicotine-containing EC aerosols, both ACE2 and TMPRSS2 expression were upregulated. Exposure to aerosolized EC flavorants alone increased ACE2 expression 2-fold while leaving TMPRSS2 expression unaffected.

Research Recommendations

Although relating these *in vitro* exposures to real-world use of these products is difficult, the clear demonstration of independent biochemical and histologic damage from flavorant aerosols is compelling. Since a wide range of examined flavorant aerosols have identified toxicity, regulatory research that guides manufacturers away from these harmful ingredients should be a priority. There is sufficient signal to confirm suspicions that user-defined exposure patterns are likely to affect the toxicity of these compounds. Future studies should continue to illuminate the potential human toxicity of these compounds, perhaps with more uniform comparators, exposure times, and real-world toxicant concentrations.

- 11. The regulatory research agenda should prioritize the precise quantification of potential toxicity among the individual components of EC aerosol, the potential synergistic effects of toxicant mixtures, and the interaction between toxicant delivery and the physical characteristics of the aerosol (eg, concentration, temperature, particle size, etc.).**
- 12. Toxicity assessments should account for wide variations in user-defined exposure patterns. Variables such as exposure duration, inter-puff interval, and depth of inhalation/delivery have the potential to influence the severity and type of injury.**
- 13. The potential population health benefit of ECs will depend on accurate placement of products on the proposed “continuum of risk.” To achieve this, researchers should strive to develop a validated risk scale that incorporates the complex data described above, and presents the relative risk of individual EC products in language accessible to a lay audience.**

Discussion

Despite individual data points describing several harmful effects of ECs, our review yielded a paucity of evidence directly investigating causal relationships between important EC aerosol exposure patterns and long-term deleterious effects. At minimum, given the breadth and consistency of currently identified associations, it is reasonable to call into question the validity of *de facto* assumptions regarding the EC's relative safety. This untenable evidentiary deficiency limits the effectiveness of regulatory agencies entrusted with promoting the population's health. High-quality

longitudinal surveillance studies will be necessary to ensure that ongoing regulatory positions remain responsive to our evolving understanding of the population health impact of these devices.

While sales restrictions seem to be a logical mechanism for regulation, there is sufficient evidence to conclude that poorly designed restrictions, particularly those that do not consider the evolving socio-cultural environment surrounding tobacco products, may be at best ineffective and at worst promote illegal trade. Much can be done to characterize the elements of effective restrictions and their anticipated impact on various sub-groups of individuals who use tobacco. Regulatory research programs aimed at promoting population health should facilitate a wide range of multi-disciplinary, quasi-experimental investigations to inform more comprehensive modeling of sale restriction impact.

It is clear that the pharmacokinetics of nicotine delivery influence the addictive liability of tobacco products and that various EC products yield a wide range of pharmacokinetic profiles. Label claims of nicotine concentration are insufficient for estimating toxicity potential since factors such as particle size, temperature, and pH affect bioavailability. However, as a general observation, lower concentration solutions are associated with reduced reinforcing capacity. Unintended consequences of restricting nicotine concentrations, such as the generation of additional toxicants or the development of compensatory behaviors, should be evaluated for each individual product to establish the balance that maximizes the population health benefit.

In addition to addictive liability, EC aerosol exposure has been associated with a variety of negative biological and psychosocial indicators. Our analysis of potential non-cardiac, non-malignant consequences leads us to strongly recommend that regulators apply a more expansive definition of potential “harms” when evaluating the impact of EC availability within a large and diverse population of consumers. Current information is sufficient to suggest that short-term safety testing of individual products within EC-naïve participants could be a required component of pre-market authorization and is likely to provide clinically significant information regarding potential long-term effects.

In vitro exposure to aerosols derived from EC flavorants clearly results in a variety of cytotoxic effects.

Consequently, concern within the medical community over whether to recommend the use of ECs as a behavioral modification technique is warranted. In preparing this report, the panel was equally impressed by outcomes that fell outside the framework of our research questions. Evidence that EC aerosols can cause increased rates of DNA damage and decreased rates of DNA repair,^{63,64} impaired airway defenses,⁶⁵⁻⁶⁷ emphysematous changes,^{68,69} and carcinogenic effects^{70,71} is equally compelling and deserves further human research.

