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E-CIGARETTE USE

EVIDENCE-INFORMED GUIDANCE ON HARMS AND BENEFITS

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*Vaping and electronic cigarette toxicity overview and recommendations (Project **VECTOR**)*

Funded by Health Canada's Substance Use and Addictions Program
The views expressed herein do not necessarily represent the views of Health Canada.

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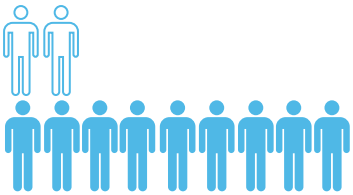
Preamble

Between October 2022 and March 2024, the Innovation, Nicotine, Tobacco, Research, Education, Programming, Implementation and Digital Health (INTREPID) Lab at the Centre for Addiction and Mental Health collaborated with international subject matter experts and people with lived experience to develop evidence-informed recommendations on the relative health outcomes of e-cigarette use. This guidance resource was developed as part of a project entitled *Vaping and electronic cigarette toxicity overview and recommendations (Project **VECTOR**)*, made possible through Health Canada's Substance Use and Addictions Program (SUAP).

E-cigarettes, also referred to as electronic cigarettes, vaping devices, vape pens or electronic nicotine delivery systems (ENDS), are battery-powered devices that heat up a liquid solution (also referred to as "e-liquids" or "vape juice") into an aerosol for inhalation (Health Canada, 2023). While e-liquid products are available with and without nicotine and/or cannabis, the following resource refers primarily to the use of e-cigarettes that contain nicotine. E-cigarette devices have undergone a substantial evolution since first-generation models in their availability, design, and e-liquid composition, including nicotine salts and flavours.

Since e-cigarettes first appeared on the Canadian market in the late 2000s, the prevalence of use has increased rapidly, especially among youth. In 2022, 18.2% of Canadians aged 15 years and older had ever used e-cigarettes (with and without nicotine), compared to only 9% in 2013 (Statistics Canada, 2013; 2023). Primary reasons for using e-cigarettes vary across different age groups. While the most commonly reported reasons for e-cigarette use among Canadian adults who vaped in the past 30 days were to reduce stress and smoking cessation—21.7% and 18.8%, respectively (Statistics Canada, 2023)—younger people aged 15 to 19 reported using e-cigarettes for stress reduction (30.5%), curiosity (27.0%), and enjoyment (22.9%). Despite this increase in prevalence of use, many health care practitioners are not adequately informed on the risks and benefits of e-cigarette use and report this as a barrier to providing support to clients (Westmaas et al., 2023; Metcalf et al., 2022).

While e-cigarette use increases the number of people exposed to nicotine, potentially impacting efforts to address nicotine dependence, it may simultaneously provide a lower-risk alternative for those who use commercial



In 2022, about

2 out of 11

Canadians aged 15 years and older had ever vaped

Definitions related to length of exposure, age range, and clinical terminology can be found at the end of the resource.

combustible tobacco. There is interest among health care practitioners and Health Canada regarding the scientific evidence on the harms and benefits of using e-cigarette products at the individual and population level. The recommendations developed through this project examine existing evidence on the health impacts of e-cigarette use to conduct a nuanced harm-benefit analysis. The recommendations are intended as a decision-making and guidance resource for both healthcare practitioners and for people who either use, or are thinking of using e-cigarettes.

The Ontario Tobacco Research Unit (OTRU) conducted systematic and umbrella reviews of literature published between September 2017 to January 2023 and January 2018 to January 2023, respectively (articles forthcoming). OTRU used the GRADE methodology to evaluate the quality and strength of the evidence. Following these initial reviews, the Project VECTOR team held a two-day, hybrid (in-person and virtual) Advisory Group (AG) meeting to review the evidence,. The AG members drafted and voted on recommendations on the use of nicotine-containing e-cigarettes using a facilitated consensus-based approach. AG membership included international tobacco, nicotine and e-cigarette experts and peolpe with lived experience using e-cigarettes. Additional consideration statements were drafted during and after the hybrid meeting and confirmed post-gathering via electronic communication.

