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Review

# E-Cigarettes Reexamined: Product Toxicity

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**ABSTRACT**

**The introduction of e-cigarettes, or electronic nicotine delivery systems (ENDS), has been accompanied by controversy regarding their safety and effectiveness as a cessation aid and by an explosion in their use by youth. Their use does not involve the combustion of tobacco and the creation of harmful combustion products; they have been seen as a "harm reduction" tool that may be of assistance in promoting smoking cessation. Recognition that ENDS can deliver an array of chemicals and materials with known adverse consequences has spurred more careful examination of these products. Nicotine, nitrosamines, carbonyl compounds, heavy metals, free radicals, reactive oxygen species, particulate matter, and "emerging chemicals of concern" are among the constituents of the heated chemical aerosol that is inhaled when ENDS are used. They raise concerns for cardiovascular and respiratory health that merit the attention of clinicians and regulatory agencies. Frequently cited concerns include evidence of disordered respiratory function, altered hemodynamics, endothelial dysfunction, vascular reactivity, and enhanced thrombogenesis. The absence of evidence of the consequences of their long-term use is of additional concern. Their effectiveness as cessation aids and beneficial impact on health outcomes continue to be examined. It is important to ensure**

**RÉSUMÉ**

**L'introduction de la cigarette électronique, ou des inhalateurs électroniques de nicotine (ENDS, de l'anglais *electronic nicotin delivery systems*), a suscité la controverse quant à son innocuité et son efficacité pour faciliter la désaccoutumance et connu une explosion de son utilisation par les jeunes. L'utilisation des ENDS n'implique pas la combustion de tabac et ne génère pas de produits de combustion nocifs; ils ont été considérés comme des outils de « réduction des dommages » qui peuvent aider à favoriser la désaccoutumance au tabac. Le fait d'avoir constaté que les ENDS peuvent présenter un éventail de produits chimiques et de substances dont les conséquences néfastes sont connues a poussé à mener un examen plus approfondi de ces produits. La nicotine, les nitrosamines, les composés carbonylés, les métaux lourds, les radicaux libres, les espèces réactives de l'oxygène, la matière particulaire et « les nouveaux produits chimiques préoccupants » comptent parmi les constituants des aérosols chimiques chauffés qui sont inhalés lorsque les ENDS sont utilisés. Les inquiétudes en lien avec la santé cardiovasculaire et respiratoire qu'ils ont suscitées méritent l'attention des cliniciens et des organismes de réglementation. Les préoccupations les plus fréquemment citées sont notamment les**

E-cigarettes, or electronic nicotine delivery systems (ENDS), are devices presumed to represent a safer alternative to combustion-tobacco products. They deliver nicotine by the inhalation of an electronically heated nicotine-containing aerosol (or vapour) free of the products of combustion produced by the burning of tobacco. Given the role of combustion products in the etiology of much smoking-caused pathology it has been reasonable to assume that the use of ENDS represents a less harmful alternative to smoking. The magnitude of their overall capacity to reduce harm continues to be examined and assessed.[1,2] Many authors have compared the use of ENDS with smoking and documented an improvement of several parameters of cardiovascular function and risk in those using ENDS.[3-8] Nevertheless, the importance of developing greater knowledge regarding the long-term use of ENDS is frequently noted.[9] In this review we describe the design of ENDS and examine the toxic products associated with their use.

The story of ENDS began in the 1960s with the appearance of a patent application in the USA for a "smokeless nontobacco cigarette."[10] It reemerges in the 1990s with the development by Philip Morris of an electric smoking device activated by puffing,[11] and in 1994, with the arrival of a device that produced a heated aerosol.[12] It was not until 2003 that novel products appeared in China and the USA.[13] Thereafter the market for ENDS grew dramatically. Increases in sales were matched by the appearance of a variety of devices, evolving designs and technologies, and the introduction of countless flavouring agents to the nicotine-containing solution (the "e-liquid").[14] Dramatic growth in their use by youth and young adults was fuelled by lifestyle advertising, the popularity of flavourings, and social-media messaging leading, predictably, to the development of nicotine addiction and concerns regarding future tobacco use.[15-24]

