Background and Context

Introduction

The emergence of e-cigarettes poses competing challenges regarding their potential health impacts at a population level. While there is interest among smokers that e-cigarettes may assist with cessation, there is also concern that e-cigarette use may lead youth to start smoking. The intent of this report is to summarize the evidence for both of these possibilities.

What Are E-Cigarettes

E-cigarettes are battery-operated devices that electronically heat a solution to create an inhalable aerosol.[1] This solution, also known as 'e-liquid' or 'e-juice', is commonly made up of propylene glycol or glycerine, water, flavourings and nicotine (although many liquids do not contain nicotine).[1] While the main constituents such as propylene glycol and flavourings are generally considered safe for ingestion, the risks associated with their inhalation are unknown.[2,3] E-cigarette aerosol has been found to contain: propylene glycol, glycerol, flavours, carbonyl compounds, volatile organic compounds (VOCs), metals, and nicotine.[4,5]

E-cigarettes can take the form of: 'cigalikes' that look like typical cigarettes and can be disposable or reusable with disposable solution cartridges; 'tank systems' that are refillable with solution and do not resemble a typical cigarette; and 'variable power e-cigarettes' systems of variable appearance on which the user can control and change the electronic output.[1] E-cigarettes are also commonly referred to as 'vape pens', 'hookah pens' or 'e-hookah' among youth.[6,7]

Rapid Evolution of E-cigarettes

E-cigarette devices available in the market have rapidly evolved since they were first introduced in the early 2000s.[8-10] Over the years, e-cigarettes have evolved from simple electronic devices that closely resembled the traditional cigarette to more complex devices that come in different shapes and sizes, with enhanced features that allow adaptation and customization through changes in device configuration and components.[8,11] Attempts have been made to characterize their basic design features including key components, materials used, nicotine content, and performance variability in terms of efficacy of vaporization, consistency of nicotine delivery, and puff volume to help standardize their design and regulate them.[8,12-14]

Newer versions of e-cigarettes, such as JUUL, incorporate nicotine salts in a novel product design.[15] These more recently available products have a higher nicotine content, have become immensely popular with users, particularly among youth, and account for a major portion of the e-cigarette market share in the US at this time.[15-18]

The e-cigarette industry is diverse and comprises many different companies, most of whom are not affiliated with any cigarette companies.[19] Transnational tobacco companies however have entered the e-cigarette market by buying smaller e-cigarette manufacturers or selling similar products of their own.[19-23] There is also a wide range of variation in terms of the framing of messaging and promotion related to e-cigarette products. For example, while some companies promote a complete switch to e-cigarettes, others are encouraging dual use.[19,24] Besides the availability of e-cigarette devices at retail outlets such as convenience stores, tobacconist shops, vape shops/cafes/lounges, etc., a major share of the marketing, sales and promotion of these devices is done through online websites and social media.[25,26] With the recent federal legislative changes (*Tobacco and Vaping Products Act*) that allow nicotine-containing vaping products to be sold to adults, and with the emergence of new products using nicotine salts, it is anticipated that the e-cigarette market in Canada will undergo rapid transformation.[27]

Direct Health Effects of E-Cigarettes

Compared to combustible cigarettes, e-cigarettes produce less chemicals and at lower levels.[4] E-cigarettes do not contain tobacco, and do not involve burning or produce smoke.[4] Many of the toxic and cancer-causing chemicals in tobacco and tobacco smoke form when tobacco is burned.[4] Switching completely from smoking cigarettes to e-cigarettes will reduce an individual's exposure to many toxic and cancer-causing chemicals.[4]

However, e-cigarette aerosol contains a number of chemicals with known toxicity (e.g., formaldehyde, acrolein).[4] Although the health effects of e-cigarettes are uncertain, long-term exposure to the e-cigarette vapour may be harmful to health.[4] Exposure to e-liquids, including accidental ingestion, eye contact, or skin exposure can also lead to adverse health effects.[4]

Nicotine is approved for use in existing smoking cessation aids such as patches and gum. As of May 2018, nicotine can be legally present in vaping products in Canada. Nicotine is an addictive substance and e-cigarette use could result in symptoms of dependence.[4] Children and youth are especially susceptible to the negative effects of nicotine including addiction.[4] In addition, nicotine is known to alter brain development and can affect memory and concentration.[4]

Many Canadian smokers use e-cigarettes while continuing to smoke. However, many individuals with 'dual use' do not reduce their exposure to harmful chemicals due to continued smoking;[5] individuals need to completely quit smoking to ensure that they reduce their health risks while using e-cigarettes.[4]

Overall Trends in Smoking and E-cigarette Use

Systems for monitoring smoking trends rely on population survey data, which take time to collect, process, and release, such that data cited may not reflect the most recent trends in this rapidly changing environment.[15]Nevertheless, the percentage of Canadians aged 15 and older who reported daily or non-daily smoking of combustible cigarettes has declined over time, from 25.2% in 1999 to 13.0% in 2015.[28] Smoking prevalence in Ontario is below the national average, and declined over time from 23.3% in 1999 to 11.3% in 2015.[28] The decline in smoking prevalence was most pronounced among Canadian youth aged 15-19 and least pronounced among adults over 45.[28] Similar trends were noted at the provincial level in Ontario.[28]

The decreased prevalence of smoking in Ontario over the past two decades appears to be mainly due to decreased rates of smoking initiation. The prevalence of ever smokers has declined markedly over the past two decades, whereas the prevalence of former smokers (past month) was relatively constant.[29]

The prevalence of past month e-cigarette use reported by Canadians aged 15 and older was 3.2% in 2015; the prevalence in Ontario was slightly lower at 2.7%. In all age groups, prevalence of past month e-cigarette use increased from 2013 to 2015.[28] Nationally, prevalence was highest among youth (15-19 years) and young adults (20-24 years), where 6.3% of youth and young adults reported the use of e-cigarettes (2015) in the past month (provincial estimates are unavailable).[28] Of note, the decline in smoking prevalence significantly preceded the rise in e-cigarette use, and trends in e-cigarette use are lacking for some populations.

Ontario-specific data was only available for e-cigarette use in the past year (vs. past month), where youth and young adults are also reporting the highest e-cigarette use of all age groups. The CAMH Monitor estimates that in 2016, 20% of Ontario young adults (18-24 years) used e-cigarettes in the past year.[30] The Ontario Student Drug Use and Health Survey (OSDUHS) estimates that in 2017, 18% of Ontario youth (grades 7-12) used e-cigarettes in the past year.[31]

Dual use is common. In 2015, 62.8% of Canadians who reported using e-cigarettes in the past 30 days also were current smokers.[28] Canadian trend data on dual use is not available.

Legislation

Jurisdictions across the world are seeking to further reduce population smoking rates. E-cigarette related policies aim to achieve a regulatory balance, considering e-cigarettes may assist with cessation among adult smokers, but may lead youth to start smoking.[5,19,32,33]

Prior to 2018, only e-cigarettes that did not contain nicotine and that made no health claims were legal in Canada. Under the *Food and Drugs Act*,[34] market authorization was needed for e-cigarettes containing nicotine or those that made a health claim.[35] Although no product received authorization, nicotine containing e-cigarettes still found their way into the Canadian market.[36]

Bill S-5, which received Royal Assent in May 2018, establishes a new legislative framework for regulating vaping products in Canada.[37] Under this framework, e-cigarettes and other vaping products are classified into two main categories based on whether they are used for recreational or therapeutic purposes.[4] E-cigarettes (with and without nicotine) that do not make any health claims are defined as 'recreational products' and regulated under the federal *Tobacco and Vaping Products Act* (*TVPA*).[32,38] The TVPA regulates the manufacture, sale, labeling and promotion of vaping products separate from tobacco products.[32] 'Therapeutic' e-cigarettes that may be used to treat nicotine dependence and allowed to make health claims are regulated under the more stringent *Food and Drugs Act.*[39] As of June 2018, no 'therapeutic' e-cigarette has been licenced in Canada.[4]

In addition to federal regulations, several provinces in Canada have enacted their own provincial legislation to further regulate the use, sale, and promotion of e-cigarettes.[40] On September 27th, 2018 the Government of Ontario introduced *Bill 36* that makes amendments to the e-cigarette provisions under the *Smoke-Free Ontario Act, 2017.*[41] These regulations have been proposed to come in to force on October 17th, 2018[42] and will replace the *Smoke-Free Ontario Act*, 2006 and the *Electronic Cigarettes Act, 2015*.[43,44]

Purpose and Scope

The objective of this report is to summarize the most up-to-date research evidence to answer three specific e-cigarette questions:

1. Is the use of e-cigarettes an effective cessation aid for smokers?
2. Does the use of e-cigarettes in non-smoking youth and young people increase the likelihood of smoking initiation?
3. Are there health risks associated with the exposure to secondhand vapour from e-cigarettes?

This report expands upon two recent time-sensitive PHO technical requests examining the evidence to answer the above questions. The first request (June 2018) summarized review-level evidence, and the second request (August 2018) summarized both review-level and primary literature and included a review of the findings by five tobacco scientists (See Appendix A).

