

Concentration of Nicotine in Vaping Products Regulations

Canada Gazette Part I Volume 154 Number 51

A commentary from an Economics perspective

March 01, 2021

Ian Irvine¹

¹ I am a professor in the Department of Economics, Concordia University, Montreal. I am grateful to several people in writing this submission. In particular, my son Neal, a vaper and former smoker, has provided me with invaluable assistance in understanding the vaping market and in writing this report. Disclosure: I have worked as a consultant to the federal government of Canada on alcohol and tobacco and to legal professionals in the private sector who specialize in nicotine. This paper and research have received no funding. Comments welcome to ian.irvine@concordia.ca

Introduction

In December 2019 Health Canada (HC) produced new regulations (henceforth the Regulation) governing the concentration of nicotine in vaping products in Canada. It decided upon a maximum of 20 milligrams per milliliter (mg/ml).

These regulations form one pillar of a multi-pronged assault on the vaping market. The federal government will formally announce restrictions on the availability of flavors in the spring of 2021. Federal/provincial excise and sales taxes are in progress, and further regulations have been promised for 2022.

HC is concerned that concentrations above this level have been both an inducement for teenagers to begin vaping and a source of continued dependence. The Regulation states that “lowering the maximum concentration of nicotine in vaping products is expected to reduce the appeal of these products to youth.”

The central policy challenge in the regulation of vaping is to strike a balance between, on the one hand, inducing smokers who would otherwise not quit smoking to transition to reduced-harm products (RHP) such as electronic cigarettes, and on the other to disincentivize youth from initiating the use of nicotine – a product that induces a high degree of dependence.

The strong growth in teen vaping since 2017 has rightly raised concerns all round. If we could devise policies to limit youth use of nicotine and tobacco that did not at the same time adversely impact our ability to transition smokers to less toxic products all would be well. Alas this is not the case: an increase in taxes affects all users, whether young or old; limiting flavors may reduce the attraction of e-cigarettes to both young new users and older would-be switchers; limiting nicotine concentration might impact youth use (though there is no evidence that it will) and it will limit the attraction to smokers of reduced harm products.

The HC Regulation mimics the European Union (EU) rule on limiting concentration to 20 mg/ml. At the time the EU rule was implemented, a group of 14 internationally recognized scientists (Etter et al, 2014) wrote to the EU Directorate outlining (a) why the limit would ultimately be counterproductive and (b) errors in the directive concerning the interpretation of the scientific literature as it existed at that time. More recently Cummings, Baylin and Swenor (2020) propose a roadmap for the use of RHPs.

About two thirds of the e-liquid market will be affected by a 20 mg/ml cap. Euromonitor (2020) proposes that the market is 20% supplied by on-line vendors, 30% by gas and convenience (G&C) stores and 50% by vape shops. Virtually all G&C store sales are of products in the 50+ mg/ml range because sales are dominated by Juul and Vuse products. An industry producer of e-liquid informed me that about 60% of product contains 21+ mg/ml and 40% 20 mg/ml or less. Of the 60% in the 21+ category at least half is in the neighborhood of 50 mg/ml. Hence two thirds of product would be eliminated under the cap. This is a severe form of product destruction. Broadly I will argue that

- The scientific literature does not provide support for the claim that a 20 mg/ml nicotine concentration will reduce habituation to nicotine; nor for the claim that will it prevent teen users who experiment with nicotine over a protracted period of time from developing a dependence.

- The Regulation assumes that vaping would become less attractive to teens if they are informed by HC that vaping products are less addictive in the presence of the limit. This is a leap of faith
- Data on teen use do not support the notion of an epidemic
- The Regulation assumes that nicotine intake on the part of the vaper is related only to the nicotine concentration in the e-liquid; a vast scientific literature indicates that this is not so
- The Regulation will impact the various sectors of the vaping industry differentially
- The penalties imposed for selling e-liquids with a concentration above 20 mg/ml appear to violate a basic principle of justice: vendors of similar products (combustible cigarettes) that yield higher nicotine and that are at least one order of magnitude more toxic are subject to no penalty.
- The cost-benefit analysis reported in the Regulation falls short of being convincing
- More effective policies are available that can meet the twin objective of limiting youth use while encouraging smokers to migrate to less risky products.

I focus upon these issues from the perspective of an economist. I am aware that researchers in the physical sciences have already submitted commentaries that are informed by the disciplines of Chemistry, Biology and Psychology.

The vaping market and vaping modalities in Canada

E-liquid comes in two forms: freebase nicotine and salt nicotine (a.k.a. unprotonated and protonated). The salt nicotine format (a.k.a. salt nix) enables the user to inhale a higher concentration than the freebase format. The latter rarely contains a nicotine concentration level above 15 mg/ml. It is used primarily in devices that permit large volume vapor inhalations. Salt nix is the format for high concentration vaping.

The more traditional devices that use freebase liquid, have large capacity tanks, operate at higher temperatures as a result of a high wattage capability and produce a larger volume of vapor that is available for inhalation. High-concentration salt nix e-liquid is vaped in lower-wattage devices. Many devices possess a variable wattage capability, meaning that the user can determine the availability of vapor produced.

Vaping devices produced by the global tobacco manufacturing firms tend to be smaller and use a high-concentration liquid. Compactness enables their users to be discrete when vaping – a feature that enables teenagers to avoid detection.

In sum: some vapers prefer high volumes with low concentration, others prefer the opposite combination. High-volume vapers are sometimes called “cloud chasers”.

A detailed overview of the vaping market for 2019 is presented in the Euromonitor report commissioned by Health Canada (Euromonitor, 2020).

A key issue is that the quantity of nicotine ingested is not determinable by looking at the nicotine concentration. A vaper using a 25-watt device and a 30 mg/ml concentration may ingest as much nicotine as a vaper who uses a 7-watt device with a concentration in the 60 mg/ml range at a given engagement with his device.

Some devices sold in vape shops can produce 200 watts using a 2500 mAh battery with a sub-ohm coil. This is thirty times the power produced by a Vuse or Juul. It is achieved by means of a more powerful battery (or two) and by controlling the resistance in the coils.² Temperatures for the high-nicotine low-watt devices are about 200 degrees c. and 300 c. for the higher-wattage devices. Combustible cigarettes typically burn in the 700+ c. range.

The scientific literature indicates that, on average, individuals vaping high concentrations are ingesting more nicotine than individuals on low concentrations, but the pattern is not uniform. As for the health risks associated with devices at the extremes: the literature suggests that the risks are somewhat higher when vaping a low concentration at high volume. Nonetheless, even at higher volume, the health risk is an order of magnitude less than smoking a combustible cigarette (c-cig). Public Health England (McNeill et al, 2015) and the Royal College of Physicians (2016) each support the use of e-cigarettes as a quitting device for smokers and indicate that the toxicity level of an e-cigarette is not more than 5% of the toxicity of a c-cigarette.