First-generation devices were described as "cig-a-likes" (they resembled a cigarette—often with a glowing electronic tip). Second- and third-generation ("tank systems") devices evolved. The latter products provide opportunities to refill the device (typically with highly flavoured, often customized e-liquids) and to replace the rechargeable battery systems. As battery

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that their production and availability are thoughtfully regulated to optimise their safety and permit their use as harm reduction devices and potentially as smoking-cessation aids. It is equally vital to effectively prevent them from becoming ubiquitous consumer products with the potential to rapidly induce nicotine addiction among large numbers of youth. Clinicians should understand the nature of these products and the implications of their use.

données probantes sur les troubles respiratoires, les perturbations hémodynamiques, la dysfonction endothéliale, la réactivité vasculaire et l'augmentation de la thrombogenèse. L'absence de données probantes sur les conséquences de leur utilisation à long terme est en outre préoccupante. Leur efficacité pour faciliter la désaccoutumance au tabac et leurs répercussions bénéfiques sur les résultats cliniques continuent de faire l'objet d'études. Il est important de s'assurer que leur production et leur disponibilité sont soumises à une réglementation réfléchie de façon à optimiser leur innocuité, à permettre leur utilisation comme dispositifs de « réduction des dommages » et à potentiellement faciliter la désaccoutumance au tabac. Il est également essentiel de prévenir efficacement l'omniprésence de ces produits de consommation qui ont le potentiel d'induire rapidement la dépendance à la nicotine chez un grand nombre de jeunes. Les cliniciens doivent comprendre les spécificités de ces produits et les conséquences de leur utilisation.

power is enhanced (increasing the temperature at which the e-liquid is aerosolized) and/or the nature of the e-liquid is customized, an evolving array of chemicals may be created in the reactor that is the e-device.[25,26] Depending on the power of the battery and the temperature to which the e-liquid is heated, complex aerosols containing multiple substances may be produced. When inhaled, these substances are rapidly delivered via the pulmonary circulation to the arterial system. ENDS evolved more dramatically with the introduction of a fourth generation of products ("pod mods") typified by those manufactured by Juul. These products use an entirely new method of nicotine delivery utilising nicotine "salts," permitting the delivery of nicotine at levels not possible with conventional cigarettes. They quickly dominated the market.[27] The arrival of disposable nicotine-salt products, aggressively marketed to adolescents and teens, has amplified existing concerns regarding the increase in the use of these devices by youth.[24,28-30] The users of ENDS devices are commonly described as "vapers." While they are vehicles for the delivery of nicotine, the devices themselves contain or produce products with significant implications for health and those are the focus of this review (Table 1).

## The Nature of the Product

All ENDS use a liquid (commonly termed the e-liquid) containing nicotine, humectants—typically propylene glycol (PG; used to create smoke in discos and on theatre stages) or vegetable glycerine (VG)—and flavouring agents. None of these have been judged safe for human inhalation, although many have been "generally regarded as safe" (GRAS) for ingestion and have typically been used in foodstuffs. At one point there were more than 250 e-cigarette brands and more than 8000 flavourings available in the USA.[31] Flavour, price, and nicotine content are the ordered priorities for users when purchasing an e-cigarette.[32] The wick, containing substances that themselves may ultimately emerge in the aerosol, carries the e-liquid to a heating coil where it is vapourized. The coil itself can further contribute heavy metals and particulates to the aerosol.