Our analysis was limited to the 4 prioritized research questions that, in our view, warrant focused and urgent consideration by the research community and regulators. Many more important questions exist. Our effort represents only a first attempt at building consensus over what should constitute a robust regulatory research agenda. As the industry continues to rapidly evolve, the market availability of new devices and distribution channels, novel derivatives of nicotine, synthetic cooling agents, and non-nicotine alkaloids will continue to challenge the research community to employ ever-more sophisticated techniques to generate the data necessary for effective regulation of this product class.

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Additional information: The e-Appendix and e-Tables are available online under "Supplementary Data."

References

- Center for Tobacco Products. Family smoking prevention and tobacco control act—an overview. US Food and Drug Administration website. Accessed September 26, 2024. <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/family-smoking-prevention-and-tobacco-control-act-overview>
- Backinger CL, Meissner HI, Ashley DL. The FDA "deeming rule" and tobacco regulatory research. *Tob Regul Sci*. 2016;2(3):290-293.
- US Food and Drug Administration. Rules and regulations related to tobacco products. US Food and Drug Administration website. Accessed September 19, 2024. <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/rules-and-regulations>
- Cahn Z, Drope J, Douglas CE, et al. Applying the Population Health Standard to the regulation of electronic nicotine delivery systems. *Nicotine Tob Res*. 2020;23(5):780-789.
- US Food and Drug Administration. Center for Tobacco. Rules, regulations & guidance—tobacco control act. US Food and Drug Administration website. Accessed October 7, 2024. <https://www.fda.gov/tobaccoproducts/labeling/rulesregulationsguidance/ucm246129.htm>
- Wipfli HL, Berman M, Hanson K, et al. Defining tobacco regulatory science competencies. *Nicotine Tob Res*. 2017;19(2):222-230.
- Ashley DL, Backinger CL, van Bommel DM, Neveleff DJ. Tobacco regulatory science: research to inform regulatory action at the Food and Drug Administration's Center for Tobacco Products. *Nicotine Tob Res*. 2014;16(8):1045-1049.
- Berman ML, Connolly G, Cummings KM, et al. Providing a science base for the evaluation of tobacco products. *Tob Regul Sci*. 2015;1(1):76-93.
- Lee JGL, Soule EK. Evidence of potential tobacco industry influence in tobacco regulatory science. *Tob Control*. 2023;32(3):400-401.
- Uluçanlar S, Fooks GJ, Hatchard JL, Gilmore AB. Representation and misrepresentation of scientific evidence in contemporary tobacco regulation: a review of tobacco industry submissions to the UK Government Consultation on Standardised Packaging. *PLoS Med*. 2014;11(3):e1001629.
- Giovenco DP, Casseus M, Duncan DT, Coups EJ, Lewis MJ, Delnevo CD. Association between electronic cigarette marketing near schools and E-cigarette use among youth. *J Adolesc Health*. 2016;59(6):627-634.