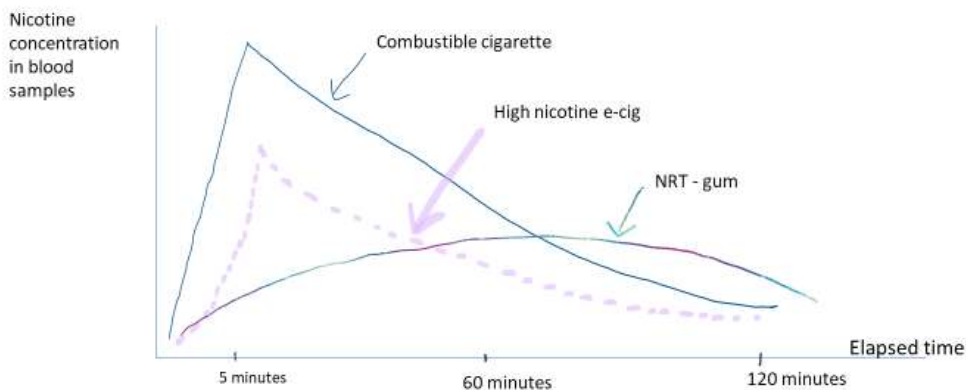
² The interested reader can do a google search to verify this range of capabilities. A couple of examples: (i) the Smok NFIX device has a 700 mAh battery; it produces 1 – 25 watts using 0.6 – 3.0 coils; (ii) The SnowwolfMFeng devices produces 10 – 200 watts using 0.2 ohm coils; (iii) the Aegis mini runs at 5 – 80 watts on a 2,200 mAh battery. Airflow is adjustable in many devices with a wide power range.

The HC Regulation omits a discussion of the health consequences of the different vaping modalities

The G&C market has assumed its current importance as a result of three main factors. First, the purchase price of nicotine through a convenience store is less than one half of the price of a corresponding quantity of cigarettes. Second, G&C stores offer convenience and certainty. Former smokers who have switched to vaping are accustomed to a set purchase pattern for decades in many cases: They do not have to go to a specialty store, which are not as plentiful as corner stores; they do not have to fill their devices or maintain their devices, even if these convenience aspects mean a greater expenditure. The fact that a G&C store product is perhaps 40% or 50% of the price of cigarettes is sufficiently attractive for many former smokers to avoid seeking a price at a vape shop that may be 25% of the price of a pack.³ Third, the characteristics of the minimalist high-nicotine cum low-wattage devices (HNLW) are compelling for a large sub-class of vapers.

Laboratory studies indicate that high-concentration vapers attain a nicotine pattern in their blood stream that mimics the pattern associated with cigarettes. High-nicotine liquid yields a 'peak' about 5 minutes after engagement. Although peak concentrations are lower in e-cigarettes on average, they are sufficiently close to the averages for cigarettes as to form a good substitute for smokers intending to quit. A vape-store owner has informed me that smokers in the process of transition to e-cigarettes almost all use the high-concentration liquid. This is consistent with the scientific findings.

Figure 1 The Pharmacokinetics of Nicotine Delivery



Consider figure 1 – an ersatz illustration of the pharmacokinetics of nicotine. The horizontal axis measures time and usually stretches to 2 hours, during which numerous fluid samples are taken from the participants. The c-cigarette peak on average dominates the high-concentration vaping peak,

³ The statement '40% of the price of a pack of cigarettes', means that when a smoker who would normally smoke a pack of cigarettes per day switches to vaping, on average he will satisfy his nicotine desire by vaping an amount of nicotine that will cost about 40% of the retail price of a pack of cigarettes.

whereas the concentration samples obtained from the users of nicotine gum are substantially different; the latter does not yield a quick 'hit satisfaction'.

Hajek et al (2019) includes an analysis of a Juul device at the EU concentration level of 20 mg/ml. They find that the peak nicotine concentration in the blood plasma occurs on average at a further-reduced level.

Experiments are normally conducted both in terms of a fixed number of puffs and separately in an *ad libitum* format, which permits puff compensation. These patterns suggest that some transitioning smokers, when faced with a reduced nicotine concentration in e-liquids will change the balance of their consumption in favor of c-cigs, and thus find it more difficult to continue their journey away from c-cigs.

The nicotine cap will hit vapers who use salt nix rather than free-base e-liquid. A vaper who uses a 55 mg/ml concentration will no longer be satisfied, nicotine wise, with the same volume of e-liquid in a 20 mg/ml format. He will have to purchase at least twice as much 20 mg/ml liquid to obtain the same nicotine intake as before. *Grosso modo*, the Regulation effectively doubles the price of nicotine to vapers who use high-concentration liquid. This is important for the cost benefit analysis undertaken by HC that is reported in the Regulation.

For high-concentration vapers the introduction of a cap is equivalent to product degradation, or approximately a doubling of the price of nicotine – with no tax revenue to show for it.

A 'light' cigarettes analogue

When light cigarettes were introduced in the 1980s the promise was that they would be less harmful and less addictive. This was an illusion. When light cigarettes were tested mechanically, they were found to yield less tar and nicotine, but the principle way in which they differ from regular cigarettes is that the filter is more porous and hence permits the entry of more air that does not pass through the tobacco stick. Researchers observed that when human subjects smoke light cigarettes they tend to reduce the porosity of the filter by gripping the cigarette so as to reduce air intake directly through the filter. Human subjects were also observed to inhale more deeply on light cigarettes than regular cigarettes. Consequently, the machine readings for light cigarettes were not reflected in correspondingly reduced toxins or nicotine for human smokers.

A similar process can be expected to play out with reduced concentration e-liquid. High-concentration vapers will compensate by purchasing more liquid and increasing their volume intake. This compensation may be substantial, though it is unlikely to fully compensate for the product destruction in the Regulation.

Cloud chasers, vaping freebase liquid, use a technique that is called direct-to-lung: the vaper inhales directly into the lung while drawing upon the device. In contrast, with a 7-watt high-concentration device the inhalation is mouth-to-lung: a much smaller volume is inhaled first into the mouth and then to the lung. While either technique is much less risky for health than smoking a c-cig, the direct-to-lung high-volume technique is riskier than the low- volume mouth-to-lung. Talih et al 2019 illustrate that toxicant yield increases beyond a specific wattage threshold, and exponentially beyond that.

Kosminder et al (2020) explored carbonyl levels emitted using two different nicotine concentration levels. They determined that carbonyl emissions increased by between 25% and 150% when the lower concentration liquid was used.