For the first request (June 2018), tobacco scientists were consulted for seminal publications and a rapid review of reviews was completed. One 2018 comprehensive review of the evidence by the National Academies of Sciences, Engineering, and Medicine (NASEM), was identified and served as the basis for the response to all three questions.[5] A non-systematic and less comprehensive overview by Public Health England (PHE, 2018) was also identified and findings were noted where relevant.[45] The second request (August 2018) expanded the search to include recent primary articles published since the NASEM searches were completed (August 2017). The current report provides a more detailed description of the evidence that was summarized in the second request.

Beyond addressing smoking and e-cigarette use in youth and young adults, it was not feasible to include consideration of impacts on population sub-groups.

Methods

The main sources of evidence included: NASEM; reviews published in the past 5 years; seminal articles identified by tobacco scientists; and primary literature published following the NASEM search cut-off (Aug 2017). Ovid MEDLINE, Embase, CINAHL, and PsycINFO databases were searched for primary studies from August 2017 to July 2018. PHO Library Services conducted systematic database searches for each of the three specific questions and to identify articles to assess the net population impact of e-cigarettes. Relevant consensus statements from the SFO-SAC (2016) report were also included, where appropriate.

Peer-reviewed published articles were eligible if they presented findings from any study design, or synthesis of existing literature. For each e-cigarette question, PHO staff screened titles and abstracts and also full-text versions of retrieved articles for inclusion. Primary studies and reviews that were already included in the NASEM report were excluded. For all included reviews and primary studies, PHO staff extracted relevant data from each article and summarized the content. Content was reviewed by senior members of the team. Quality appraisal of systematic review-level literature was performed. Similar to NASEM, industry sponsorship was assessed (i.e., funding sources and conflict of interest) (Appendix B). With the exception of any modelling studies, articles were not excluded for any of these reasons.

To prepare the August 2018 technical request and this narrative report, the authors were guided by the following principles: consistency or inconsistency with evidence in NASEM, consistency or inconsistency in direction of the evidence across studies, study design and volume of evidence.

Results

Q1. Is the use of e-cigarettes an effective cessation aid for smokers?

Ontario context and Cessation trends

The proportion of smokers who intended to quit has remained stable over the past decade with 59.5% of Ontario smokers aged 18 and older intending to quit in the next six months in 2016.[46] The proportion of smokers trying to quit has also remained stable over the past decade. In 2016, 42.6% of Ontario smokers aged 18 and older made one or more quit attempts in the past year.[46]

Despite the high proportion of quit intentions and attempts, quit rates remain low. The adjusted annualized quit rate is defined as the number of past-year smokers who reported they quit for at least 30 days, adjusted for the estimated relapse rate for the following year. Based on self-reported smoking and quit rates, Ontario's adjusted recent quit rate was 1.7% in 2014; essentially unchanged from 1.8% in 2007.[46]

Across Canada, 33.5% of current smokers reported using e-cigarettes as a quit aid in 2015, up from 22.9% in 2013.[28] In 2015, 62.8% of Canadians who reported using e-cigarettes in the past 30 days also reported that they smoked combustible cigarettes on a daily or non-daily basis, indicating high prevalence of dual use.[28]

SFO-SAC Statement

The SFO-SAC (2016) authors stated that "The effectiveness of e-cigarettes as a cessation aid is unclear. There needs to be more research on the effectiveness of e-cigarettes (with or without nicotine) as a smoking cessation device."[47]

NASEM

EVIDENCE STATEMENTS

The 2018 NASEM report provides a summary of the current state of knowledge about the health risks and benefits of e-cigarette use and concluded:

- *"Conclusion 17-1. Overall, there is **limited evidence** that e-cigarettes may be effective aids to promote smoking cessation.*
- *Conclusion 17-2. There is **moderate evidence** from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.*

- *Conclusion 17-3. There is **insufficient evidence** from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration-approved smoking cessation treatments.*

- *Conclusion 17-4. While the overall evidence from observational trials is mixed, there is **moderate evidence** from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation."*[5]

NASEM SYNTHESIS SUMMARY

The NASEM (2018) report notes a limited number, size, and quality of studies examining the effectiveness of e-cigarettes as a cessation aid. NASEM considered different study types in turn. Two meta-analyses pooled the same two RCTs assessing the effectiveness of nicotine-containing e-cigarettes versus non-nicotine placebo e-cigarettes. Both meta-analyses observed increases in smoking cessation with relative risks ranging from 2.03 to 2.29.[5] Whether the meta-analyses' results were statistically significant was dependent on how the missing data in the RCTs were addressed.[5] The NASEM report noted limitations of the RCTs' design including: participants not limited to smokers wanting to quit; using early e-cigarette models with low nicotine content and poor battery life; and, low levels of behavioural supports (e.g., instruction on proper use).

In addition to the two e-cigarette RCT studies, NASEM considered additional indirect evidence from RCTs assessing non-e-cigarette nicotine replacement products as cessation aids. Based on the direct evidence from the two e-cigarette RCT studies and the additional indirect evidence, NASEM concluded that there was moderate evidence that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.

Observational studies found statistically significant increases in cessation with e-cigarette use. Daily or very frequent e-cigarette use may be associated with cessation while intermittent or less frequent use may not.[5] However, interpreting these studies is complicated because important factors that may affect the cessation success of e-cigarettes are not always accounted for in the analysis. Potential confounding factors include: self-selection; the e-cigarette product (e.g., type of device, nicotine content and delivery, flavourings or other contents of the e-liquid); pattern of current use (e.g., frequency of use, duration of use); and user characteristics (e.g., motivation for e-cigarette use, quit attempt history, nicotine dependence, prior history of e-cigarette use, demographics and smoking history).[5] Based on the biological plausibility and the strong, consistent body of evidence from higher-quality observational studies published more recently compared to earlier studies, the NASEM report concluded that there was moderate evidence from observational studies that more frequent e-cigarette use is associated with quitting smoking. Since observational studies are more subject to biases and the limited evidence from RCTs, NASEM's overall conclusion was that there was limited evidence that e-cigarettes may be effective aids to promote smoking cessation.

The NASEM report highlighted two related key public health questions. First, how does the effectiveness of e-cigarettes compare to cessation aids of known effectiveness? Only one trial was available and it showed no statistically significant difference in quit rates comparing e-cigarette use to a nicotine patch. The second is: does availability of e-cigarettes induce more smokers to try to quit?

Recent literature

The PHO librarian assisted search identified 996 articles since the NASEM search, of which one systematic review and meta-analysis,[48] one systematic review[49] and 28 primary studies[50-77] were included. All studies examined the effectiveness of e-cigarette use as a cessation aid and/or harm reduction. Cessation is the process of stopping the use of any tobacco product, with assistance, also called "quitting".[78,79]

Harm reduction involves strategies to reduce harm caused by continued tobacco/nicotine use; for example, reducing the number of cigarettes smoked, or switching to different brands or products (e.g., potentially reduced exposure products (PREPs) and smokeless tobacco).[78] At the current time, it is unknown whether a reduction in harm occurs with dual use. Although e-cigarettes pose less risk to an individual than smoking, there is no available evidence whether or not long-term e-cigarette use among smokers (dual use) changes morbidity and mortality compared with those who only smoke.[5] NASEM further notes that: "due to the health risks of combustible tobacco smoke from even low levels of use, e-cigarette use among those who continue to smoke (i.e., dual use) may only confer benefits if dual use is merely a transitional state, after which a user transitions completely to e-cigarettes (i.e., quits combustible tobacco cigarettes)."[5]

Examples of smoking cessation outcomes included: 7 day and 30 day point prevalence abstinence, quit attempts, and biochemical validation (i.e., carbon monoxide and cotinine). Examples of harm reduction outcomes included change in smoking status (i.e., daily to occasional smoker), reduction in cigarette consumption, and smoking frequency in the past 30 days. The greatest proportion of studies was from the USA, [49,51,54-56,58-61,64,66,67,70-77] five were from European Union countries,[62,63,65,68,69] and there was one study each from South Korea,[57] China,[53], the UK[50] and Canada.[52] Among the primary studies, three were randomized control trials (RCT),[63,67,74] 12 were longitudinal (often prospective cohort studies), [52-54,59,61,64,69,71-73,76,77] three were time series,[50,51,75] two were pre-post,[56,60] and eight were cross-sectional studies.[55,57,58,62,65,66,68,70]

SYSTEMATIC REVIEWS

The literature search retrieved two systematic reviews analyzing the effectiveness of e-cigarettes for smoking cessation and/or reduction results. The relevant findings from the Public Health England (PHE) 2018 overview are noted below as well.