OTRU conducted a second systematic review of literature published between January 2023 to December 2023 to capture any relevant up-to-the-minute evidence (articles forthcoming). To read the declared conflicts of panel members, please contact the INTREPID Lab team at Intrepid.Lab@camh.ca.

A Note on Sex- and Gender-Based Analysis Plus

There is insufficient evidence from human studies investigating the impact and interactions of sex-related (biological) factors and gender-related (social) factors, and their intersections with factors such as age, income, race, ethnicity, etc., on health outcomes from e-cigarette use, including dependence. However, extensive research on tobacco use demonstrates how both sex- and gender-related factors can affect nicotine metabolism and smoking behaviours (Benowitz et al., 2006; Carpenter et al., 2006). Additional research on e-cigarette use is needed to fill the evidence gap regarding sex and gender plus subgroups.

Disclaimers

1. There is currently no consensus among experts on the use of the language around nicotine use disorder or nicotine dependence when referring to people who use e-cigarettes and want to quit (CAMH, 2022).
2. The recommendations in this resource are meant to provide general guidance applicable to a broad audience. Due to the lack of available research, no specific adaptations for equity-deserving populations have been made at this time.
3. Findings from future research may modify the recommendations listed in this guidance resource. At this time, additional research is needed to better understand the potential long-term health effects of e-cigarette use.
4. The ongoing evolution and variability of e-cigarettes and e-liquids presents a challenge in understanding the full breadth of health effects associated with vaping. Newer e-cigarette products may deliver nicotine more effectively and may not have the same design, components, and ingredients as older devices. Some harmful ingredients included in earlier e-liquids (e.g., diacetyl) have since been prohibited in Canada or no longer are in use. Future research on newer products may identify new chemicals and produce novel findings on their health effects and toxicity.

General Considerations

1. While e-cigarettes are currently assumed to be less harmful than combustible tobacco cigarettes, they are not risk-free, and their use has the potential to cause harm.

2. E-cigarette use is associated with increases in dependence. There are biopsychosocial factors that determine chronic use and level of dependence. Several factors can influence the level of dependence among people who use nicotine-containing e-cigarettes, including prior use of nicotine products and duration of use. In general, the greater frequency and time spent using a substance, the higher the risk of dependence.

3. Dual use of e-cigarettes and commercial combustible tobacco products should be discouraged as it exposes users to an increased number of chemicals, which may increase their risk of harm.

4. It is important for researchers and health care practitioners to consider how both biological and social factors may affect e-cigarette use and health outcomes, including dependence. Practitioners should always center a person's biology, and social and cultural identities, and use intersectional, equity-oriented, and trauma-informed approaches when creating treatment plans with clients.

5. The oral ingestion (intentional or accidental) of nicotine-containing e-liquid should be avoided, as this can result in serious adverse events, including coma, respiratory arrest and brain death. E-liquid containing nicotine can also be harmful if absorbed through the skin. E-liquids should be properly stored and clearly labeled to prevent children from accidental exposure.

6. Several factors can influence the level of exposure to nicotine and non-nicotine toxicants in e-cigarettes, including the voltage/power of the device, device type (e.g., disposable, generation), e-liquid ingredients and concentration, and patterns of use, including puff topography (NASEM, 2018). A combination of these factors may lead to variable effects on health.

7. Vaping-Associated Lung Illness (VALI), also referred to as E-cigarette or Vaping Use Associated Lung Injury (EVALI), according to studies in the United States, appears to be predominantly associated with vitamin E acetate, an additive in some cannabis (i.e., THC, CBD) e-liquids. Vitamin E acetate is generally not found in regular nicotine e-liquids.

Recommendations

This section includes recommendations and considerations for the following topics: cancer, cardiovascular health, dependence, and respiratory health.

The recommendation development group, composed of both subject matter experts and people with lived experience, voted on the evidence quality and each recommendation's strength using a consensus approach.

Evidence Quality

High

There is strong confidence in the evidence to predict actual outcomes.

Moderate

There is strong confidence that the evidence is close to the actual outcomes.