Son et al (April 2020 and May 2020) explore a wide range of factors that influence the intake of nicotine and carbonyls. They find that virtually every characteristic of the devices used in the experiments is important in determining outcomes. They conclude at the same time that carbonyl levels are between 10 and 10,000 times less for e-cigarettes than for combustible cigarettes.

Farsalinos and Gillman (2027) are particularly interested in the possibility of over-heating. They provide individual reviews of 34 papers in the area. They caution that while high temperatures (associated with a 'dry hit') are easy to produce in a laboratory environment, they are much more difficult to create in a human vaping environment. This is because a dry hit is particularly harsh, and vapers would not persist with dry puffs. Hence, some laboratory experiments that see high levels of carbonyls emitted are not meaningful. Poor e-liquid supply was a feature of older devices where the liquid had to travel a considerable distance from the tank to the wick/heating coil.⁴

Voos et al (2019), in their paper titled "What is the nicotine delivery profile of e-cigarettes?", review 99 papers on the subject. They find that the nicotine ingested from an e-cigarette is not well measured by the nicotine content of the e-liquid.

⁴ I am informed of this by a vape-shop owner.

Researchers have also explored the role of different combinations of PG and VG on nicotine and toxin intake.

To conclude: Vaping that involves a higher volume of e-liquid consumed at higher temperatures is associated with higher toxin risk. This will be one outcome from the nicotine cap. The literature is compactly summarized in the submission to HC by Dawkins, Cox and Kimber, 2021.

The literature on nicotine yield and toxin emissions is not cited in the HC Regulation.

Dependence levels – Very Low Nicotine Cigarettes

A large literature describes the characteristics and potential uses of very low nicotine cigarettes VLNCs – products designed to have below-dependence nicotine levels. An informative survey is presented in the FDA’s ruling on the application of the corporation 22nd Century to bring its VLNC products to market (FDA, 2019)

The literature on VLNCs can inform the HC initiative. Universally the published research literature on VLNCs adopts a definition that corresponds to the name – a very low nicotine concentration. Generally, a ‘very low’ concentration is one that means the VLNCs contain just a few percent of the nicotine of regular cigarettes. More than just a minute concentration is not considered to be a non-dependence concentration level.

While this literature is not cited in the Regulation, it suggests that reducing nicotine concentration roughly in half for the majority of vapers would do little to reduce nicotine dependence or the development of a dependence.

It is not even clear that a prohibition on salt nicotine combined with a limit of 3 mg/ml would be sufficient to enable users to avoid dependence, given that a non-negligible part of freebase users vape at that concentration.

To conclude: HC is rightly concerned about excessive youth use, but the literature on VLNCs indicates that reducing nicotine ‘somewhat’ will be futile, (I will argue later that controlling access by youth to nicotine products is key to reducing use).

Youth and adult vaping and smoking

Data suggest a 'somewhat rational' approach to risk by youth

Canada and the US have each experienced a tidal wave of commentary detailing the 'epidemic' of youth vaping. This is a two-sided story. On the one hand vaping has taken off among youth, and on the other smoking has declined very steeply.

Patterns in the US are almost identical to those in Canada. The Centers for Disease Control in the US (CDC) report that the 2020 usage rate among high school students was 19.6% and almost 40% of these vape more than 20 days per month, making for a high-frequency rate of 8%. Smoking rates have dropped dramatically – to a few percent.

The Canadian Student Tobacco and Drugs Survey (CSTADS) details steep increases in vaping among Canadian students and an accompanying decline in cigarette use for the period 2017-2019. The 2% daily smoking rate (an average over grades 10-12) is a result of smoking declines averaging 20% in *each* of the years 2018 and 2019. The Ontario Student Drug Use Surveys (OSDUS) details a similar pattern. The scale of this decline in youth smoking is 'historic', and remarkable given that the declines came at a point when youth prevalence was already low.

The OSDUS illustrates that, beyond the dramatic and opposing movements in vaping and smoking rates, youth are increasingly conscious of safe behaviour: We have seen major declines in alcohol abuse and drunkenness and other hazardous behaviors. The Ontario survey points to a decline of 50% in the rate at which youth are willing to accept a ride from a driver who has consumed alcohol or cannabis during the period 2011-2019, for example. In other words, youth has dramatically restructured its 'sin' patterns. Seen in this way, some risky youth behaviors can be perceived as quasi rational: a core of youth inclined towards risk taking has reoriented its choice of risky behaviors. Yet at the same time, youth that is less inclined to be risk-taking has increased its experimentation with vaping.

Data for August 2020 from the International Tobacco Control project indicate that vaping rates in Canada, England and the US declined dramatically relative to the values in August 2019 and February 2020 for individuals aged 16-19 (Hammond, 2021). The past-30-day rate in Canada (England, US) fell from 19.1% (14.0%, 18.8%) in February to 12.7% (11.1%, 13.6%) in August, while the high-frequency smoking rate (20 or more days during the past 30 days) fell from 6.2% (3.0%, 7.4%) to 4.0% (2.6%, 4.9%). If correct, these declines in vaping bring past-30-day rates among youth almost back to where they were before the arrival of Juul and Vuse in Canada in 2018.

The new nicotine consumption technologies have induced massive substitution in youth risk-taking patterns. Policy that is aimed solely at reducing smoking or reducing vaping is likely to be less successful unless it analyzes the interplay of different nicotine delivery devices.

The gateway hypothesis

Studies too numerous to mention report that the odds of being a young smoker are substantially higher for individuals who have previously vaped than for individuals who have never vaped. This temporal pattern is then associated with causation, though efforts are made in some empirical work to distinguish between causation and temporal patterns.

The logic of causality is explored in Phillips (2015), and reviews of the empirical literature are given in Lee et al (2019) and Chan et al (2020). These reviews conclude that it is very difficult to interpret the evidence so that it supports a gateway hypothesis, because vaping and smoking are common liabilities: smoking and vaping are more likely to be engaged with by individuals with similar risk-taking characteristics.

The massive decline in smoking among both teens and young adults in Canada suggests that e-cigarettes are in fact a reverse gateway, that is, on balance they prevent smoking which would otherwise have been adopted. As cited earlier, smoking in high school declined by 40% in Canada between 2017 and 2019, and smoking rates among young adults (age less than 25) have also declined by more than among older smokers (CTADS and CTNS).

Examining data patterns is one exploratory avenue. Another is to conceptualize the decision for a young person to migrate from a vaping device to a combustible cigarette. This was best described to me by a young reverse-gateway vaper as follows: "Are there a lot of kids, who are currently getting their nicotine fix from vaping, who would chose to switch to a product that gives them bad breath, yellow teeth, stinking clothes and vastly higher health risks, at a cost between two and four times their current nicotine cost?"