A systematic review and meta-analysis conducted by Liu et al. (2018) included 14 publications: three RCTs, seven observational studies, and four online surveys.[48] Two of the three RCTS were already included in the NASEM report and the third RCT was not on e-cigarettes. The rest of the included studies were from 2014 or earlier, therefore this systematic review is analysing older studies.[48] Overall, the

authors found that e-cigarettes were effective for smoking reduction.[48] There were no significant differences in carbon monoxide levels before and after e-cigarettes use. The authors concluded that e-cigarettes are moderately effective for smoking reduction and cessation, which is in-line with NASEM's conclusions of moderate evidence from observational studies that e-cigarettes increase the likelihood of smoking cessation.[48]

A systematic review by Gentry, Forouhi and Notley (2018) analyzed e-cigarette effectiveness among vulnerable groups (i.e., mental illnesses, homelessness, substance use, or criminal justice system involvement).[49] The review included nine studies, five quantitative and four qualitative. The five quantitative were: one secondary analysis of an RCT, one prospective cohort study, and three uncontrolled before and after studies. Of the four qualitative studies, three had focus groups and one was an analysis of online postings. Although four of their quantitative studies' results were clinically and statistically significant, three of them were uncontrolled, with sample sizes less than 30 respondents.[49] The prospective cohort study did not find cessation differences between users and non-users of e-cigarettes.[49] The authors' concluded that they were hesitant whether e-cigarettes are effective for smoking cessation within vulnerable populations.[49]

The Public Health England (PHE, 2018) overview identified 14 systematic reviews and seven meta-analyses about e-cigarettes for smoking cessation or reduction.[45] According to PHE, the systematic review authors indicated more RCT evidence was needed to draw conclusions about the effectiveness of e-cigarettes as a cessation aid. Consistent with NASEM, PHE reported mixed meta-analysis evidence; four were inconclusive, two showed positive results and one showed negative results.[45] PHE reported discrepancies among the meta-analyses' findings were due to: the types of studies pooled, the diverse range of participants (i.e., current and ex-smokers), varying lengths of follow-up, and differences in how missing data was addressed.[45] PHE concludes that e-cigarette use alone or combined with other supports (e.g., NRT, support service) may be helpful for quitting in the short term and that more RCTs are needed.

RECENT PRIMARY LITERATURE

Most cessation studies assessed e-cigarettes compared to a placebo, non e-cigarette users or no control. Some studies assessed e-cigarettes compared to proven cessation aids and these studies will be addressed separately.

From the included primary literature, two RCTs compared e-cigarette users with non e-cigarette users and placebo e-cigarettes without nicotine.[63,74] One RCT found e-cigarettes with nicotine significantly increased smoking cessation and decreased cigarette consumption compared to non e-cigarette users, while the other RCT found no association of e-cigarette use with smoking cessation and cigarette consumption compared to placebo.

More specifically, a study by Masiero et al., (2018), conducted a double-blind RCT to determine the efficacy of e-cigarettes in a study population of 210 highly motivated (to quit) participants that were part of long-term lung cancer screening program.[63] The study arms were free e-cigarettes with nicotine (8 mg/mL), free e-cigarette without nicotine (placebo), and a non-intervention control group.[63]

Participants in all three arms received low intensity telephone counselling. At three months, the percentage of participants that stopped smoking was significantly higher in the e-cigarette nicotine group (25.4%) and non-nicotine placebo e-cigarette group (23.4%) compared to the control group (10.34%) ($\chi 2(2) = 4.899, p = .044$).[63] In terms of harm reduction (at three months), the e-cigarette nicotine group had a consumption of 7.7 cigarettes/day that was significantly lower than the control with 10.0 cigarettes/day, but not compared to the placebo group with 9.1 cigarettes/day.[63] The rate of reduction between the three groups was not statistically different when participants who discontinued smoking were excluded from the analysis.[63]

A RCT by Baldassarri et al., (2018) found no significant differences (at 24 week follow-up) between e-cigarettes with and without nicotine in terms of smoking status (defined by 7-day point prevalence; abstinence confirmed biochemically). The study population consisted of 40 motivated participants that were recruited primarily from local medical clinics.[74] A 2nd generation e-cigarette model was used with 24 mg/ml or 0 mg/ml of nicotine (placebo) and all participants were given nicotine patches and financial incentives.[74] At week 24, the proportion abstinent was: 20% (4/20) e-cigarette with nicotine; and 10% (2/20) placebo (CI= 0.362 to 14.0). Reduced cigarette consumption at week 24 was 5.5 cigarettes/day for e-cigarette with nicotine compared with 8.04 cigarettes/day for the placebo group (CI= -9.9 to 4.9).[74] Out of the nine participants that quit during the study, three relapsed and those three were all in the placebo group.[74]

Ten longitudinal studies from the primary literature showed mixed results; three studies found a positive association while seven studies found a negative or no association between using e-cigarettes for cessation and/or reduction.[52-54,59,61,64,71,72,76,77] The longitudinal studies are summarised below in turn.

Berry et al., (2018) analyzed data from two waves of the United States' national Population Assessment of Tobacco and Health (PATH) Study (2013-2015).[72] The authors found that users of e-cigarettes had 7.9-fold higher odds of a minimum 30-day cigarette cessation compared to non-users, specifically if second-generation and third-generation e-cigarettes were used.[72] Compared to non-e-cigarette users, cigarette smokers who began e-cigarette use every day and didn't successfully quit had 5.7 (95% CI: 3.47 to 9.35) times the odds of decreasing their daily cigarette consumption by at least 50%.[72]

A study by Chen, (2018) using the same data from the PATH study (2013-2015) analyzed which specific e-cigarette flavours were associated with cigarette reduction and cessation.[71] After adjusting for age, gender, past-year quit attempts, and cigarette dependence, e-cigarettes users with one flavour (adjusted odds ratio (AOR) = 2.5) and multiple non-tobacco/non-menthol flavours (AOR = 3.0) were significantly more likely to reduce or quit smoking cigarettes in the past year compared to non e-cigarette users.[71]

Mantey et al. (2017) found that among 627 young adults in Texas colleges, those who reported using e-cigarettes for cessation had improved odds of cessation at six and 12 month follow-ups, compared to those reporting e-cigarette use for other reasons (e.g., experimenting with new technology, or trying flavours like cherry and bubble gum).[64]

In contrast, seven longitudinal studies found negative associations between e-cigarettes and smoking cessation and or harm reduction.

For example, a study by Zawertailo et al., (2017) analyzed 6,526 participants from 187 primary care clinics across Ontario Canada that were enrolled in the Smoking Treatment for Ontario Patients (STOP) program.[52] They found e-cigarettes were negatively associated with abstinence after controlling for confounders (adjusted odds ratio [AOR] = 0.706, 95% CI= 0.607–0.820) and negatively associated with abstinence at 6-month follow-up (AOR = 0.502, 95% CI = 0.393–0.640) compared to non e-cigarette users.[52]

A secondary analysis of a RCT by Rigotti et al., (2018), found participants who reported any use of e-cigarettes in the last 3 months were significantly less likely to be biochemically abstinent at 6 months than those not using e-cigarettes (10.1% vs. 26.6%; risk difference, -16.5% [95% CI, -23.3% to -9.6%]).[61] The study population was 1,357 from the Helping HAND 2 study (of hospitalized cigarette smokers who planned to quit smoking), where patients were randomly assigned to post-discharge standard care (control) or sustained care (intervention).[61]

Three other studies found similar results and found e-cigarette use was not associated with smoking cessation. [53,54,76] Two further studies found that among current cigarette smokers and those that are highly nicotine dependent, e-cigarette use was associated with smoking cessation and harm reduction. However, among former cigarette smokers, never-smokers and non-nicotine dependent smokers, e-cigarette use was associated with greater odds of smoking relapse[80] and not associated with future smoking cessation and reduced cigarette consumption.[59,80]

A total of three time series studies showed mixed results; two studies showed that using e-cigarettes was associated with smoking cessation and harm reduction while one study did not find an association.[50,51,75]

Anic et al. (2017) used data (n=20,270) from the National Adult Tobacco Survey (2012-2014) to estimate the prevalence of cigarette smokers switching to e-cigarettes and smokeless tobacco.[75] The proportion of recent quitters who reported completely shifting from cigarettes to e-cigarettes increased significantly between the two years (15.3% for 2012 to 25.7% for 2014).[75]

Another time series study by Zhu et al. (2017) used the 2014-15 US Current Population Survey-Tobacco Use Supplement (n=161,054), and found e-cigarette users compared to non-users were more likely to attempt quitting (65.1% vs. 40.1%), and more likely to successfully quit smoking (8.2% vs.4.8%).[51]

In contrast, a time series analysis by Beard et al. (2018) of a representative sample of smokers and ex-smokers (n=199,483) from England's Smoking Toolkit Study using data from 2006 to 2016, found no association between e-cigarette use (β -0.012, 95% CI: -0.026 to 0.002) and NRT (β 0.015, 95% CI: -0.026 to 0.055) in reducing daily cigarette consumption and temporary abstinence among current smokers.[50]

The search for recent primary literature also identified seven cross-sectional studies; all seven reporting that using e-cigarettes was not associated with smoking cessation.[55,57,58,62,65,68,70]

evidence of plausibility and specificity of a possible causal effect of e-cigarette use on smoking… the committee considered the overall body of evidence of a causal effect of e-cigarette use on transition from never to ever smoking to be substantial."[5]

NASEM noted a number of limitations of their included literature. The first relates to the measurement of e-cigarette and cigarette use. The definitions of smoking initiation vary greatly across studies. Many studies used measurements of 'ever use', meaning that youth could have used e-cigarettes or cigarettes once or twice through experimentation instead of measuring regular use.[45] Other challenges reported about these studies include the duration of follow-up. Due to the relatively recent introduction of e-cigarettes on the market, NASEM noted it is difficult to determine the extent to which e-cigarette use by non-smoking youth leads to additional and regular long-term smoking as most studies did not have a sufficient follow-up period.[5]