12. D'Angelo H, Patel M, Rose SW. Convenience store access and E-cigarette advertising exposure is associated with future E-cigarette initiation among tobacco-naïve youth in the PATH Study (2013-2016). *J Adolesc Health*. 2021;68(4):794-800.
13. Bateman J, Robertson LA, Marsh L, Cameron C, Hoek J. An analysis of E-cigarette marketing in New Zealand tobacco retail outlets prior to legislative change. *Nicotine Tob Res*. 2020;22(7):1221-1224.
14. Wagoner KG, Song EY, King JL, et al. Availability and placement of electronic nicotine delivery systems at the point-of-sale. *Nicotine Tob Res*. 2017;20(8):1020.
15. Gaiha SM, Henriksen L, Halpern-Felsher B, et al. Sources of flavoured e-cigarettes among California youth and young adults: associations with local flavoured tobacco sales restrictions. *Tob Control*. 2022;31(5):659-662.
16. Gravely S, Meng G, Hammond D, et al. Electronic nicotine delivery systems (ENDS) flavours and devices used by adults before and after the 2020 US FDA ENDS enforcement priority: findings from the 2018 and 2020 US ITC Smoking and Vaping Surveys. *Tob Control*. 2022;31(suppl 3):s167-s175.
17. Romm KF, Henriksen L, Huang J, et al. Impact of existing and potential e-cigarette flavor restrictions on e-cigarette use among young adult e-cigarette users in 6 US metropolitan areas. *Prev Med Rep*. 2022;28:101901.
18. Dove MS, Gee K, Tong EK. Flavored tobacco sales restrictions and teen e-cigarette use: quasi-experimental evidence from California. *Nicotine Tob Res*. 2023;25(1):127-134.
19. Hawkins SS, Kruzic C, O'Brien M, Coley RL. Flavoured tobacco product restrictions in Massachusetts associated with reductions in adolescent cigarette and e-cigarette use. *Tob Control*. 2022;31(4):576-579.
20. Hajek P, Przulj D, Phillips-Waller A, Anderson R, McRobbie H. Initial ratings of different types of e-cigarettes and relationships between product appeal and nicotine delivery. *Psychopharmacology (Berl)*. 2018;235(4):1083-1092.
21. Higgins ST, Bergeria CL, Davis DR, et al. Response to reduced nicotine content cigarettes among smokers differing in tobacco dependence severity. *Prev Med*. 2018;117:15-23.
22. Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)*. 2016;233(15-16):2933-2941.
23. Kosmider L, Kimber CF, Kurek J, Corcoran O, Dawkins LE. Compensatory puffing with lower nicotine concentration E-liquids increases carbonyl exposure in E-cigarette aerosols. *Nicotine Tob Res*. 2018;20(8):998-1003.
24. Phillips-Waller A, Przulj D, Smith KM, Pesola F, Hajek P. Nicotine delivery and user reactions to Juul EU (20 mg/ml) compared with Juul US (59 mg/ml), cigarettes and other e-cigarette products. *Psychopharmacology (Berl)*. 2021;238(3):825-831.
25. Smets J, Baeyens F, Chaumont M, Adriaens K, Van Gucht D. When less is more: vaping low-nicotine vs. high-nicotine E-liquid is compensated by increased wattage and higher liquid consumption. *Int J Environ Res Public Health*. 2019;16(5):723.
26. PhenX Toolkit. Collections. PhenX Toolkit website. Accessed November 3, 2024. <https://www.phenxtoolkit.org/collections/view/3>
27. Varella MH, Andrade OA, Shaffer SM, et al. E-cigarette use and respiratory symptoms in residents of the United States: a BRFSS report. *PLoS One*. 2022;17(12):e0269760.
28. Barrameda R, Nguyen T, Wong V, et al. Use of E-cigarettes and self-reported lung disease among US adults. *Public Health Rep*. 2020;135(6):785-795.
29. Wiernik E, Airagnes G, Lequy E, et al. Electronic cigarette use is associated with depressive symptoms among smokers and former smokers: cross-sectional and longitudinal findings from the Constances cohort. *Addict Behav*. 2019;90:85-91.
30. Obisesan OH, Mirbolouk M, Osei AD, et al. Association between e-cigarette use and depression in the Behavioral Risk Factor Surveillance System, 2016-2017. *JAMA Netw Open*. 2019;2(12):e1916800.