When phrased in such emotive, though precise, terms, it is difficult to conclude that there is a significant risk that a sizeable proportion of the youth vaping population will migrate to smoking.

Toxin consumption

Health Canada is rightly concerned about teen nicotine dependence. A particular focus of the Regulation is upon a group of teens who savor the buzz associated with a nicotine hit, which is frequently derived from a high-nicotine low-watt engagement.

Health Canada presents no data that indicate how widespread this pattern is, nor evidence that this group would cease to seek the buzz upon the imposition of a lower concentration limit. To believe that the buzz seekers will cease risk taking in the absence of additional measures to limit teen access is perhaps naive.

Despite the rise in vaping since about 2017, Jackson Brown and Jarvis (2021) report that, based on US data between 2011 and 2019, there has been no increase in dependence among all youth, as measured by the Fagerstrom test (use of nicotine product in the first 30 minutes of the day) or a 'craving in the past 30 days' test on the part of the youth population. Furthermore, dependence is markedly lower among vapers than smokers.

This decline in the per person dependence is not a cause for indifference. However, it illustrates that the media treatment of the use of vaping devices is not well described. Virtually every piece of coverage describes the high rate of experimentation as an epidemic. Yet, scientifically, we know that the toxin intake of today's high-frequency vapers is about one fiftieth of the intake of their smoking homologues in the late nineties. In the nineties, daily smoking rates were in the neighborhood of 25%, whereas today daily and almost daily vaping rates are about one third of that number. Since there are twenty times fewer toxins in e-cigarettes than combustible cigarettes, this means that today's high-frequency youth vapers are consuming maybe 60 times fewer toxins than their smoking counterparts in the late nineties. Using Hammond's data for August 2020 in which vapers aged 16-19 have a high-frequency vaping rate

of 4.0%, the same calculations indicate that today's young vapers are consuming 1/120th of the toxins consumed by high-frequency youth smokers in the nineties. This should give pause to the journalist community, which rarely recognizes the monumental gains to youth health.

It is difficult to forecast how under-age youth will react to a nicotine cap in their choice of vaping modality. There will be two countervailing forces. The first is that for the group of teens who consume high-concentration liquid, the cap will be essentially a doubling of price, and there will certainly be a reduction in the quantity demanded on that account. On the other hand, when HC announces that e-cigarettes are no longer as habit forming or addictive, youth should be inclined to experiment more rather than less. Thus, it is difficult to form a numerical estimate of how youth nicotine intake in the aggregate will change.

The Quoros Report buzz

The most influential input to HC's decision to promote a nicotine cap of 20 mg/ml is the content of the Quoros Report prepared for HC in May 2020. This report interviewed 103 youth, of whom 36 were regular vapers aged 16-19. It delivers an informative description of the lives of the teens in many dimensions.

When the youth were asked what they believed the best thing about vaping was, the highest frequency response was the "buzz" or "hit". A second notable double feature of the interviews informs the gateway and substitution debates: the regular vapers generally believed that they did not view vaping as a gateway to smoking, and that they would be smoking if they were not vaping (page 38). These responses, even though based upon small samples, are consistent with the daily smoking rates reported for high-school students of just 1% reported in the Regulation (page 6).

An optimistic view of the Quoros report and the statistics reported early in the Regulation is that they write a quasi-obituary for youth smoking.

Adults

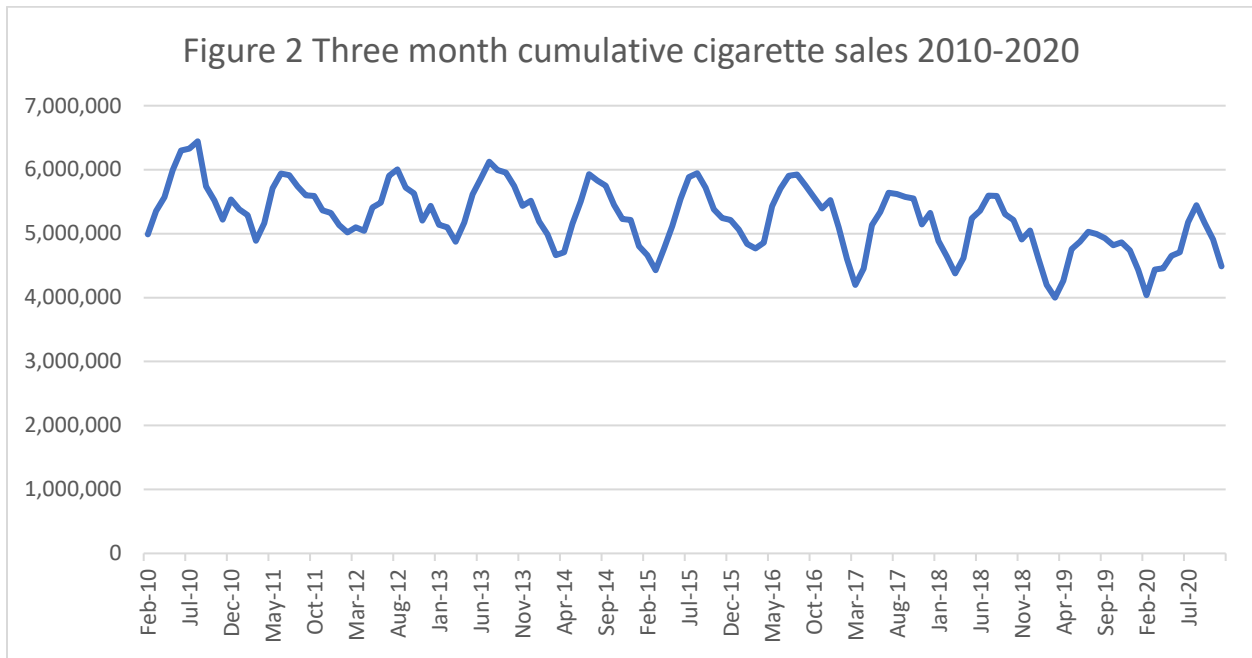
While the primary concern of HC and the health community at large is youth vaping, it would be an error to neglect the impact that vaping has had on the total tobacco market. Figures 2 and 3 detail the monthly shipments of cigarettes nationally. They are based upon Statistics Canada data. Figure 2 uses a sum of past 3-month sales and figure 3 uses a sum of past 12-month sales.

The dominant features of this past decade data are: (a) the slow decline in sales until 2019, (b) the dramatic fall in sales in 2019 and (c) the non-conforming pattern of the data in 2020. I have argued elsewhere (Irvine, CDHowe, 2020) that the major decline in 2019 sales (about 7% in a single year) cannot be explained by 'traditional' forces such as prices or new regulations, and that the only possible explanation is the arrival of Vuse and Juul in the marketplace in the spring and fall of 2018. This is verified independently by work from Health Canada's Tobacco Directorate: Nugent, 2020, presents fascinating data on the growth of the vaping market that indicates a high degree of synchronicity between the growth in e-liquid sales on the one hand and the decline in cigarette shipments on the

other. The health gains associated with a permanent decline of about 1.2 billion⁵ cigarettes. per year are substantial.