Recent Literature

One review was identified that was not included in the NASEM report. This was found during the initial rapid review-level search. An additional 325 articles were identified from the primary literature search and 11 primary studies were included.[77,82-91] All primary studies examined the effect of e-cigarette use on smoking initiation among youth and young adults. Nine of the 11 primary studies examined youth (ages 11 to 21),[82-86,88-91] one focused on young adults (ages 18 to 30),[87] and one included youth, young adults and adults ages 12 and older.[77] The greatest proportion of studies were from the US,[77,84,87,89,91] two were from the UK,[83,90] while others were from Germany,[85] Romania,[86] Netherlands,[88] and Canada.[82] The majority of studies were longitudinal studies (often prospective cohort studies),[77,82,83,85-90] with the exception of two cross sectional studies.[84,91]

SYSTEMATIC REVIEWS

The review by Chaterjee et al.,(2016) examined four longitudinal studies and found that e-cigarette use was associated with an increase in combustible cigarette smoking even among youth (mean ages 14 to 21) who were not deemed susceptible to smoking (e.g., adolescents who had earlier indicated a decision they would not smoke).[92]

The overview by Public Health England (2018) examined studies that looked at e-cigarette use among children and young people and concluded that e-cigarette use among this population is associated with subsequent smoking, but observed from population trends that "e-cigarettes do not appear to be undermining the long-term decline in cigarette smoking in the UK among young people."[45]

RECENT PRIMARY LITERATURE

Consistent with the findings of the review level literature, all included primary studies suggested that e-cigarette use is associated with subsequent (cigarette) smoking initiation among youth and young adults.[77,82-91] This finding was consistent across all study types and jurisdictions.

Among the longitudinal studies that examined youth, those who used e-cigarettes at a baseline were more likely to initiate smoking at follow-up (e.g., six months to two years later) compared to those who did not use e-cigarettes (Odds ratios (OR) ranging from 1.34 to 11.9;[77,83,88-90] Adjusted odds ratios (AOR)

ranging from 2.78 to 5.28;[82,86] relative risk 2.18[85]). For example, East (2018) examined whether ever e-cigarette use and escalation were associated with smoking initiation (ever smoking at follow-up) among baseline never smoking British youth ages 11 to 18 years.[83] They found that individuals who were ever e-cigarette users (compared to non-users) and those who escalated their e-cigarette use (compared to those who did not) were more likely to initiate smoking (OR: 11.89, 95% CI: 3.56 to 39.72 and OR = 7.89, 95% CI: 3.06 to 20.38, respectively).[83]

Similarly, a longitudinal US study found that among never smoking young adults (ages 18 to 30), e-cigarette use at baseline was associated with smoking initiation at 18 months follow-up (AOR = 6.8, 95% CI: 1.7 to 28.3).[87]

Further, the two cross sectional studies examining youth reported positive relationships between trying e-cigarettes and later smoking. Hines et al., (2017) found that e-cigarettes were the second most commonly reported introductory tobacco/vaping product among US youth (Grades 8 and 11) who had ever used cigarettes (cigarette use was the most common).[91] The second cross sectional study by McCabe et al., (2017) found that early onset of e-cigarettes (i.e., aged 14 or younger) was significantly ($p < .001$) associated with increased odds of cigarette smoking among US high school seniors;[84] the adjusted odds of lifetime smoking among early onset e-cigarette users was over 14 times greater than those who had never used e-cigarettes (AOR = 14.2).[84] A greater percentage of youth who had begun using e-cigarettes in ninth grade or earlier (i.e., early onset) reported current and lifetime cigarette smoking compared to those who began using e-cigarettes later (i.e., 12th grade).[84]

Other factors that have been shown to influence the relationship between e-cigarette use and subsequent smoking initiation include: age,[83,87] ethnicity,[87] household income,[77] susceptible to smoking,[82,83] propensity to smoke/risk of smoking,[88] having at least one parent who smokes,[83] sensation-seeking,[85,87] rebelliousness,[87] psychiatric or substance use disorders,[77] whether or not friends smoked at baseline,[90] and whether or not e-cigarettes contained nicotine.[88]

Overall, e-cigarette use appears to be a risk factor for initiating smoking separate from susceptibility or propensity to smoke; e-cigarette use is associated with an increased risk of smoking even among those who are considered to be 'low risk' (i.e., not susceptible or low propensity to smoke). For example, Aleyan et al., (2018) found that the association between e-cigarette use and smoking initiation was stronger among Canadian high school students (grades 9-11) who were not susceptible to smoking (AOR: 5.28, 95% CI: 2.81 to 9.94) compared to those who were susceptible (AOR: 2.78, 95% CI: 1.84 to 4.20).[82] Similarly, Treur et al., (2018) found that the propensity to smoke (i.e., a construct reflecting personality traits, susceptibility to peer pressure and intention to smoke) was a strong predictor of smoking initiation among Dutch youth ages 11 to 21.[88] Similar to the findings of Aleyan et al., (2018), they found that this association was especially strong for youth with low propensity to smoke (which is consistent with the 'gateway' hypothesis).[88] In both studies, while risks of smoking initiation were elevated in low propensity to smoke youth that used e-cigarettes, this group reflected a small proportion of never smokers overall.

An additional study by Conner et al., (2017) found that among British adolescents (ages 13 to 14) the association between 'ever use' of e-cigarettes and initiation of smoking was particularly strong among youth who did not have friends who smoked at baseline (a group usually considered to be less susceptible to smoking initiation) compared with those that had a few (OR: 1.87 95% CI, 1.35 to 2.58) or most friends (OR: 2.99, 95% CI: 1.52 to 5.87) who smoked at baseline.[90]

Additionally, Treur (2018) found that the presence or absence of nicotine within e-cigarettes influences smoking initiation. They found that Dutch youth who (ever) used e-cigarettes with nicotine were nearly 12 times more likely to report smoking 6 months later, compared to those who never used an e-cigarette with nicotine (OR: 11.90 95% CI: 3.36 to 42.11);[88] these odds were 5.36 (95% CI: 2.73 to 10.52) for e-cigarettes without nicotine.[88]

Question 2 – Summary

- NASEM concluded that e-cigarette use was associated with increased risk of ever smoking, and among these youth and young adults, increased frequency and intensity of subsequent smoking.[5] There was limited evidence that e-cigarette use increased the duration of subsequent smoking.[5]

- Other reviews were consistent with the findings of the NASEM report.[45,92] In the most recent literature, all included primary studies suggested that e-cigarette use is associated with subsequent smoking initiation among youth and young adults.[77,82-91] Interpreting these associations is complicated by the existence of common risk factors that influence e-cigarette use and subsequent smoking initiation.

- Further research is required to better understand the trajectory of e-cigarette and smoking in those with little or no smoking experience. This includes learning how different e-cigarette product characteristics (e.g., design features, flavours) are associated with different risks of e-cigarette and smoking initiation and progression. Researching the influence of social media and social exposure, especially among those with high use of social media who are also susceptible to smoking, is also needed.

Q3. Are there health risks associated with the exposure to secondhand vapour from e-cigarettes?

Ontario Context and Protection Trends

There is no currently available information on secondhand exposure to e-cigarette aerosol for Ontario or Canada. Ontario has very limited data on exposure to secondhand vapour. This includes an absence of population level trends data regarding people's exposure over time to secondhand e-cigarette aerosol emissions.

SFO-SAC Statement

The 2016 SFO-SAC authors state that the "available research suggests that e-cigarettes emit harmful compounds (e.g., volatile organic compounds (VOCs) such as carbonyls and formaldehyde) that may pose a health risk to bystanders, though the magnitude of these emissions is low compared to conventional cigarettes."[47]

NASEM

EVIDENCE STATEMENTS

The 2018 NASEM report provides a summary of the current state of knowledge about the health risks and benefits of e-cigarette use and concluded:

- *Conclusion 3-1. There is **conclusive evidence** that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels.*
- *Conclusion 18-5. There is **moderate evidence** that secondhand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes.*

NASEM SYNTHESIS SUMMARY

Prior to addressing the health impacts of secondhand exposure to e-cigarettes, the NASEM report summarizes what is known about e-cigarette aerosols. The report concludes that exposure to nicotine is highly variable and depends upon product characteristics and how the device is operated. E-cigarette users tend to take puffs of longer duration and larger volume than traditional cigarettes, and these tend to increase with experience. Nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible tobacco cigarettes. In addition to nicotine, e-cigarettes emit potentially toxic substances, including metals. Overall, e-cigarette aerosol contains fewer numbers and lower levels of toxicants than smoke from combustible tobacco cigarettes.

The NASEM report based their conclusions regarding secondhand e-cigarette aerosols on nine primary studies conducted in exposure chambers, recreated rooms, real-life settings in homes of e-cigarette

users and vaping conventions. All studies found statistically significant increases of particulate matter and nicotine compared to background levels.[5] Levels were higher in settings with more than one vaper and were extremely high in studies conducted at vaping conventions.[5] These exposure studies indicate that e-cigarette vaping contributes to some level of indoor air pollution, which is lower than secondhand exposures from combustible tobacco cigarettes, but is above the smoke-free level recommended by the U.S. Surgeon General and the WHO FCTC.[5] The effects of these exposures on health remain unknown. Vulnerable populations such as children, pregnant women, the elderly, and individuals with cardiorespiratory diseases may be at special risk.[5] In addition, the vaping convention studies indicate that e-cigarette aerosol exposure could be substantial for convention workers.[5]

Recent Literature

One review was identified that was not in the NASEM report (Hess et. al., 2016).[93] In addition, four primary studies were identified from the search for primary literature. A fifth primary study was provided by a tobacco scientist. Among the primary studies, one examined e-cigarette aerosols in realistic indoor social settings, specifically at a large e-cigarette event/convention;[94] two were lab-based/simulated room experimental studies measuring exposure to e-cigarette aerosol emissions;[95,96] and two other studies modelled the excess risk of lung cancer from e-cigarettes.[97,98]

SYSTEMATIC REVIEWS

The systematic review by Hess et al., (2016) reached similar conclusions to the 2018 NASEM report.[93] The overview by Public Health England (2018) examined passive aerosol exposure, but was not based on a systematic search of the literature and is not reported here.