31. Saeed OB, Chavan B, Haile ZT. Association between E-cigarette use and depression in US adults. *J Addict Med*. 2020;14(5):393.
32. Adzrago D, Harrell MB, Fujimoto K, Jones A, Wilkerson JM. Association between E-cigarette use behaviors and anxiety/depression among Black/African American adults based on sexual identity. *Int J Environ Res Public Health*. 2023;20(3):2078.
33. Antwi GO, Rhodes DL. Association between e-cigarette use and depression in US cancer survivors: a cross-sectional study. *J Cancer Surviv*. 2023;17(5):1452-1460.
34. Striley CW, Nutley SK, Hoeflich CC. E-cigarettes and non-suicidal self-injury: prevalence of risk behavior and variation by substance inhaled. *Front Psychiatry*. 2022;13:911136.
35. Kim CW, Jeong SC, Kim JY, et al. Associated factors for depression, suicidal ideation and suicide attempt among asthmatic adolescents with experience of electronic cigarette use. *Tob Induc Dis*. 2020;18:85.
36. Culbreth RE, Spears CA, Brandenberger K, et al. Dual use of electronic cigarettes and traditional cigarettes among adults: psychosocial correlates and associated respiratory symptoms. *Respir Care*. 2021;66(6):951-959.
37. Cwalina SN, Pacek LR, Barrington-Trimis JL, Tackett AP, Pentz MA. Cross-sectional associations of multiple tobacco product use with depressive and anxiety symptoms among young adult E-cigarette users. *Subst Use Misuse*. 2021;56(12):1807-1814.
38. Grant JE, Lust K, Fridberg DJ, King AC, Chamberlain SR. E-cigarette use (vaping) is associated with illicit drug use, mental health problems, and impulsivity in university students. *Ann Clin Psychiatry*. 2019;31(1):27-35.
39. Kaplan B, Marcell AV, Kaplan T, Cohen JE. Association between e-cigarette use and parents' report of attention deficit hyperactivity disorder among US youth. *Tob Induc Dis*. 2021;19:44.
40. Okunna N. A comparison of mental and behavioral health risks factors associated with current dual use of electronic cigarette and conventional tobacco cigarettes with exclusive tobacco cigarette use and nonuse among adults in the United States. *Am J Addict*. 2021;30(2):138-146.
41. Chivers LL, Hand DJ, Priest JS, Higgins ST. E-cigarette use among women of reproductive age: impulsivity, cigarette smoking status, and other risk factors. *Prev Med*. 2016;92:126-134.
42. Dearfield CT, Chen-Sankey JC, McNeel TS, Bernat DH, Choi K. E-cigarette initiation predicts subsequent academic performance among youth: results from the PATH Study. *Prev Med*. 2021;153:106781.
43. Prasad KN, Bondy SC. Electronic cigarette aerosol increases the risk of organ dysfunction by enhancing oxidative stress and inflammation. *Drug Chem Toxicol*. 2022;45(6):2561-2567.
44. Magna A, Polisena N, Polisena L, Bagnato C, Pacella E, Carnevale R, et al. The hidden dangers: E-cigarettes, heated tobacco, and their impact on oxidative stress and atherosclerosis—a systematic review and narrative synthesis of the evidence. *Antioxidants*. 2024;13(11):1395.
45. Chatterjee S, Tao JQ, Johncola A, et al. Acute exposure to e-cigarettes causes inflammation and pulmonary endothelial oxidative stress in nonsmoking, healthy young subjects. *Am J Physiol-Lung Cell Mol Physiol*. 2019;317(2):L155-L166.
46. Tattersall MC, Hughey CM, Piasecki TM, et al. Cardiovascular and pulmonary responses to acute use of electronic nicotine delivery systems and combustible cigarettes in long-term users. *Chest*. 2023;164(3):757-769.
47. Moheimani RS, Bhetraratana M, Yin F, et al. Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk. *JAMA Cardiol*. 2017;2(3):278-284.
48. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli FW. Acute effects of electronic cigarette aerosol inhalation on vascular function detected at quantitative MRI. *Radiology*. 2019;293(1):97-106.
49. Wehrli FW, Caporale A, Langham MC, Chatterjee S. New insights from MRI and cell biology into the acute vascular-metabolic