### Nicotine

Nicotine is the fundamental desired element of the aerosol produced by ENDS. Arguably the most tenaciously addictive drug in our communities, nicotine addiction occurs rapidly following the acquisition of inhalation skills, and has unique effects across the human lifespan.[33,34] Any consideration of the toxicology associated with the use of ENDS must recognise nicotine's highly addictive nature,[33] the consequences of nicotine addiction when acquired by adolescents,[23,35-43] and the propensity for users of ENDS to continue to smoke, becoming "dual users" with no attenuation of risk and a diminished likelihood of cessation.[44-48] It has been suggested that for every smoker who successfully quits using ENDS, 80 adolescents become addicted to nicotine.[49] Recent evidence, however, suggests that the feared sequela of adolescent e-cigarette use—an increased rate of smoking—has not emerged.[50] Nevertheless, given the large numbers of adolescents who vape, many of whom are never-smokers, concerns about the known neurologic consequences of nicotine exposure during a critical period of brain development are paramount. They may foreshadow an array of future substance abuse and mental health challenges.[35,51-56]

Animal and human models of exposure to nicotine provide evidence of diminished weight gain,[57] airway hyperresponsiveness,[58,59] changes in alveolar and bronchial function,[60] arterial stiffness,[61] and increases in heart rate and systolic blood pressure,[62] and altered cardiac function.[63,64] Distorted endothelial function and a prothrombotic state have been identified following exposure to nicotine-containing e-cigarette aerosols.[64-66]

### Propylene glycol and vegetable glycerine

Typically, the largest components of the liquid within an e-cigarette are the carriers (PG or VG) of nicotine and added flavouring agents. Thermal degradation of PG can result in the formation of propylene oxide, which is recognised as a class 2B carcinogen.[67] Acute exposure to PG or VG does not appear to produce changes in pulmonary function, but chronic exposure warrants scrutiny.[68] When heated, PG contributes to the formation of carbonyl compounds—acrolein, formaldehyde, acetaldehyde, acetone, and other secondary products.[69,70] Carbonyl formation can be dramatically influenced by a "dry puff": In the absence of sufficient e-liquid the temperature of the heating coil can rise dramatically and produce significantly higher concentrations of formaldehyde, acetaldehyde, and acrolein than those

**Table 1.** E-cigarette products and their health impact

| Chemical emitted | Health effects |
|---|---|
| Nicotine | Addiction |
| | Lung tumour promoter |
| | Increases HR an BP |
| | Vasoconstriction |
| | Sympathomimetic |
| | Altered brain development—adolescents |
| Acetaldehyde | Carcinogen |
| | Aggravation of liver damage |
| Acrolein | Respiratory irritation |
| | Gastrointestinal irritation |
| | Ocular irritation |
| Formaldehyde | Carcinogen |
| | Bronchitis |
| | Pneumonia |
| | Asthma |
| Propylene glycol | Throat, airway irritation |
| | Carcinogen |
| | Gastric distress |
| | Asthma |
| | Ocular irritation |
| Glycerine | Lipoid pneumonia |
| | Ocular, dermal, pulmonary irritant |
| Nitrosamines | Carcinogen |
| Chromium | Pulmonary irritation/inflammation |
| | Nasal mucosa atrophy and ulcerations |
| | Reproductive and fertility issues |
| Cadmium | Increased risk of lung cancer |
| | Pulmonary and nasal irritation |
| Lead | Hypertension |
| | Renal damage |
| | CNS damage |
| Nickel | Carcinogen |
| | CNS and pulmonary damage |
| | Renal and hepatic toxicity |

CNS, central nervous system.



produced by a conventional cigarette.[71] Acrolein, an irritant, damages lung tissue and contributes to cardiovascular disease (CVD) by increasing oxidative stress and endothelial inflammation, contributing to the progression of atherosclerosis.[72] Formaldehyde, a recognised carcinogen, can react further with PG and glycerol to produce hemiacetals, known formaldehyde-releasing agents used as industrial biocides.[73] In addition, PG can produce methylglyoxal, acetaldehyde, and propionaldehyde. Methylglyoxal can give rise to glycation end-products associated with diabetes and neurodegenerative disorders.[74] The production of these compounds and their interactions are all affected by the nature of the e-liquid and the temperature to which it is heated. These may vary considerably as users increase battery power and otherwise modify their devices.[70,75]