Low

The predicted outcomes in the evidence may be markedly different from the actual effects.

High/Moderate

A consensus of the recommendation development group members designated the overall quality of the evidence as high or moderate, with a larger proportion rating the certainty of the evidence as high.

Moderate/High

A consensus of the recommendation development group members designated the overall quality of the evidence as high or moderate, with a larger proportion rating the certainty of the evidence as moderate.

Moderate/Low

A consensus of the recommendation development group members designated the overall quality of the evidence as moderate, low, or very low, with the largest proportion rating the certainty of the evidence as moderate.

Strength of Recommendation

All recommendations in the guidance resource received a consensus vote of "Strong" by the recommendation development group, except for recommendation 2b in the "Dependence" section where no consensus could be reached.

Strong	implies that most or all individuals will be best served by the recommended course of action
Conditional	implies that not all individuals will be best served by the recommended course of action
No consensus	Among the recommendation development group members, a consensus could not be reached regarding the strength of the recommendation.

Cancer

Recommendation	Evidence Quality
1. **People who do not smoke should not use e-cigarettes in order to avoid exposure to cancer-causing chemicals.**	High/Moderate 
2. **Tobacco users* who have been unable/unwilling to quit using current best evidence-based approaches, should switch completely to e-cigarettes to reduce exposure to tobacco-related cancer-causing chemicals.**	High/Moderate 
3. **People who use e-cigarettes should avoid long-term use of e-cigarettes (where relapse to combustible cigarettes is not a concern) in order to reduce exposure to cancer-causing chemicals.**	Moderate/High 

Consideration Statement

While there is no current evidence from human studies to suggest that e-cigarettes cause cancer, there is evidence that people who use e-cigarettes are exposed to cancer-causing chemicals. Using e-cigarette products instead of smoking combustible tobacco leads to a significant reduction in exposure to cancer-causing chemicals.

Health care practitioners should discuss the potential overall health risks associated with using e-cigarette products with their clients. For commercial combustible tobacco cigarette smokers, the potential health risks of e-cigarettes should be compared with other evidence-based treatment options, such as nicotine replacement therapy.

*Tobacco users as a term refers to individuals who use commercial combustible tobacco products, including cigarettes, cigars, hookah, or pipes. This recommendation will need adaptation if applied to children and adolescent tobacco users.

Cardiovascular Health

Recommendation	Evidence Quality
1. People who do not smoke should not use e-cigarettes in order to avoid exposure to:	
1a) cancer-causing chemicals.	High/Moderate 
1b) adverse effects on the cardiovascular system.	Moderate/High 
2. Tobacco users* who have been unable/unwilling to quit using current best evidence-based approaches, should switch completely to nicotine-containing e-cigarettes to reduce:	
2a) exposure to cardiovascular toxicants and	Moderate/High 
2b) improve measures of cardiovascular function.	Moderate/Low 

Consideration Statement

Health care practitioners should exercise caution when recommending e-cigarettes to clients who have had cardiovascular events, such as myocardial infarctions. This is because:

1. Acute use of nicotine-containing e-cigarettes is associated with increases in heart rate and blood pressure equivalent to the acute use of combustible cigarettes.
2. Acute use of nicotine and non-nicotine-containing e-cigarettes is associated with increases in endothelial dysfunction (flow-mediated dilatation) and arterial stiffness.

*Tobacco users as a term refers to individuals who use commercial combustible tobacco products, including cigarettes, cigars, hookah, or pipes. This recommendation will need adaptation if applied to children and adolescent tobacco users.

Dependence

Recommendation	Evidence Quality
1. **Those who do not smoke should not use nicotine-containing e-cigarettes as it may lead to dependence.**	High/Moderate 
2. **Tobacco users* who have been unable/unwilling to quit using current best evidence-based approaches, should switch completely to nicotine-containing e-cigarettes to:**	
2a) increase their chance of remaining smoke-free	High/Moderate 
2b) reduce their dependence**	Moderate/Low 
3. **People who use nicotine-containing e-cigarettes should avoid long-term use (where relapse to combustible cigarettes is not a concern) as this maintains dependence.**	Moderate/High 

Consideration Statements

There is insufficient evidence to describe criteria for an e-cigarette use disorder since only cravings, tolerance and withdrawal have been described. To meet the criteria for an addiction, there is not enough evidence beyond the preceding criteria and loss of control over use. Other criteria for a use disorder, such as continued use despite harm, and use in places where it is dangerous to do so, are not met.