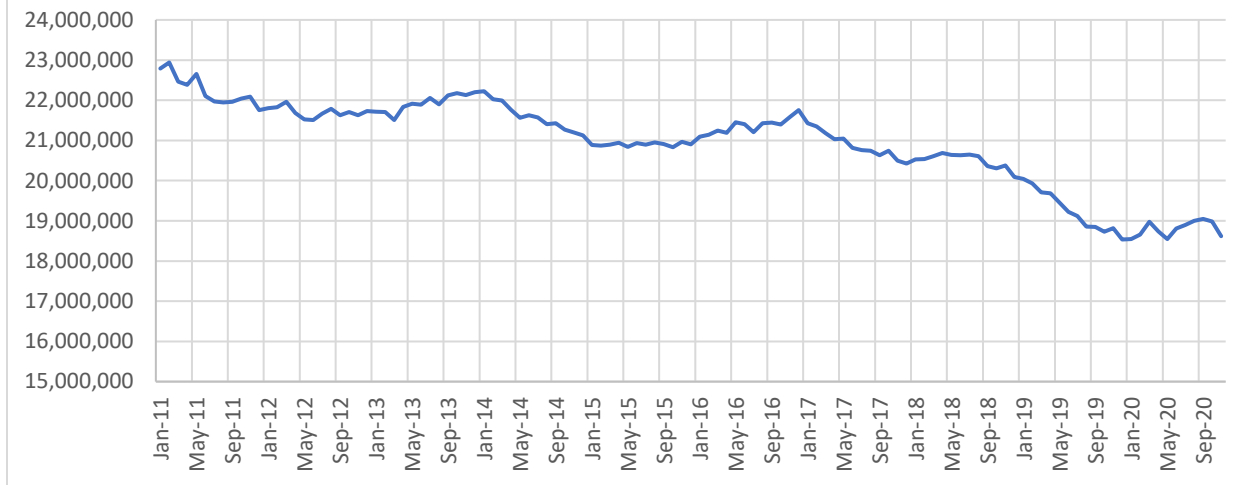
The year 2020 is more difficult to interpret on account of the arrival of Covid and the additional attacks on the vaping market in several provinces. What is clear is that the decline in cigarette sales has come to an abrupt halt

To conclude: Any new regulatory framework must take seriously the major health benefits that accrue from a reduction in cigarette sales. It is unfortunate that almost 100% of the media coverage is devoted to only youth use of vaping products and ignores the declines in smoking rates among youth and the decline in cigarette sales that coincide with the increase in vaping. A broader perspective is required.



⁵ With annual sales of 20b, if 6 points of the 7-point decline are attributable to e-cigs, we obtain 1.2b.

Figure 3 Twelve-month cumulative shipments 2011-20



Quits using e-cigs

A key policy issue is whether e-cigs really do help smokers to quit. The data above do not tell us if the decline in cigarette sales is due to an increased number of quitters or a bigger number of dual e-cig and c-cig users. There exists an enormous literature on the role of e-cigs in helping smokers to quit. A dispassionate overview of this literature is contained in a Cochrane Review (Hartmann-Boyce et al, 2020). The Cochrane reviews are undertaken by scholars whose funding comes from government and independent granting agencies. The review of the role of e-cigs in stimulating quits is positive. The authors review many studies and present their findings in layperson's language:

More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (3 studies; 1498 people), or nicotine-free e-cigarettes (3 studies; 802 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioral support only (4 studies; 2312 people).

For every 100 people using nicotine e-cigarettes to stop smoking, 10 might successfully stop, compared with only six of 100 people using nicotine-replacement therapy or nicotine-free e-cigarettes, or four of 100 people having no support or behavioral support only.

What is important here is that e-cigs are now the most popular aid to smoking cessation. That is, more smokers use them than any other aid – such as NRT (the patch), or therapy or drugs (e.g. varenicline). Even if the success rate for e-cigs were lower than for, say, NRT, e-cigs would still have a major role to play because they are the preferred choice of intending quitters. Getting smokers to quit or reduce should not be a contest between different methods: if smokers are heterogeneous and thus differ in their preferences for a quitting aid, it is vital that a variety of such aids be available. Some research papers that use randomized control trials neglect this heterogeneity.

Economic modelling: Assumptions and data analysis

Like all economic models, Health Canada's model of the vaping market invokes specific assumptions. Typically, a model and its assumptions are tested by repeated simulation, that is by varying the inputs (assumptions) one or several at a time. The HC model computes the present dollar value of reduced mortality and morbidity over a 30-year horizon, in addition to costs incurred and concludes that the benefits would dominate with just a small decline in youth initiation.

Big models depend upon assumptions and it is critical to simulate models subject to a variety of parameter values. But 'good' estimates are not necessarily 'certain' estimates and it is vital to explore the degree of such uncertainty.

The Health Canada model presents several concerns.

1 General versus partial analysis

The federal government at the time of writing (early 2021) is committed to introducing not just a cap on nicotine concentration but also a ban on flavors. It is also just a matter of time before federal excise taxes are imposed, and Health Canada announced in February 2021 that it will introduce yet further restrictions in 2022. This general environment is not addressed in HC's modelling exercise. The HC simulation model is run for 30 years forward in time and it compares simulated outcomes attributable to the 20 mg cap with outcomes (under specific assumed conditions) in the base period. But for 29 of those 30 years the base may be different from what the model assumes on account of the announced policy measures beyond the nicotine concentration limit.

Consider a group of smokers who are contemplating quitting by transitioning through the use of e-cigs. At a certain moment they are told that that high-concentration liquid will no longer be available.

Some of these smokers will continue with their intent to quit by experimenting with lower-strength nicotine, and let us call the percentage of intending quitters who actually move to experimenting with e-cigarettes alpha.

Next imagine that the group of intending quitters is told: "as of this month, not only will you not have access to nicotine in a high-concentration low-power delivery format, you will also not have access to the flavors that past quitters had as a choice". The literature on flavors indicates that an overwhelming percentage of transitioners choose a flavored product (other than 'tobacco' flavor). The percentage of intending quitters would fall significantly relative to where a full range of flavors is available. Let us call the reduced ratio beta.

Finally, suppose the group of intending quitters is told that, in addition to the nicotine cap and a ban on most flavors, the price of vaping will increase as a result of an excise tax and that restrictions will be imposed upon the size of vaping devices and the volume of liquid permissible in the device tank. It is unnecessary to repeat the logic here – the percentage of intending experimenters will go down still further – to gamma.