## Flavours

Any understanding of the toxicity of ENDS is complicated by the almost countless array of flavouring agents that may be added to the e-liquid at levels likely to produce cytotoxicity, which has been described as "an unrecognised health hazard."[68,76,77] They may have been approved for ingestion in foodstuffs, not for inhalation, and accumulating evidence demonstrates that they can be toxic and produce dermal and airway irritation.[68] Initially, tobacco and menthol flavours were preferred; fruit flavours soon topped the popularity list particularly among youth.[78] Flavour usage has been noted as "more prevalent in the vaping industry than in any other."[79] They are described using unique and often provocative names like watermelon wave, love potion, and unicorn puke, and constitute a powerful sensory inducement to ENDS use.[22]

Evidence suggests that "flavoured e-cigarette users could be at risk for inhalation toxicity across a range of flavouring types."[80] Diacetyl and cinnamaldehyde have been identified as particularly toxic.[81] Diacetyl, used to impart a buttery flavour, has been implicated in the development of bronchiolitis obliterans ("popcorn lung") an irreversible lung disease among food industry workers.[82-84] No cases of popcorn lung have as yet been identified in ENDS users, but it has been noted that they are exposed to a significantly higher noncarcinogenic risk of lung injury as a result of exposure to diacetyl.[84] A replacement for diacetyl, 2,3-pentanedione, has been associated with airway fibrosis in animal models and seen to be as problematic as diacetyl itself.[85] Flavours not only contribute to product appeal,[86] but also may mask the harshness of inhaled aerosols, thereby potentiating the likelihood of nicotine dependence.[87] They are seen to be involved in the production of oxidative stress, the release of inflammatory cytokines, decreased phagocytosis, and diminished inflammatory responses in respiratory tissues.[88,89] Synthetic cooling agents are added at levels that pose additional potential health risks to users.[90,91] *In vitro* investigations using respiratory cell lines have demonstrated that flavours can induce cytotoxic responses producing epithelial injury and stimulating profibrotic lesions.[92,93] Recognition of the role of flavours as a factor in the use of ENDS by youth and their associated respiratory hazards has led governments to regulate or ban their use entirely. Since 2020, the use of any flavours other than tobacco and menthol in cartridge-based ENDS (ie, pods) has been banned in the USA and attention has now shifted to the impact of menthol and tobacco flavourings.[78] ENDS using menthol flavours are favoured by consumers because menthol results in an improvement in taste permitting the delivery of higher levels of nicotine.[94] The European Union bans the use of additives that have carcinogenic, mutagenic, or reprotoxic properties and requires that "ingredients may not pose a risk to human health in heated or unheated form." It is anticipated that, in Canada, regulations addressing flavouring agents in ENDS will be introduced in 2022.

## Metals

E-cigarettes are a source of exposure to a broad variety of toxic metals (Box 1).[95] The brand of e-liquid, coil construction, presence of flavours, and modifications affecting battery voltage, coil resistance, and heating temperature can all influence production of, and exposure to, metals.[96,97] Multiple metals and metalloids have been identified in e-cigarette products and user biosamples. Many are found at higher levels in biosamples of e-cigarette users than in those of conventional smokers.[95,98] Serious health impacts—neurotoxicity, CVD, respiratory disease, renal damage, and lung cancer —can follow such exposure.[99-101] Particular metals (eg, manganese and nickel) may be present in excess of chronic minimum risk levels and many, such as nickel, have known serious adverse effects as carcinogens and contributors to diminished lung function.[96,102] Specific

**Box 1. Metals/metalloids derived from e-cigarette samples[95]**

- Aluminum
- Antimony
- Arsenic
- Cadmium
- Chromium
- Cobalt
- Copper
- Iron
- Lead
- Manganese
- Nickel
- Selenium
- Tin
- Zinc

flavours (tobacco and menthol) may potentiate exposure to aluminum, iron, selenium, uranium, and tungsten.[96]