RECENT PRIMARY LITERATURE

Among the recent primary studies, overall they reported similar findings to the NASEM report. For example, the levels of particulate matter at large indoor e-cigarette events with many users/active e-cigarettes were demonstrated to be high compared to baseline levels.[94] Volatile organic compounds were identified in air samples collected at the event.[94]

The authors report variability in the levels of particulate matter due to certain environmental conditions, such as room size, the number of active e-cigarettes/users, the type of e-cigarette being used, and the users' behaviour.[94] In addition, the type of e-cigarette, battery power, e-juice liquid being used, and the users' puff frequency, duration, and volume also contribute to the variability of aerosol emission levels.[94]

For the two studies in controlled laboratory/simulated rooms,[95,96] the researchers used various methods to measure exposure to e-cigarette aerosol emissions (e.g., nicotine exposure and particulate matter exposure). In one study, a simulated room was created in which the researchers had non-e-cigarette users exposed to e-cigarette aerosol emissions from users. Each participant was exposed for two, two-hour sessions, and with each session using a different type of e-cigarette (i.e., first-generation disposable e-cigarette and second-generation tank-style e-cigarette).[95] Based on biological measures (i.e., serum cotinine levels), findings showed that non-users experienced systemic nicotine absorption

from acute exposure to secondhand e-cigarette aerosols.[95] However, the generalizability of this may be limited due to the heterogeneity of the e-cigarette devices, the e-juice liquid being used, and the vapers' behaviour (e.g., puff duration, frequency and volume). A second study in a room-simulating exposure chamber used human volunteers to smoke e-cigarettes and used mannequins as bystanders to measure spatial temporal patterns of exhaled e-cigarette aerosol emissions.[96] To mimic more realistic e-cigarette vaping sessions, the researchers only defined the vapers' puff frequency (i.e., number and interval length) and didn't instruct the vapers for other behaviours (puff duration, volume, inhalation and exhalation duration).[96] The particle concentration after each e-cigarette puff/exhalation increased in the same order of magnitude compared to background levels, and then quickly (i.e., a rapid decrease) returned to similar background levels due to evaporation. The greatest concentration of emission was within 0.5 metres compared to no recorded concentration at two metres.'[96]

Two simulation studies conducted in Italy measured exposure to secondhand e-cigarette emissions.[97,98] One study used the excess lifetime cancer risk model among e-cigarette users,[98] and the other used a model to calculate e-cigarette aerosol emission rates in a simulated room.[97] The extra 'excess lung cancer risk' for someone exposed to secondhand e-cigarette emissions is five orders of magnitude less than being exposed to secondhand cigarette smoke.[97] However, the extent of the risk is influenced by the exposure dose (which can depend on the vapers' vaping behaviour, hence the particle concentration) and the toxicity of the particles emitted that passive smokers are exposed to.[97] While quantifying the actual exposure to secondhand e-cigarette aerosol is challenging, the authors' estimation of the excess lung cancer risk for exposure scenarios for various numbers of years of passive exposure to various numbers of e-cigarettes was consistently lower than one in 100,000. [98] The inputs used for the above risk model were: e-cigarette emission data (i.e., particle number, surface area, mass concentration, and size distribution); identifying and quantifying the compounds of the emitted particles; and evaluating the dose-response characteristics of each compound. There are various factors which can influence secondhand e-cigarette aerosol exposure, though exposure to them is relatively less harmful than traditional cigarettes.[98]

Question 3 – Summary

- NASEM concluded that compared to background levels, e-cigarette use increases airborne concentrations of particulate matter, nicotine and other toxicants (e.g., propylene glycol, glycerol, VOCs, carbonyls, and some heavy metals) in indoor environments.[5]

- Compared with combustible cigarettes, secondhand exposure to e-cigarette aerosol has lower levels of many substances (e.g., nicotine, particulates), but some exposures may be higher (e.g., some metals).[5]

- The most recent literature included a study of e-cigarette aerosol emissions in a real-world indoor setting,[94] indoor lab/room simulated studies,[95,96] and modelling studies.[97,98] Across studies, there is variability in the levels of particulate matter due to various environmental conditions such as room size, the number of active e-cigarettes/users, the type of e-cigarette

being used (e.g., first generation, second generation and voltage type), and the users' behaviour (e.g., puff frequency, duration, volume).[94-97]

- Neither the NASEM report nor the subsequently published literature included studies addressing exposures in outdoor locations.

- The included literature reports that levels of indoor air pollution from e-cigarettes may be harmful to bystanders' health, in particular those who are exposed for prolonged periods of time (e.g., in a workplace setting). More research is needed on health risks from exposure to e-cigarette secondhand aerosol emissions, as well as more information on what happens to the aerosol emissions in various indoor (e.g., in multi-unit housing or adjoining rooms) and outdoor environments (e.g., patios, public spaces).

Net Impact of E-Cigarettes

The net impact of e-cigarettes at a population level will depend on their intrinsic harm (both direct and through second hand exposure), as well as on their combined effects on the initiation and cessation of smoking, and the propensity to sustain smoking among dual users. This section endeavours to address the net impacts of e-cigarettes at the population level considering some of these factors.

As noted in the background section of this report, the percentage of Canadians aged 15 and older who reported daily or non-daily smoking of combustible cigarettes has declined over the past 10 years or more. This decline has been observed in Ontario[28] and appears to be mainly due to decreased rates of smoking initiation. Whereas the prevalence of ever smokers has declined markedly over the past two decades, the prevalence of former smokers (past month) was relatively constant.[29]

In contrast, as noted also in the background section, the prevalence of e-cigarette use has increased substantially in recent years. For example, e-cigarette use (past-30 day use) by Canadian youth aged 15-19 increased from 2.6% in 2013 to 6.3% in 2015, while in adults aged 45 and older it increased from 1.0% in 2013 to 2.1% in 2015.[28] In 2015, 62.8% of Canadians who reported using e-cigarettes in the past 30 days, also reported that they smoked combustible cigarettes on a daily or non-daily basis.[28] There is no trend data currently available on dual use.

SFO-SAC Statement

The 2016 SFO-SAC authors state that the "Regulating e-cigarettes to make them preferable to cigarettes and to prevent non- or never-smokers from initiating e-cigarette use may reduce the prevalence of tobacco use in Ontario."[47]

NASEM

The 2018 NASEM report did not include any evidence statements with respect to modelling to assess the possible effects of e-cigarette use at the population level. NASEM did incorporate modelling work, which is included in the synthesis section that follows.

NASEM SYNTHESIS SUMMARY

The NASEM report observed that effects at a population level include the possibility:

- Some groups experiencing harm (e.g., youth who initiate smoking)
- Some groups experiencing benefits (e.g., adult smokers who completely quit or reduce their smoking).

Modelling is dependent on the assumptions used for these two possibilities. As described in preceding sections of this report, these possibilities are not yet clearly known and may change as ongoing research provides more evidence, and as products and the marketplace evolve.

Reflecting the uncertainty regarding the extent of harms and benefits, NASEM conducted a sensitivity analysis involving differing assumptions. Assuming e-cigarettes increase net cessation rates of existing smokers, modelling projects that the use of these products will generate a net public health benefit, at least in the short term. Any harms associated with increased smoking initiation by youth and young adults will take time to manifest. When projected to the long-term (e.g., 50 years), the net public health benefit is substantially less and is negative under some scenarios. Projected net public health harms become negative in the short and long terms if the products do not increase smoking cessation in adults.