A flavor ban combined with taxes and further regulations would constitute an earthquake in the vape market. The impact of imposing, for example, a nicotine cap and a flavor ban simultaneously (same year) cannot be assumed to be equal to the sum of the impacts where each is assumed to be imposed alone, in the absence of the other. Intuitively, if a recent convert from smoking to vaping who is vaping a

flavored product with a high nicotine content (most converts) and a nicotine cap alone is implemented, he may continue to vape and avoid cigarettes because he can compensate in his nicotine intake as described earlier. Likewise, if he is hit with a flavor ban but can continue to vape at high concentrations he may continue to vape. But, if he is also hit with a flavor ban, he may decide to return to smoking, or go into the illegal market. This needs to be addressed in the HC model.

2. Switching assumptions – dealing with uncertainty

A key parameter is the rate at which smokers switch to e-cigs. On page 21 of the Regulation (Sensitivity Analysis) a simulation is performed where it is assumed that the base rate of transition from smoking to vaping declines by a further 1% or 10% as a result of the cap. This means that if (let us say) 5% is the base switching assumption in the model, the sensitivity test is to assume that rate declines to 4.95 % or 4.5%. These are exceedingly small variations even for a cap alone.

Researchers in this area recognize the huge degree of uncertainty surrounding ‘best estimates’ of behaviors. This is well illustrated in the HC-commissioned report “Elicitation of expert opinion ..” (Industrial Economics, 2017). Five internationally recognized scholars were asked for their best estimates of how smokers would respond to the introduction of very low nicotine cigarettes.⁶ Figure 3 below is chart 3-5 from the Report; it describes the answers to one particular question.

As is evident, the degree of uncertainty surrounding each expert’s best guess is enormous. For example, Expert C is ‘almost certain’ that between 5% and 70% of individuals will initiate e-cigarettes (the limiting dots) in response to the introduction of a very low nicotine standard for combustible cigarettes; he is 95% sure that the number of individuals who will make that choice is above 10% and is 95% certain that the number making the decision falls below 60% (horizontal lines), and he is 75% sure in relation to the 25% and 55% bounds.

The notable aspect of expert opinion is the awareness of uncertainty. Wisdom does not give rise to certainty, quite the contrary. In this graphic each expert has a similar wide range of uncertainty regarding outcomes. But in answers to other questions, not only are the confidence bands extremely wide for each individual expert, but those bands do not coincide among the experts. This is illustrated in the Report’s figure 3-9 (figure 5 below), where the difference between the opinions of experts A and C is enormous.

The HC simulation described above, in which the central estimate assumption is varied by 1% or 10% is minute in this context. In the face of uncertainty, comprehensive models are simulated hundreds or thousands of times subject to a variety of parameter-value assumptions, and the distribution of the

⁶ The report that HC cites when justifying some of the model’s decision parameters was designed to gauge the fall-out from the potential imposition of a very low nicotine standard on all combustible tobacco products. Five internationally recognized scholars were asked for their opinions on how tobacco users would react in several dimensions. The responses came with confidence levels from the experts. The responses were based upon an assurance that (page 1-3):

“the nicotine content of tobacco products would be too low to establish or sustain physiological dependence in the vast majority of users,” and

“that nicotine yields would be below the point at which compensatory smoking or compensatory use of non combusted tobacco products would be possible.”

These conditions are not analogous to the conditions governing the nicotine-cap regulations for e-cigarettes.

outcomes can then be assessed. Once probability bounds are established for each uncertain parameter, running the model repeatedly is feasible.

Figure 4

EXHIBIT 3-5. ELICITED ESTIMATES OF THE PERCENTAGE OF QUITTERS WHO WOULD INITIATE USE OF E-CIGARETTES IN THE YEAR FOLLOWING IMPLEMENTATION OF THE POTENTIAL PRODUCT STANDARD

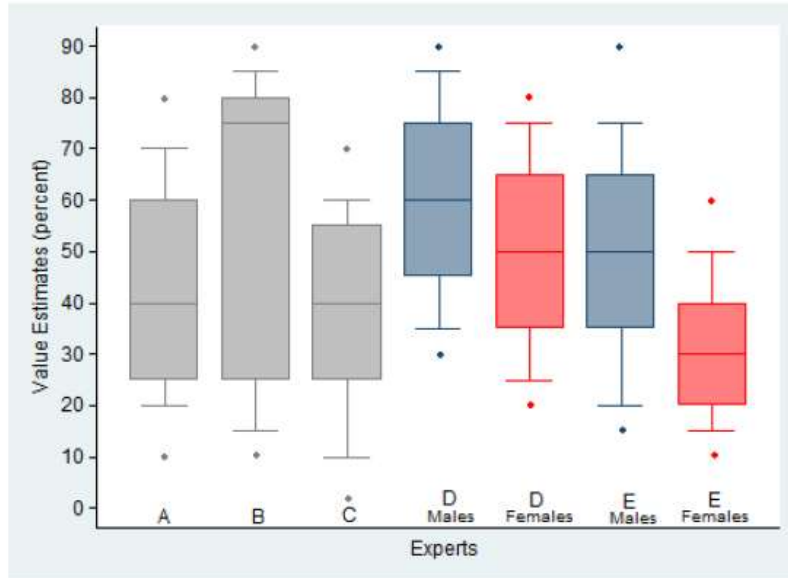
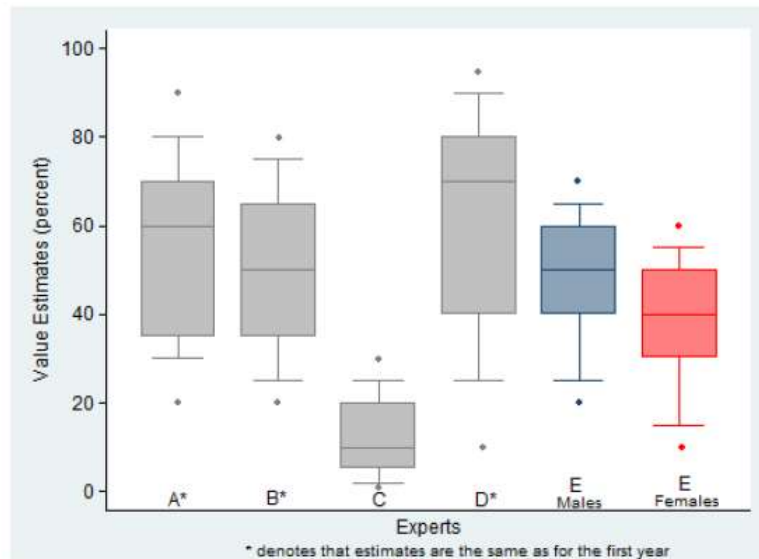