It is hypothesised that metallic elements are found in the heating coil, transferred to the e-liquid and ultimately inhaled in the aerosol. Metals commonly used in the construction of the heating coils include lanthal (chromium, iron, and aluminum) and nichrome (nickel and chromium); magnesium and zinc also have been identified, and tin may be used in the construction of joints.[99] Chromium and nickel have been identified as potentially the most significant contributors to cancer and noncancer risks from vaping[101]; their presence in saliva and urine mirror levels found in e-cigarette aerosols.[103] Lead, chromium, arsenic, and nickel are also found in e-liquids and aerosols.[99] The detection of lead is a cause of concern not only for the health of ENDS users, but also for those involuntarily exposed to the aerosol they produce, especially children.[99,104]

It has been noted that "e-cigarette liquids and aerosols are a significant and highly variable source of metals, leading to unacceptably high cancer and noncancer risks at the middle and high end of the reported ranges. Chromium and nickel are the leading contributors to these risks, with cadmium, lead, manganese, and arsenic as minor contributors."[101]

**Table 2. Vaping's impact on the respiratory system**

| Tissue | Effect |
|---|---|
| Nasal epithelia | Down-regulation of immune genes |
| | Inhibition of ciliary beating |
| Sputum | Altered sputum proteome |
| | Increased proteases |
| | Impaired macrophage function |
| Bronchial epithelia | Altered protein expression |
| | Inhibition of ciliary beating |
| | Airway dehydration |
| | Cellular toxicity |
| | Increased cytokine secretion |
| | Altered gene expression |
| Alveoli | Increase in lipid laden macrophages |
| | Impairment of gas exchange |
| | Increased vascular stiffness |

Data from Gotts et al.[115]

### Emerging chemicals of concern

ENDS, typically constructed of metals, plastics, and glass, may contain a number of emerging chemicals of concern (ECCs), including phthalate plasticizers, phenolic compounds, and flame retardants.[105] The significance and safety concerns of these constituents may not generally be appreciated or understood. Phthalates are the most prevalent ECCs found in ENDS, followed by parabens and organophosphate flame retardants. Such chemicals are widely used as plasticizers, flame retardants, preservatives, lubricants, surfactants, and antifoaming stabilisers in a wide variety of electronic, medical, and consumer products.[106,107] Recognition of their presence in the population and their association with a number of health concerns prompts ongoing concern.[108-112] Many of these chemicals have been recognised as endocrine disruptors capable of upsetting normal hormonal activities, with implications for carcinogenesis, neurotoxicity, and reproductive and endocrine dysfunction.[110,113] They are more frequently detected in the mouthpieces, cartridges, and tanks of ENDS than in the e-liquid and may leach or outgas, leading to human exposure.[114] The potential negative health impact of such agents requires ongoing scrutiny. Their presence in, and release from, ENDS underscore the reality that the constituents of e-devices and the products of their use raise concerns and issues that are more complex than generally realized.

## Clinical Considerations—Respiratory

The inhalation of heated aerosols containing a complex mixture of chemical products raises immediate concerns regarding respiratory health (Table 2). PG, VG, nicotine, flavouring agents, and degradation products (eg, formaldehyde, acetaldehyde, acrolein, glycidol) have all been shown to have deleterious effects on respiratory tissues and function,[115,116] ENDS use has been associated with increased risk for respiratory disease independent of cigarette smoking.[117] There is growing evidence that their use causes lung inflammation and injury.[118] Users report a variety of negative nasopharyngeal, oral, and respiratory symptoms consistent with evidence derived from human and animal studies.[115,119-121] Recent reviews, incorporating human and animal studies, demonstrate that ENDS disrupt normal lung physiology, alter gas exchange, affect airway resistance and reactivity, promote airway obstruction and inflammation, stimulate epithelial to mesenchymal transition changes in epithelial tissues, and diminish respiratory immunity.[57,122-126] Metabolic processes in the lung may be altered, and molecular markers of pulmonary disease are up-regulated in the airways of vapers.[126] Animal models reveal evidence of systemic inflammation, altered mucin production, mucociliary dysfunction, and increased susceptibility to infection.[127]