Recent Literature

The searches for evidence about the effects of e-cigarettes on overall smoking prevalence and other health effects identified a range of sources including primary modelling studies. The included literature comprised of one evidence-based consensus report[5], one population time series study,[50] six non-industry sponsored modelling studies, and three jurisdictional scans. Modelling studies projecting the net effects of e-cigarette use were considered in addition to the modelling work reported in NASEM.[5,99-104] Bennett's (2012) reporting guidelines for modelling studies were used to guide review of the six papers modelling the health effects of e-cigarettes.[105] Two papers were excluded due to industry sponsorship (tobacco, or tobacco use cessation aids).[106,107]

RECENT PRIMARY LITERATURE

Overall, the modelling evidence is consistent with NASEM finding the greatest impact to be gained is by encouraging smokers to quit and discouraging exposure to tobacco and nicotine by youth.[5,99-104] These studies collectively underscore a need for accurate, detailed and up to date inputs, recommending their outcomes be interpreted with caution.[5,99-104] Outcomes reported consider mortality and life years gained, but do not consider morbidity and disability burden of smoking; for example, consideration of outcome measures such as Disability-Adjusted Life Years (DALYs) may be useful.[104]

A single paper projected health costs related to e-cigarette use, assuming e-cigarette use health 'costs' were from 1% to 50% as dangerous as conventional cigarettes.[103] This study found economic benefits across all possible health categories except among those who never smoked, estimated as a 10% absolute increase in e-cigarette use from never users.[103] Health costs were also incurred where

increased e-cigarette use accompanied decreased quit intentions, and where young people who had never smoked begin smoking due to having tried e-cigarettes.[103]

The impact of e-cigarettes as a quitting aid and as a potential gateway to smoking may change over time given new alternative nicotine delivery systems (ANDs) and heated tobacco products. It will be important to continue to consider whether products aimed to aid in cessation and also create uptake will produce a net public health benefit or cost.[104]

Three recent available jurisdictional comparisons show influence of the regulatory environment on the impact of e-cigarettes with use being lower in more regulated compared to less regulated environments.[108-110] For example, a cross-sectional survey from 14 countries in the International Tobacco Control Policy Evaluation (ITC) Project showed that generally, ever and current use of e-cigarettes was lower in countries with high restrictive e-cigarette policies (ever –use: 7.0% to 49.1%; current use: 0.3% to 3.2%), relative to countries with low restrictive policies (ever-use 37.9% to 66.9%; current use: 4.9% to 16.4%) and moderate policies (ever-use: 9.1% to 63.7%; current use 1.8% to 14.7%).[109] In countries with higher income levels, higher awareness and use of e-cigarettes may be reflective of their being widely available and affordable.[109]

Net Impacts – Summary

- NASEM's and subsequent modelling studies have attempted to assess net impacts, but due to the uncertainties of the assumed harms and benefits associated with e-cigarettes, their outcomes need to be interpreted with caution.

- The models highlight the importance of encouraging smokers to quit and discouraging exposure to tobacco and nicotine by youth.[5,99-104] There is a need for more accurate, detailed and up-to-date inputs into models.

- Recent scans show the regulatory environment influences the impact of e-cigarettes with use being lower in a more regulated compared to a less regulated environment.[108-110] However, this is a dynamic relationship with a large number of potential other factors that influence the use of e-cigarettes beyond the regulatory environment.

- Further research is required to assess the harms and benefits of e-cigarette use, including dual use among those who do not quit smoking. For example, understanding changes in, and reasons for, use of e-cigarettes particularly as the products and the marketplace are rapidly evolving.[111]

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Appendix A: Report Summary (August 2018)

Background

This appendix is a summarized version of the 2nd request for a technical response to the Ministry of Health and Long-term Care in August 2018.

A key feature of the August 2018 response was a consultation step with five tobacco scientists who attended a Scientific Advisory Meeting on July 27, 2018. An earlier version of the technical response was pre-distributed to the scientists who discussed and provided feedback at the meeting. Their comments were incorporated into a revised version that was subsequently circulated to them on July 30, 2018. The final version of the technical response incorporates their feedback.

We would like to thank the following scientists who attended the Scientific Advisory Meeting on July 27, 2018 to discuss and provide feedback on an earlier version of the bulleted summary of the technical response:

- Adam Cole, PhD(c), University of Waterloo
- David Hammond, PhD, University of Waterloo
- Pamela Kaufman, PhD, Ontario Tobacco Research Unit, University of Toronto
- Shawn O'Connor, PhD, Ontario Tobacco Research Unit, University of Toronto
- Laurie Zawertailo, PhD, Centre for Addiction and Mental Health

The content below includes the evidence summaries as they appeared in the technical response following the feedback from the scientists. Additional background sections that were reviewed by the scientists, but not replicated in this appendix include: Direct Health Effects of E-Cigarettes, Trends, Legislation, Rapid Evolution of E-cigarettes, and NASEM (2018) Conclusions. The main body of this report includes and expands upon this material and the evidence summaries.

Q1: Is the use of e-cigarettes an effective cessation aid for smokers?

Evidence Summary

- E-cigarette effectiveness as an aid to quit smoking can be assessed at individual and population levels:
    - Challenges exist in conducting both types of studies. For individual-level studies, these include achieving sufficiently large sample sizes and following participants for a sufficient period. For population-level studies, challenges include knowing whether those using e-cigarettes are intending to quit or to reduce their smoking, and whether they are using nicotine-containing products in a manner likely to support cessation.
    - It cannot be assumed that effectiveness at the individual level will translate into population-level effectiveness. Individuals participating in controlled studies may differ from the general population of smokers in important ways such as motivation to quit and pattern of e-cigarette usage. At a population level, sufficient reach is required to have a population effect.
- The body of evidence examining the impact of e-cigarettes as a cessation aid for smokers included an evidence-based consensus report (NASEM),[5] and an evidence review (PHE),[45] as well as one systematic review and meta-analysis,[48] one systematic review,[49] and 28 primary studies[50-77] published since the NASEM report search conducted in Aug 2017.
- Overall, the NASEM report concluded that there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation.
- Comparing the NASEM report with the most recent literature, more recent evidence from RCTs and observational studies do not provide additional support for e-cigarettes as an effective cessation aid. Specifically,
    - A recently published systematic review assessed e-cigarette effectiveness among vulnerable groups (i.e., mental illnesses, homelessness, substance use, or criminal justice system involvement) with the authors' concluding that they were hesitant whether e-cigarettes are effective for smoking cessation within vulnerable populations.[49] The second systematic review and meta-analysis re-analysed the two RCTs and other studies already included in the NASEM report.[48]
    - RCTs: Two RCTs that were included in NASEM showed that nicotine-containing e-cigarettes are more effective than e-cigarettes without nicotine for smoking cessation and harm reduction. Two more recent RCTs did not find a statistically significant difference in cessation or harm reduction comparing nicotine and non-nicotine e-

cigarettes. In one study, the study population was too small for the observed difference in cessation rates to reach statistical significance.[74] In the other study, both the nicotine and non-nicotine e-cigarettes achieved similarly significant cessation rates versus a control group.[63]

- Observational studies: While the results were mixed, NASEM concluded that there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation. Of eleven recently published longitudinal studies, four studies found a positive association [64,69,71,72] while seven studies found a negative or no association between various measures of e-cigarettes use and smoking cessation and/or harm reduction.[52-54,59,61,76,77] Two pre-post studies found a positive association between e-cigarettes and cessation.[56,60] All seven cross-sectional studies found that using e-cigarettes was not associated with smoking cessation.[58,65] Among these 20 studies, only five reported whether the e-cigarettes contained nicotine and only three of these specified the specific nicotine content.

- Considering the effectiveness of e-cigarettes compared with other cessation aids, NASEM concluded that there was insufficient evidence regarding the effectiveness of e-cigarettes compared with proven smoking cessation treatments. From the more recent literature, based on one RCT,[67] two longitudinal[59,73] and two cross-sectional studies,[66,68] e-cigarettes were less effective for smoking cessation and harm reduction compared to standard cessation treatments such as financial incentives, NRT, and pharmacotherapy (e.g., bupropion and varenicline). While the RCT had a sufficient number of study participants to detect a difference among treatment groups, it did not find a significant cessation effect for either e-cigarettes or any of the proven cessation therapies, calling into question the certainty of these findings.

- The NASEM report described population-level studies in which e-cigarette use was associated with one or more of quit attempts, quit attempt success rates, and cessation. Two more recent time series studies from the US and England observed differing results. The US study observed that e-cigarette use was more prevalent among unsuccessful quitters and recent quitters with an increase in the proportion of recent quitters who reported switching completely from smoking to e-cigarettes.[51,75] The English study, however, did not find a clear association between e-cigarette use and smoking, daily cigarette consumption, smoking reduction, or temporary abstinence.[50]

- There needs to be more research on the effectiveness of e-cigarettes (with or without nicotine) as a smoking cessation aid and identify groups for which e-cigarettes may be more effective as a cessation aid. Further research is also required on the health effects of dual use.

Q2: Does the use of e-cigarettes in non-smoking youth and young people increase the likelihood of smoking initiation?

Evidence Summary

- The body of evidence examining the impact of e-cigarette use on smoking initiation among non-smoking youth and adults included an evidence-based consensus report (NASEM),[5] an evidence review (PHE)[45] and a systematic review,[92] as well as 11 primary studies[77,82-91] published since the NASEM report search conducted in Aug 2017.

- Overall the NASEM report concluded that e-cigarette use was associated with increased risk of ever smoking, and among these youth and young adults, increased frequency and intensity of subsequent smoking.[5] There was limited evidence that e-cigarette use increased the duration of subsequent smoking.[5]

- Other reviews were consistent with the findings of the NASEM report.[45,92] In the most recent literature, all included primary studies suggested that e-cigarette use is associated with subsequent smoking initiation among youth and young adults.[77,82-91] However, common risk factors influence the relationship between e-cigarette use and subsequent smoking initiation.

- More research is needed on the trajectory of e-cigarette and smoking in those with little or no smoking experience including:

    - how different e-cigarette product characteristics (e.g., flavouring, nicotine levels, product design) are associated with different risks of e-cigarette and smoking initiation and progression; and,

    - the influence of social media and social exposure, especially among those with high use of social media who are also susceptible to smoking.

Q3: Are there health risks associated with exposure to secondhand vapour from e-cigarettes?