Figure 5

EXHIBIT 3-9. ELICITED ESTIMATES OF THE PERCENTAGE OF THOSE WHO CONTINUE TO SMOKE WHO WOULD INITIATE USE OF E-CIGARETTES IN EACH SUBSEQUENT YEAR



3. Morbidity costs

HC assumes that the morbidity costs of vaping are in the range of 20% of the cost of smoking. This is a very high number, in view of the reports from Public Health England and the literature cited above.⁷ Furthermore, low-heat devices that use high-concentration salt nix were just coming onto the market at the time of the first PHE report, and the evidence reviewed above indicates that they are even less risky than the earlier devices, because they work at lower temperatures. Switching vapers (particularly those who vape both high and low concentrations) from the low-watt high-nicotine devices to higher-watt lower-concentration devices increases the risk and is thus a negative aspect of the policy. The HC model is not designed to deal with this reality.

4. Tax revenue and illegal supply costs

The Regulation does not address the losses that will attend the growth of the illegal market once the nicotine cap (in conjunction with flavor bans and excise taxes) become operative. Canada has a rich and disturbing history of highly successful illegal markets in c-cigarettes, and it would be naive to think that extreme limits on nicotine in e-cigarettes combined with other restrictions would not equally produce an illegal market.

The production of e-liquid is not a complex process. As HC details in the Regulation, Canada has hundreds of producers selling e-liquid online and through about 1,400 vape shops. There are no technological barriers to entry in the vape market, and this greatly facilitates an illegal sector.

While the continued production of high-concentration liquid in an illegal market can be anticipated, I make the obvious point that Canada shares a 9,000 km porous border with a jurisdiction where no such limits apply.

Sales and excise tax revenues will be lost. Policing costs will be incurred, and social capital will deteriorate. A reasonable projection is that every province will have an excise tax in place in addition to a sales tax by 2022, either in the form of a uniform federal tax or a special provincial tax. This means that tax-revenue losses must be considered for about 29 of the 30-year horizon in the HC simulation model. Such estimates are absent from the model.

Some vapers who are accustomed to purchasing their supplies at vape shops are at ease with adding a drop or two of nicotine to their mix. The purchase of nicotine is not illegal. By the same token, if flavor bans become operative such users will be able to purchase flavoring in supermarkets or online and inject a couple of droplets into their 30 ml bottles of product. While experienced users can manage these tasks, accidents will arise as a result of pure nicotine being available in domestic environments, and it is in the interest of public health that the use and titration of nicotine be in the hands of professionals.⁸

To conclude: The HC Regulations do not address the costs of having an illegal market or a grey market. This omission is difficult to understand in view of Canada's history of illegal supply in the combustible

⁷ One of the recognized difficulties associated with computing relative risks for vapers is that most older vapers have a history of smoking and there are residual smoking-related risks on that account.

⁸ It is possible that illegal supply will have sub-standard components and that such components will be injurious to health.

cigarette market, which some estimates place at about 25% of the total cigarette market in Ontario (O’Riordan, 2020).

5. Asymmetric impacts and profitability in the marketplace

On the retail front, the regulation will hit the G&C stores more heavily than vape shops and on-line business, because the G&C stores are specialized in high-concentration sales. Vape shops will be impacted also, because some high-concentration vapers will reduce their e-cig purchases in favor of c-cigs even if a majority switch to lower concentration liquid. Some G&C buyers may migrate to vape shops where they can purchase supplies that will enable them to maintain a nicotine dose closer to the pre-Regulation level. It remains to be seen what percentage of high- concentration users will maintain their allegiance to Juul and Vuse products in the face of a de facto doubling of the price of their e-liquid. All suppliers will be impacted both on account of a nascent illegal sector and a reduction in the number of smokers transitioning to vaping.

The HC Regulation contains a provocative section on profitability (page 17). It indicates that the industry might become more profitable under the nicotine limit:

Since it is more profitable for the vaping industry to manufacture vaping products with 20 mg/ml nicotine or below, it is anticipated that the vaping industry could in fact benefit from the proposed regulations assuming a 100% switch rate.

Economics would suggest otherwise. The vaping industry is ‘competitive’ in that entry is relatively free, as is exit.⁹ This implies that above-normal profits are competed away through supply increases. Basic economic forces ensure that higher-than-normal profits attract new suppliers. In contrast, in the HC model a claim is made that freebase e-liquid is less costly to supply than salt nix and therefore profits could increase following a forced migration to freebase if all salt nix users were to migrate.

Freebase e-liquid is less costly to manufacture and sells at about one half of the price of salt nix, but users generally expend more on freebase because the associated additional volumes used outweigh the lower price per milliliter.

The price of e-liquid varies hardly at all with variations in the nicotine content within a class, because suppliers do not experience a significant difference between the cost of producing a 6 mg or a 12 mg concentration in freebase, or between a 30 mg and a 50 milligram in salt nix. Costs are composed of capital and labor and materials and if the nicotine content is changed, the impact of that on cost is so small that it is rarely reflected in the price.

The competitive dynamic I describe here is reflected well in the cannabis markets of the early-to-legalize states in the US. Oregon produced an oversupply as a result of excessive entry in 2018/19. Colorado has seen a reduction in the number of producers since the early days of recreational legalization. Entry rates were initially high, but exits and consolidation have since been necessary.

⁹ Some observers might call the market a multi-product competitive market or even a monopolistically competitive market in which products display slight differences. The key issue is freedom of entry (exit). That is what ensures above-normal (below) profits are extinguished.

Since the vaping market is competitive, entry and exit will equilibrate whatever excess supply or demand may characterize the market at a given time and will equally compete away above-normal profits.

6. Dual users

There is a repeating theme in the Regulation that dual users experience no health gain unless they transition completely to e-cigarettes. Research indicates that if dual users in the longer term maintain their smoking habit, most of the risk reduction is indeed lost. The relationship between smoking duration and intensity on the one hand and the incidence of disease on the other depends upon whether lung cancer or coronary heart disease (CHD) is at issue. For CHD, risks materialize even at very low levels of smoking (Hackshaw et al, 2017). The relationship between smoking and lung cancer, in contrast, is more proportionate and the relative risks are higher. Remen et al (2018) find that the relative risk for a pack per day smoker is ten times as great as for a non-smoker. They explore the independent role of smoking duration and intensity and find that both variables are statistically significant in their model of risk-reduction. Thus, risks do decline for dual users, but the declines in risks are moderate. It will be important to track future CTNS results to determine how switchers to dual status behave in the longer term.