1. Given the prevalence[†] and health risks associated with polysubstance use, health care practitioners should assess clients who use nicotine-containing e-cigarettes for co-use of other substances, including cannabis, alcohol, and/or tobacco, and modify their treatment approach accordingly.
2. E-cigarettes might not completely eliminate symptoms of nicotine withdrawal compared to combustible cigarettes.

*Tobacco users as a term refers to individuals who use commercial combustible tobacco products, including cigarettes, cigars, hookah, or pipes. This recommendation will need adaptation if applied to children and adolescent tobacco users.

**Among the recommendation development group members, a consensus could not be reached regarding the strength of recommendation 2b in the "Dependence" section. The recommended course of action may or may not best serve all individuals.

[†]There is substantial evidence that e-cigarette use is associated with use of other substances. According to the 2020 Canadian Tobacco and Nicotine Survey, among people aged 15 years and older who had used non-cannabis vaping products in the past 30 days, 36.6 percent reported smoking cigarettes, 47.9 percent reported cannabis use, and 47.0 percent reported weekly or daily alcohol use (Czoli, Luongo, & Mischki, 2023).

Respiratory Health

The following recommendations are based on current evidence about the health effects of vaping on respiratory health (includes the airways, lungs, and blood vessels) and respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD).

Recommendation	Evidence Quality
1. **People who do not smoke should not use e-cigarettes in order to avoid respiratory dysfunction and symptoms.**	High/Moderate 
2. **Tobacco users* with pre-existing respiratory diseases (e.g., COPD, asthma) who have been unable/unwilling to quit using current best evidence-based approaches, should switch completely to e-cigarettes for better lung health.**	Moderate 
3. **People who use e-cigarettes should avoid long-term use (where relapse to combustible cigarettes is not a concern) to reduce exposure to respiratory toxicants and potentially minimize respiratory symptoms and dysfunction.**	Moderate/Low 

Consideration Statement

Health care practitioners should note that among people who use e-cigarettes, there is an increase in self-reported symptoms of asthma.

*Tobacco users as a term refers to individuals who use commercial combustible tobacco products, including cigarettes, cigars, hookah, or pipes. This recommendation will need adaptation if applied to children and adolescent tobacco users.

Additional Considerations

This section examines the following topics: toxicants; adolescent health; bone health; fetal health; oral and dental health; and otolaryngology. These topics had insufficient evidence to generate a recommendation; however, important clinical considerations for health care practitioners with patients who use or are considering using nicotine-containing e-cigarettes have been outlined below.

Toxicants

Although many chemicals found in e-liquids, such as some flavourant substances, are generally recognized as safe (GRAS) for ingestion, the safety of inhaling these substances and how they might interact at high temperatures is unknown. Certain additives in e-cigarettes, including vitamins, minerals, colouring agents, and flavourants, are prohibited for commercial sale and manufacture in Canada under the *Tobacco and Vaping Products Act (TVPA)*. Health care practitioners should be aware that users may still be able to access e-cigarette products that contain potentially harmful additives via modifications and/or importing for personal use. People who use or are considering using e-cigarettes should avoid unlabeled products, only use e-liquids that are within their shelf life (usually 2 years from the manufacturing date), and avoid using products from non-retail (social) sources if the ingredients cannot be verified.

There is substantial evidence that nicotine-containing e-liquids and the aerosols they produce (which vary by product type and concentration) often contain chemicals known to be toxic, however, levels are shown to be significantly lower when compared to smoke from tobacco cigarettes. People should be made aware of the potential negative health effects of inhaling the chemicals contained in e-cigarette aerosols, including respiratory and cardiovascular effects, cancer, kidney damage, and nervous system effects.