Evidence Summary

- The body of evidence examining the health risks associated with secondhand e-cigarette aerosol emissions included an evidence-based consensus report (NASEM 2018),[5] and five primary studies[94-98] published since the NASEM report search conducted in Aug 2017.

- Overall, the NASEM report concluded that e-cigarette use increases airborne concentrations of particulate matter, nicotine and other toxicants (e.g., propylene glycol, glycerol, VOCs, carbonyls, and some heavy metals) in indoor environments compared with background levels.[5]

- Compared with combustible cigarettes, secondhand exposure to e-cigarette aerosol has lower levels of many substances (e.g., nicotine, particulates), but some exposures may be higher (e.g., some metals).[5]

- Neither the NASEM report nor the subsequently published literature included studies addressing exposures in outdoor locations.

- The most recent literature included a study of e-cigarette aerosol emissions in a real-world indoor setting, indoor lab / room simulated studies, and a modelling study. Across studies, there is variability in the levels of particulate matter due to various environmental conditions such as room size, the number of active e-cigarettes/users, the type of e-cigarette being used (e.g., first generation, second generation and voltage type), and the users' behaviour (e.g., puff frequency, duration, volume).[94-97] Findings from specific study settings include:

    - A real-world study that found indoor concentrations of e-cigarette particulate matter and VOCs during e-cigarette use are higher compared to baseline levels when no e-cigarettes are being used.[94]

    - Lab-based / room simulated studies that found increased levels of exposure to secondhand aerosol emissions (i.e., particle concentrations)[96,97]and results from biological measures (i.e., serum cotinine levels) demonstrating that non-users experience systemic nicotine absorption from acute exposure to secondhand e-cigarette aerosols.[95]

    - A lab based / room simulated study which showed exhaled e-cigarette aerosol particle concentration is greater when in closer proximity to the e-cigarette aerosol emission source (i.e., greatest concentration within 0.5 metres compared to no recorded concentration at 2 metres).[96] The concentration of particles was shown to decrease to background levels after 10 seconds following the e-cigarette exhaled puff.[96]

- A modelling study found that the excess lifetime risk of lung cancer was lower from exposure to secondhand e-cigarette aerosol emissions compared to secondhand cigarette smoke, recognizing that various factors (e.g., dose exposure of e-cigarette emissions, toxicity of the e-juice or the compounds of the liquid in the e-cigarette) can influence the extent of e-cigarette aerosol exposure.[98]

- More research is needed on health risks from exposure to e-cigarette secondhand aerosol emissions, as well as more information on what happens to the aerosol emissions in various indoor (e.g., in multi-unit housing or adjoining rooms) and outdoor environments (e.g., patios, public spaces).

Putting It All Together

Evidence Summary

- The body of evidence exploring the effect of e-cigarettes on overall smoking prevalence and other health effects included an evidence-based consensus report (NASEM),[5] a population time series study,[50] six non-industry sponsored modelling studies[99-104] and three jurisdictional comparison studies.[108-110]

- The NASEM report indicated that the net impact from e-cigarettes is dependent upon:

  - the possibility that some groups experience harm (e.g., youth initiation of smoking), and the possibility that some groups experience benefits (e.g., adult smokers who quit or reduce smoking).[5]

- Reflected in the preceding evidence summaries for Questions 1 and 2, these possibilities are not yet clearly known and may change as ongoing research provides more evidence, and as products and the marketplace evolve.

- NASEM's and subsequent modelling studies have attempted to assess net impacts, but due to the uncertainties of the assumed harms and benefits associated with e-cigarettes, their outcomes need to be interpreted with caution. Overall, the models highlight:

  - A need for accurate, detailed and up-to-date inputs into models

  - The importance of encouraging smokers to quit and discouraging exposure to tobacco and nicotine by youth.[5,99-104]

- A population 10-year, time series study from England is available that assessed the impact of e-cigarettes on cigarette consumption.[50] There was no substantial association between the rise in use of e-cigarettes and changes in cigarette consumption per day.

- Three recent available jurisdictional comparisons show that the regulatory environment has influence on the impact of e-cigarettes with use being lower in a more regulated compared to a less regulated environment.[108-110] However, this is a dynamic relationship with a large number of potential other factors that influence the use of e-cigarettes beyond the regulatory environment.

Appendix B: Funding Sources

This table provides details about the direct funding of journal articles included in this report. 'Funding Source' lists all relevant sources of funding for the study. 'Competing Interests' describes previous funding not related to present work, author employment or provision of goods or services (for example, participation on an advisory board). Additional comments have been added where the study was either sponsored by industry or the authors had competing interests. These may include tobacco, pharmaceutical, chemical, and laboratory equipment/technology companies. Public Health Ontario reported based on information available in the published documents and did not conduct independent research to determine funding or industry participation.

Table 1: Funding Sources: Cessation Articles

Article	Funding Source	Competing Interests	Comments (if any)
Amato (2017)[76]	ClearWay Minnesota	No competing interests	None
Anic (2017)[75]	Food and Drug Administration's Center for Tobacco Products and Centers for Disease Control and Prevention's Office of Smoking and Health	No competing interests	None
Baldassarri (2018)[74]	Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart Lung, and Blood Institute Grant	Dr. Toll received grant from Pfizer for medicine for a research study; funding as expert witness against industry Dr. Chupp- received grants from NIH, Genetech, Glaxo Smith Kline, Astra Zeneca/Medimmune and Boston Scientific	Competing interests with Pharmaceutical Companies

Article	Funding Source	Competing Interests	Comments (if any)
Beard (2018)[112]	Cancer Research UK, Pfizer, GSK, Department of Health-UK	Consultancy and travel funding from smoking cessation medication manufacturers, grants from Pfizer	Study partially funded by Pharmaceutical Companies. Competing interests with Pharmaceutical Companies
Benmarhnia (2018)[73]	Tobacco Related Disease Research Program, and the National Heart, Lung and Blood Institute (NHLBI)	No competing interests	None
Berry (2018)[72]	National Heart, Lung, and Blood Institute of the National Institutes of Health and the Center for Tobacco Products	No competing interests	None
Chen (2018)[71]	Not reported	No competing interests	None
Ekanem (2017)[70]	No funding received	No competing interests	None
Etter (2018)[69]	Swiss Tobacco Prevention Fund (Swiss Federal Office of Public Health)	No competing interests	None
Gentry (2018)[49]	No funding received	No competing interests	None
Gorini (2017)[68]	Italian Ministry of Health/National Centre for Disease Prevention and Control	No competing interests	None

Article	Funding Source	Competing Interests	Comments (if any)
Halpern (2018)[67]	Vitality Institute grant (global health tank with focus on reducing chronic disease risk) to the University of Pennsylvania Center for Health Incentives and Behavioral Economics.	Dr. Troxel reports Other from VAL Health- a behavioral economics consulting firm, outside the submitted work. Dr. Volpp reports grants and personal fees from CVS Health, personal fees from VAL Health, grants from Humana, grants from Merck, grants from Weight Watchers, grants from Hawaii Medical Services Association, grants from Oscar Health Insurance, outside the submitted work.	Competing interests with Pharmaceutical Companies
James (2016)[66]	Not reported	Not reported	None
Kulik (2018)[65]	University of California Tobacco Related Disease Research Program Grant, FAMRI, NCI, FDA Center for Tobacco Products	No competing interests	None
Liu (2018)[48]	Not reported	No competing interests	None
Mantley (2017)[64]	NCI, FDA Center for Tobacco Products	No competing interests	None
Masiero (2018)[63]	Fondazione Umberto Veronesi (Umberto Veronesi Foundation)	No competing interests	None

Article	Funding Source	Competing Interests	Comments (if any)
Pasquereau (2017)[62]	Santé publique France, the National Public Health Agency	No competing interests	None
Rigotti (2018)[61]	National Heart, Lung, and Blood Institute	Rigotti reports a grant from Pfizer, UpToDate outside the submitted work	Competing interests with Pharmaceutical Companies
Rohsenow (2018)[60]	Brown University's Center for Alcohol and Addiction Studies, NIDA-NIH	Eissenberg- paid consultant against tobacco industry, and pending patent for device that measures puffing behaviour of e-cig	None
Selya (2017)[59]	NCI-NIDA, NIH	No competing interests	None
Subialka (2018)[58]	ClearWay Minnesota, Florida Dept. of Health, Oklahoma Tobacco Settlement Endowment Trust, Professional Data Analysts, Inc	No competing interests	None
Sung (2018)[57]	No funding received	No competing interests	None
Valentine (2018)[56]	New England Mental Illness Research, Education and Clinical Center; U.S. Department of Veterans Affairs; NIH, FDA	Consulting fees from Palo Alto Health Sciences and Mathematics Policy Research.	None
Vickerman (2017)[55]	Centers for Disease Control and Prevention (CDC)	Employed with Alere Wellbeing- provider of quitline services in this study	None