Evidence of the impact of vaping on lung function has been mixed. Some studies have demonstrated changes in forced 1-second expiratory volume (FEV1),[128,129] but others have not.[130,131] It has been noted that "such measures may not be a sensitive index of the early effects of vaping and should be interpreted with caution."[126] Vaping has been noted to disrupt ventilation-perfusion matching, suggesting subclinical alterations in lung function not identified by spirometry.[132] Cessation from vaping for 5 days, however, can

**Table 3.** Vaping and cardiovascular considerations

| Mechanism | Potential implication |
|---|---|
| Sympathetic stimulation | Hypertension |
| Increased oxidative stress | Tachyarrhythmia |
| Endothelial dysfunction | Peripheral vascular disease |
| Altered flow-mediated dilatation | Coronary artery disease |
| Angiogenesis | Ischemic heart disease |
| Thrombogenesis | Thrombosis |
| Decreased anticoagulation | Myocardial infarction/stroke |
| Cardiac remodelling | Cardiomyopathy |
| | Congestive heart failure |

increase forced expiratory flow at 25% of forced vital capacity, suggesting an improvement in lung function.[65]

ENDS users are at higher risk of wheezing-related respiratory symptoms, asthma, bronchitis, emphysema, and chronic obstructive lung disease (COPD).[133-135] Individuals with preexisting lung conditions are deemed to be most at risk.[136,137] An increase in the odds of developing COPD is associated with increasing use of e-cigarettes among those with no history of smoking (OR 1.75, 95% CI 1.25-2.45); the risk is greater in those using ENDS daily (OR 2.64, 95% CI 1.43-4.89).[133] E-cigarette vapour can enhance the inflammatory potential and virulence of known respiratory pathogens.[138,139]

Nonhuman animal models demonstrate that exposure to ENDS aerosol can result in the development of lung cancer.[140] Passive exposure to second-hand aerosols leads to rapid alteration in respiratory mechanics and exhaled biomarkers of inflammation.[141] Such exposure has implications for the respiratory health of those exposed to second-hand vaping.[142]

## Clinical Considerations—Cardiovascular

It is important to acknowledge the evidence that exists regarding ENDS use and its impact on cardiovascular function (Table 3) and equally important to recognise that there is a nonlinear relationship between exposure to tobacco products and CVD development.[143] Our knowledge of the long-term impact of e-cigarette use on the cardiovascular system is limited but evolving.[126,144-146] A systematic review scrutinising studies involving human and other animal cardiovascular tissues found evidence of potentially harmful effects of e-cigarettes in the majority of the investigations examined.[147] Enhanced risk of atherosclerosis, thrombosis, and increased sympathetic activity were deemed to increase the risk of cardiovascular harm.[147-149] Nicotine has known complex effects on the cardiovascular system, among which are its effects on heart rate, blood pressure, lipids, myocardial contractility, angiogenesis, and coronary vasoconstriction.[62,67,150,151]

Changes in vascular function and reactivity have been demonstrated in vapers and in animal studies.[152,153] Chronic intermittent exposure to e-cigarettes has led to changes suggestive of cardiomyopathy and diminished ejection fractions in mice[63] and have led to the development of CVD in mice at a rate that is similar to that noted with cigarette smoking.[154] Human and animal models show that flow-mediated dilation, arterial stiffness, nitric oxide production, and endothelial cell function are all affected by exposure to e-cigarettes.[66,155-157] Exposure to aerosol from fourth-generation pod devices (eg, Juul) impairs endothelial function in rodents to a level similar to that produced by conventional cigarette smoke.[158] Animal models demonstrate that e-cigarettes stimulate platelet activity, increase arterial stiffness and impair normal vascular reactivity responses, thereby increasing the risk of thrombogenic events.[61,159] Enhanced platelet activity, greater than that produced by smoking, has been noted with chronic vaping.[160]