- implications of electronic cigarette vaping. *Front Physiol.* 2020;11:492.
50. Cirillo P, Morello M, Titolo G, et al. E-cigarettes induce expression of procoagulant tissue factor in cultivated human endothelial cells. *J Thromb Thrombolysis.* 2025;58(1):62-70.
 51. Damay VA, Setiawan, Lesmana R, et al. Electronic Cigarette and atherosclerosis: a comprehensive literature review of latest evidences. *Int J Vasc Med.* 2022;2022(1):4136811.
 52. Espinoza-Derout J, Hasan KM, Shao XM, et al. Chronic intermittent electronic cigarette exposure induces cardiac dysfunction and atherosclerosis in apolipoprotein-E knockout mice. *Am J Physiol-Heart Circ Physiol.* 2019;317(2):H445-H459.
 53. Barkhuizen W, Dudbridge F, Ronald A. Genetic overlap and causal associations between smoking behaviours and mental health. *Sci Rep.* 2021;11(1):14871.
 54. O'Farrell HE, Brown R, Brown Z, et al. E-cigarettes induce toxicity comparable to tobacco cigarettes in airway epithelium from patients with COPD. *Toxicol In Vitro.* 2021;75:105204.
 55. Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget.* 2016;7(47):77196-77204.
 56. Tommasi S, Blumenfeld H, Besaratinia A. Vaping dose, device type, and E-liquid flavor are determinants of DNA damage in electronic cigarette users. *Nicotine Tob Res.* 2023;25(6):1145-1154.
 57. Behar RZ, Luo W, McWhirter KJ, Pankow JF, Talbot P. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. *Sci Rep.* 2018;8(1):8288.
 58. Morris AM, Leonard SS, Fowles JR, Boots TE, Mnatsakanova A, Attfield KR. Effects of E-cigarette flavoring chemicals on human macrophages and bronchial epithelial cells. *Int J Environ Res Public Health.* 2021;18(21):11107.
 59. Herbert J, Kelty JS, Laskin JD, Laskin DL, Gow AJ. Menthol flavoring in e-cigarette condensate causes pulmonary dysfunction and cytotoxicity in precision cut lung slices. *Am J Physiol Lung Cell Mol Physiol.* 2023;324(3):L345-L357.
 60. Baughn LB, Sharma N, Elhaik E, Sekulic A, Bryce AH, Fonseca R. Targeting TMPRSS2 in SARS-CoV-2 infection. *Mayo Clin Proc.* 2020;95(9):1989-1999.
 61. Masso-Silva JA, Moshensky A, Shin J, et al. Chronic E-cigarette aerosol inhalation alters the immune state of the lungs and increases ACE2 expression, raising concern for altered response and susceptibility to SARS-CoV-2. *Front Physiol.* 2021;12:649604.
 62. Hamon R, Ween MP. E-cigarette vapour increases ACE2 and TMPRSS2 expression in a flavour- and nicotine-dependent manner. *Int J Environ Res Public Health.* 2022;19(22):14955.
 63. Tang M-S, Lee H-W, Weng M-W, et al. DNA damage, DNA repair and carcinogenicity: tobacco smoke versus electronic cigarette aerosol. *Mutat Res Mutat Res.* 2022;789:108409.
 64. Lee HW, Park SH, Weng M wen, et al. E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci.* 2018;115(7):E1560-E1569.
 65. Kesimer M. Another warning sign: high nicotine content in electronic cigarettes disrupts mucociliary clearance, the essential defense mechanism of the lung. *Am J Respir Crit Care Med.* 2019;200(9):1082-1084.
 66. Kalininskiy A, Kittel J, Nacca NE, Misra RS, Croft DP, McGraw MD. E-cigarette exposures, respiratory tract infections, and impaired innate immunity: a narrative review. *Pediatr Med Hong Kong China.* 2021;4:5.
 67. Reidel B, Radicioni G, Clapp P, et al. E-cigarette use causes a unique innate immune response in the lung involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med.* 2018;197(4):492-501.
 68. Bircan E, Bezirhan U, Porter A, Fagan P, Orloff MS. Electronic cigarette use and its association with asthma, chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap syndrome among never cigarette smokers. *Tob Induc Dis.* 2021;19:75.
 69. Perez MF, Atuegwu NC, Mead EL, Oncken C, Mortensen EM. Adult E-cigarettes use associated with a self-reported diagnosis of COPD. *Int J Environ Res Public Health.* 2019;16(20):3938.
 70. Mravec B, Tibensky M, Horvathova L, Babal P. E-cigarettes and cancer risk. *Cancer Prev Res (Phila).* 2020;13(2):137-144.
 71. Bittoni M, Carbone D, Harris R. Vaping, smoking and lung cancer risk. *J Oncol Res Ther.* 2024;9(3):10229.