Article	Funding Source	Competing Interests	Comments (if any)
Weaver (2018)[54]	NIH/NIDA, FDA-CTP	No competing interests	None
Wu (2018)[53]	Hong Kong Council on Smoking and Health (COSH)	No competing interests	None
Young-Wolff (2018)[77]	Permanente Medical Group Delivery Science Rapid Analysis Program, Tobacco-Related Disease Research Program, NCI, NHLBI,	Prochaska- Pfizer which makes Smoking cessation medicine and been an expert witness against tobacco companies	Competing interests with Pharmaceutical Companies
Zawertailo (2017)[52]	Ontario MOHLTC	CIHR, CCS, Ontario Brain Society, Ontario MoH, OLA, CCO, CTCRI, GRAND, Pfizer Canada Inc., Health Canada, ECHO, NIDA, Johnson & Johnson Consumer HealthCare Canada, NABI Pharmaceuticals, V-CC Systems Inc., Ehealth Behaviour Change Software Co.	Competing interests with Pharmaceutical Companies
Zhu (2017)[51]	NCI-NIH	No competing interests	None

Table 2: Funding Sources: Youth Susceptibility Articles

Article	Funding Source	Competing Interests	Comments (if any)
Aleyan (2018)[82]	Canadian Institutes of Health Research (CIHR), Institute of Nutrition, Metabolism and Diabetes	No competing interests	None
East (2018)[83]	Cancer Research, UK; UK Public Health Research Consortium	UK Centre for Tobacco And Alcohol Studies, National Institute for Health Research Biomedical Research Centre, Public Health England, Action on Smoking and Health, British Heart Foundation, Cancer Research UK	None
McCabe (2018)[84]	National Cancer Institute, NIDA-NIH	No competing interests	None
Morgenstern (2018)[85]	Federal Center for Health Education- Federal Ministry for Health	No competing interests	None
Penzes (2018)[86]	Fogarty International Center and National Cancer Institute-NIH	No competing interests	None
Primack (2018)[87]	National Cancer Institute	No competing interests	None
Treur (2018)[88]	European Research Council, Netherlands Organization for Health Research and Development, National Institute for Public Health and Environment (RIVM)	Not reported	None

Article	Funding Source	Competing Interests	Comments (if any)
Watkins (2018)[89]	US National Cancer Institute and Food and Drug Administration Center for Tobacco Products- NIDA, National Center for Advancing Transnational Sciences	No competing interests	None
Young-Wolff (2018)[77]	Permanente Medical Group Delivery Science Rapid Analysis Program, Tobacco Related Disease Research Program, NCI, NHLBI, State of California Tobacco-Related Disease Research Program	Dr. Prochaska- consulted to Pfizer, which makes smoking cessation medications, and has been an expert witness for plaintiffs' counsel in court cases against tobacco companies.	Competing interests with Pharmaceutical Companies
Conner (2017)[90]	UK Medical Research Council/ National Preventive Research Initiative	No competing interests	None
Chatterjee (2016)[92]	Not reported	No competing interests	None
Hines (2015)[91]	Oregon Health Authority	No competing interests	None

Table 3: Funding Sources: Health Risks Articles

Article	Funding	Competing Interests	Comments (if any)
Avino(2018)[97]	National Institute for Insurance against Accidents at Work (INAIL) Grant	Not reported	None
Scungio (2018)[98]	Not reported	Not reported	None
Melstrom (2018)[95]	Not reported	No competing interests	None
Martuzevicius (2018)[96]	Fontem Ventures B.V. Imperial Brands Group plc- (E-cig Manufacturer)	Authors are full time employees of Imperial Brands Group	Study funded by Tobacco Company. Competing interest with Tobacco Company
Kaufman (2018)[94]	Lung Association Ontario, OTRU, MOHLTC, CDC-NIDA	No competing interests	None

Glossary

Abstinence: Abstinence refers to having stopped tobacco use for a period of time; abstinence may be defined in various ways.[78]

> **Continuous abstinence**: Also called 'sustained abstinence' or 'prolonged abstinence', is a measure of cessation often used in clinical trials that involve avoidance of all tobacco use (not even a puff) since a point in time (e.g., end of treatment or a quit date) until the time the assessment is made. The definition allows for occasional lapses. This is the most rigorous measure of abstinence.[78]
>
> **Point prevalence abstinence (PPA)**: A measure based on behaviour at a particular point in time, or during a relatively brief specified period. The most common point prevalence measure is no tobacco use (not even a puff) in the last seven days.[78]

'Cold Turkey': Quitting smoking abruptly, and/or quitting without behavioural or pharmaceutical support.[78]

'Dual Use': E-cigarette use among those who continue to smoke.[5]

Harm reduction: Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g., potentially reduced exposure products (PREPs).[78] Note: whether a reduction in harm occurs with dual use is currently unknown. According to NASEM, "due to the health risks of combustible tobacco smoke from even low levels of use, e-cigarette use among those who continue to smoke (i.e., dual use) may only confer benefits if dual use is merely a transitional state, after which a user transitions completely to e-cigarettes (i.e., quits combustible tobacco cigarettes)."[5]

Nicotine: An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking.[78]

Nicotine Replacement Therapy (NRT): A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence, while users are adapting to being tobacco-free. The nicotine dose can be taken through the skin using patches, by inhaling a spray, or by mouth using gum or lozenges.[78]

Quit attempt: An activity by a tobacco user in which the person tries to stop using with the intention of never using again. Some surveys only classify periods of abstinence as quit attempts that last for > 24 hours.

*The definition is not universal across studies. There are variations in time period, and quit attempts are often self-reported.[113]

Number of recent: The number of smokers who have made one or more quit attempts (stopped smoking for at least one day) in the past 12 months.

Incident: A single attempt to quit smoking for at least one day in the last six months.

Planned: A quit attempt that was planned ahead of time, perhaps by setting a quit date or obtaining treatment or assistive measures to support success in quitting.

Unplanned: A sudden or abrupt decision not to smoke any more cigarettes including those that might be remaining in the current pack.

Aided/assisted: A quit attempt in which the smoker used pharmaceutical or behavioral interventions.[114]

Unaided/ unassisted: A quit attempt in which the smoker did not use assistance in the form of pharmaceutical or behavioral interventions. [114,115]

Successful quit attempt: No longer smoking for a quantified length of time (e.g., one year, three months, etc.), achieving some form of abstinence.[116]

Quit intentions: Quit intentions represent the overall motivation, willingness, want or desire to quit smoking. Quit intention is typically measured in reference to a specific time frame (i.e., over the next seven days, 30 days, six months).[117,118]

Quit lines: Telephone-based tobacco cessation counselling that offers a variety of services to help tobacco users quit.[119]

Quit rates: Proportion of smokers who are smoke-free for a given number of days at a given (time) follow-up.[120] e.g.,

1. Proportion of smokers smoke-free for seven days at six-month follow-up
2. Proportion of smokers smoke-free for 30 days at six-month follow-up
3. Proportion of smokers smoke-free for six months at six-month follow-up.

Relapse: A return to regular smoking after a period of abstinence. Terms sometimes used for a return to tobacco use after a period of abstinence, include a ‘lapse’ or ‘slip’, which might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may be effective to help people recover from a lapse.[78]

Secondhand smoke (SHS): Tobacco smoke inhaled by people who are not actively engaged in smoking, which consists of a mixture of exhaled mainstream smoke and side stream smoke released from a smouldering cigarette or other smoking device (cigar, pipe, bidi, etc.) and diluted with ambient air. Secondhand tobacco smoke is also referred to as "environmental" tobacco smoke (ETS).[121]

Secondhand e-cigarette aerosol: In contrast to combustible tobacco products, e-cigarettes do not produce sidestream emissions. Secondhand e-cigarette aerosol emissions are produced as the exhaled emissions from e-cigarette users (i.e., mainstream aerosol emissions).[8]

Smoker

Current: Someone who has smoked in the last 30 days and has smoked 100 or more cigarettes in their life.[120,122]

Daily: Someone who reports smoking cigarettes every day (does not take into account the number of cigarettes smoked).[123]

Heavy: 25 or more cigarettes per day; [123] 20 cigarettes or more per day.[124]

Moderate: 15 to 24 cigarettes per day;[123] 11-19 cigarettes per day.[124]

Light: 14 or fewer cigarettes per day;[123] 1-10 cigarettes per day.[124]

Ever: Someone who has ever tried a cigarette, even a few puffs.[125]

Experimental: Those who have smoked less than 100 cigarettes in their life and have either smoked a whole cigarette over 30 days ago or smoked in the last 30 days.[125]

Former: Smoked at least 100 cigarettes in his/her lifetime and has not smoked at all during the past 30 days.[125]

Never: Someone who has never tried a cigarette, not even a few puffs.[125]

Non: Former smokers and never-smokers combined.[123]

Nondaily Occasional: Proportion of smokers smoking at least once in the past 30 days – not every day (this includes former daily smokers who now smoke occasionally).[120,123]

Puffer: Someone who has just tried a few puffs of a cigarette, but has never smoked a whole cigarette.[125]

Smoking initiation: Beginning to smoke, smoking onset or the progression from non-smoker to experimental or regular smoker.[126,127]

Smoking progression/escalation: An increase in the frequency of smoking from baseline measure (e.g., progressing from smoking occasionally to smoking daily). Stages can include (a) non-susceptible non-smokers, (b) non-susceptible experimenters, (c) susceptible experimenters, (d) light smokers and (e) committed heavy smokers.[128,129]

Smoking reduction: Cutting down the number of cigarettes smoked per day (i.e., smoke two cigarettes fewer per day).[130]

Smoking susceptibility: The absence of a firm decision not to smoke.[131]

Tobacco cessation: The process of stopping the use of any tobacco product, with or without assistance, also called "quitting".[78,79]

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