Exposure to ENDS causes inflammation and oxidative stress, leading—even in the absence of nicotine—to endothelial dysfunction, a known factor in the development of vascular disease.[152,156,157] Increased arterial stiffness, a marker for thrombosis-dependent CVD, occurs after minimal exposure to e-cigarettes in humans.[156] Studies involving humans and other animals have implicated acrolein as a principal disruptor of endothelial function.[161-164] Second-hand exposure to acrolein is of significance in closed environments typified by home settings.[165] Other investigators have suggested that metals, known to be cardiotoxic and present in e-cigarettes, play a role in disrupting normal vascular function.[100] The carbonyls—typically aldehydes—are present in ENDS aerosols and have been noted to induce cardiovascular toxicity.[145,166,167] Ultrafine particles ($< 2.5$ μm) are present in ENDS aerosols[168,169] and have been linked to hypertension, atherosclerosis, coronary artery disease, myocardial infarction, and arrhythmia.[170-173] There is a nonlinear relationship between particulate exposure and cardiovascular mortality; low-level exposures can contribute to cardiovascular outcomes.[145]

A significantly higher risk of CVD has been noted in dual users of e-cigarettes and conventional products compared with smoking alone.[174] Recent investigations have suggested that those using e-cigarettes, compared with smokers, do not have a more favourable vascular profile when assessed by measurements of vascular function.[175] Other investigators have noted that smokers, particularly females, show significant improvement in vascular health within one month of switching to e-cigarettes.[176] It is important to recognise that the hemodynamic impact of ENDS use is lessened compared with that noted with the use of conventional tobacco products, and a reduction in biomarkers of exposure occurs after a transition to sole ENDS use,[177] signalling a potential harm-reduction benefit for those who switch completely to ENDS.[178] The risk of ENDS for cardiovascular health, while thought to be less than that of smoking, remains uncertain.[179,180]

## Harm Reduction and Smoking Cessation

It is important to contextualise claims about the relative safety of ENDS. The oft-repeated, but unsubstantiated, assertion that ENDS are "95% safer" than combustion products has been described as a factoid.[181,182] More recent estimates of the consequences of e-cigarette use (which do not consider the implications of their use by youth) suggest that they are at most one-third as harmful to health as smoking.[1] Although ENDS may rightly be regarded as less harmful, they are not harmless.[183,184] A 6-year follow up of ENDS users found no evidence of a significant decrease in the rate of diseases potentially related to tobacco, and no substantial improvement in self-reported health."[185]

There is clear evidence that ENDS, in clinical trials, can enhance rates of smoking cessation compared with other cessation aids.[186-192] As consumer products in community settings, however, the evidence is less encouraging: E-cigarettes in many studies do not appear to be associated with enhanced

rates of quitting.[47,193-206] Most users report using ENDS to assist with smoking cessation; dual use is, however, the most common pattern of use reported, and long-term studies are required to assess the health impacts that may follow.[9] Former smokers who vape are more likely to relapse to smoking and are an additional focus of concern.[9,48] No ENDS manufacturer has applied for permission to market their products as a medical device to assist with smoking cessation.

## The Way Ahead?

Any examination of ENDS must acknowledge their potential to reduce harm while noting that concerns remain regarding their use and safety. There have been appeals to balance considerations of their risks and benefits with an emphasis on weighing "vaping's potential to reduce adult smoking-attributable mortality."[206] Others have decried the creation of a controversy between those who seem to oppose harm reduction ("fervent opponents") and those who endorse their use as cessation and harm-reduction aids ("enthusiastic supporters") and urge a more balanced consideration of these devices.[184,207]

Regulation of these products in Canada has been neither appropriate nor timely.[208] Many provincial governments acted to fill the regulatory void produced by the lack of initial federal oversight of ENDS by introducing regulations that restricted levels of nicotine, banned flavouring agents, and addressed the marketing excesses of the vaping industry. More federal regulation is anticipated in 2022.

Thoughtful regulation of these products will seek to ensure the minimisation of the risks associated with their use by regulating nicotine content and eliminating the presence of flavouring agents (with the exception of tobacco) to facilitate their use as smoking-cessation or harm-reduction products. At the same time it will be necessary to apply the tools that have proved effective in the struggle against conventional tobacco products: elimination of marketing, pricing, and availability strategies and appropriate retail regulations to forestall an epidemic of youth vaping. Though less harmful than cigarettes, ENDS are not harmless.

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