Adolescent Health

There is insufficient evidence on the safety and health effects of e-cigarettes among adolescents at this time to develop specific recommendations. The use of nicotine-containing e-cigarettes may have distinct negative health outcomes for this age group, considering the potential for nicotine to affect brain development. The effects of e-cigarette use on respiratory health and development in adolescents remain unknown.

Bone Health

There is no current evidence on the effect of e-cigarette use on bone fracture healing.

Fetal Health

1. E-cigarettes are currently considered to be harm-reducing during pregnancy compared to combustible tobacco use, but any nicotine use increases the risk of negative effects to the fetus.
2. Fetal exposure to e-cigarette nicotine and/or aerosol in animal studies suggest a negative effect on neurobiology, cardiovascular and respiratory systems, cognition, renal development and birth weight.
3. To date, limited evidence on humans suggests that e-cigarette use during pregnancy has little effect on birthweight. E-cigarette use during pregnancy is a last resort for those unable or unwilling to use nicotine replacement or medications for smoking cessation.

Oral and Dental Health

Due to a lack of strong evidence, no conclusive statements can be made at this time on the overall effects of e-cigarette use on oral and dental health. Some evidence suggests e-cigarette use may lead to periodontal disease.

Otolaryngology

There are concerns around e-cigarette use and otolaryngology, as e-cigarette aerosols have been shown to be toxic to cells found in the ear, nose and throat (ENT). The most common side effects of e-cigarette use are mouth/throat irritation and cough. Current evidence on a link between nicotine-containing e-cigarette use and ENT health outcomes is inconclusive.

Definitions

Length of Exposure

Acute exposure: e-cigarette use/smoking ranging from one time to 7 days
Short- to medium-term exposure: 8 days to 12 months
Long-term exposure: more than 12 months

Age Range

The following age ranges are based on those used in the literature review (Sanchez et al., 2023).

Children and adolescents: 2–17 years old
Youth: 18–24 years old
Adults: 25 years old and above

Clinical Terminology

Dependence: A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the criteria noted in the DSM-5, occurring within a 12-month period (American Psychiatric Association, 2013).

Dual use: people who use both tobacco and electronic cigarettes.

E-cigarettes: also referred to as electronic cigarettes, vaping devices, vape pens or electronic nicotine delivery systems (ENDS), are battery-powered devices that heat up a liquid solution (or "e-liquid") into an aerosol for inhalation (Health Canada, 2023).

Freebase nicotine: Freebase nicotine is nicotine that has been dissolved in a liquid mixture, typically propylene glycol and/or vegetable glycerin, and other chemicals (Health Canada, 2023).

Generally recognized as safe (GRAS): designation by the US Food and Drug Administration that there is no available evidence that suggests a substance is hazardous when ingested under their intended use and at reasonable levels; GRAS designation means that a product is safe to ingest, not that it is safe to inhale. Thus, GRAS designation is irrelevant to e-cigarette and flavouring safety and scientific uncertainty remains. In Canada, food additives are regulated by Health Canada under the 15 Lists of Permitted Food Additives and the additive tables found in Division 16 of the *Food and Drug Regulations*.

Nicotine Salts: A nicotine salt is formed when the freebase chemical form of nicotine is transformed into a protonated "salt" form (includes an extra positively-charged hydrogen ion) by combining a nicotine base and a weak organic acid (Eaton et al., 2018; Talih et al., 2020). Compared to freebase nicotine, nicotine salts are reported to have a less harsh or bitter flavour, facilitating inhalation of higher concentrations of nicotine (Duell et al., 2020). Examples include nicotine lactate and nicotine benzoate.

Respiratory dysfunction: impaired function of the lungs and airways, which may include the onset or worsening of self-reported symptoms, such as chest tightness and other breathing-related problems.

Toxic chemicals: Examples of toxic chemicals identified in liquids and aerosols emitted from e-cigarettes include formaldehyde, acetaldehyde, benzaldehyde, benzene, nitrosamines, and toxic metals like cadmium, chromium, and lead.

Use disorder: a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems (American Psychiatric Association, 2013).

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