7. Discounting the future

The use of a very high discount rate (7%) means that events in the future are discounted heavily relatively to events that take place in the near term. This issue alone warrants a detailed analysis. In models where lives are lost and gained it is essential to report such losses and gains in terms of life years. The HC model does not. To illustrate: a life-year lost in year 30 of the model, with a discount rate of 7% works out to be worth about \$6,500, assuming a statistical life year to be worth \$50,000 in real time ($= \$50,000/(1.07^{30})$).

Most of the published literature in this area cites life years lost and gained when considering policies that have an intertemporal nature. When turned into a dollar value and discounted heavily life years become essentially valueless if the gains and losses occur in the future. In this example, a life year in year 30 is worth just one eighth of a life year today.

This particular issue is well-known in cost benefit analysis, particularly in the environmental field. One of the first major reports on climate change (the Stern report, 2007) devoted a separate chapter to discussing the discount rate and came down in favor of a very low rate because lives lost in the future should not be considered to be of low value, that is a life gained today should not be considered socially equivalent to eight lives lost 30 years from now as the HC model implies.

The high discount rate, combined with a high assumed health-cost of vaping plus the assumption of a strong growth in the vaping market in the near term means that the model puts a very high cost on vaping and a low cost on lives saved in the future. There are very strong ethical and moral issues underlying this model that need to be clarified.

8. Specific model issues

1. On page 16, the Regulation assumes that users who switch to lower-nicotine concentrations will maintain the same level of consumption. This is uncertain given that such a consumption level might yield just half of their accustomed nicotine load. A vaper might have to double his

previous outlay to consume the same quantity of nicotine. To these users, the cap is a pure product quality-destruction mechanism.

2. In assuming that 75% of vapers would stay with vaping and 25% would not, following a cap, the model do not clearly describe how the residual 25% are dealt with in the cost-benefit analysis. If they return to smoking, then smoking-related diseases will increase, and life expectancy will be curtailed. A less costly individual health choice would be to go to the illegal vape market.
3. The model appears to make a pair of assumptions that may not be consistent. On page 15 it is stated that those vapers who transition to 20 mg concentrations will consume the same quantity as those who are already vaping at 20 mg or less; at the same time it is stated that these 75% will maintain their expenditure as it was prior to the cap. How this pair of assumptions is aligned is not developed in the description. We do know that a very high proportion of current users above the 20 mg/ml level use concentrations in the 50 mg/ml neighborhood. This is a major cost for consumers, and how the model computes this loss is not spelt out.
4. The model is also not explicit on how the cost of the reduced transitions from smoking to vaping is treated. If fewer smokers transition to vaping on account of the cap, then deaths will increase relative to the baseline.
5. The model assumes that between 2020 and 2024 the vaping market will increase by 75% and stay flat thereafter (in the base case scenario). However, if a flavor ban becomes operative in the near term, on top of a nicotine cap, and additional taxes are imposed, the market could conceivably contract to half of its current size. Conversations with vape-shop owners support such fears. If this does materialize, then the HC model assumption that the vaping market will be three and a half times the size feared by suppliers is problematic. No mention is made of this in the Regulation.

9. Other research models are more positive

Several multi-year models address the benefits and costs of policies that envisage a move from combustible cigarettes to e-cigarettes. They are well cited in the literature and arrive at substantial benefits measured in terms of life years saved. Their objective is not the same as the HC model. Examples are Levy, Borland, Lindblom, et al. (2018), Levy, Cummings, Villanti et al. (2017) and Warner and Mendez (2019).

Alternative policies to product destruction

The decision by HC to promote a nicotine policy cap raises the issue of why that particular policy was chosen and analyzed relative to the status quo. For example, would a policy of taxation designed to curb the consumption of high-concentration e-liquid be superior to the cap policy? Or would a serious information policy better incentivize users and potential users? Or would more enforcement of youth-access laws be a superior policy?

Health Canada reports that a significant fraction of 36 teens who were interviewed by Quorus Consulting declared that they got a buzz from vaping. That is one foundation stone for the Regulation. HC believes that a 20 mg/ml concentration will leave vaping intensity unchanged in that teens will not take longer puffs or more frequent puffs of a reduced-concentration product, and that dependence will decline. HC also appears to believe that an announcement that 20 mg/ml e-liquid is less dependence forming will encourage fewer teens to experiment. This is a very strong set of assumptions.

Teen access to nicotine products is critical. If teens continue to have the same degree of access as at present and take longer and more frequent puffs then they will be unlikely to move to a state of less dependence. In conversations with industry suppliers I have learned of their frustration with rogue G&C stores that do not enforce the legal age-of-access rules. This is highly relevant, because unless access by teens is reduced, a policy of reduced concentration represents just a hope that teen use will decline. Industry also informs me that HC is understaffed in having too few inspectors. The need for enforcement cannot be over-emphasized. Enforcement is a targeted policy in that it does not deter adult smokers from switching.

It is also the case that e-liquid can be purchased in high concentrations online by any purchaser with access to a credit card, despite regulations requiring Canada-Post delivery and a sign-upon-receipt policy by an age-valid purchaser.

A nicotine cap is not a substitute for teen access control.

While I do not recommend a policy of discriminatory taxation on high-concentration vapor products, taxation would not be as harmful as the proposed product destruction. For a large segment of vapers currently using 20+ concentrations, the elimination of those products from the menu of options is broadly equivalent to a heavy tax: the price of nicotine, for many users, will double.

Taxation would have a similar behavioral impact on the market as product destruction. A tax that would drive most legal users to a 20 mg/ml concentration would simultaneously drive some users to the illegal market and some back to combustible cigarettes. The difference is that product destruction is a pure loss for consumers whereas taxation represents a partial resource transfer to the government.

As a vastly superior alternative to both taxation and a nicotine cap, a policy with high potential would be to provide information to smokers. Smokers, and the wider population, are largely ignorant of the relative toxicity of e-cigarettes (CTNS, 2019). A policy that would inform smokers about risk-reduced products would incentivize smokers to switch. Such messaging could be placed on one side of cigarette packs. Irvine and Nguyen (2021) recommend that the currently-mandated two-sided negative warnings required by HC on cigarette packs be replaced with a system where one side would remain negative (as at present) and the other side contain a 'positive' switch-to-vaping message. If accompanied by a serious access policy this combination would have greater benefits than one based upon product destruction.

Conclusions

Health Canada's proposed nicotine cap on e-liquid has the following characteristics:

- It will drive vapers to use slightly higher-risk products
- It will encourage the development of an illegal market. Canada has a vigorous history of tobacco illegality
- It will discourage smokers from switching to reduced harm products
- It is equivalent to product destruction with no quid pro quo for the vaper
- Combined with a flavor ban and taxes the measure will destroy a large part of a market based upon a Canada-sourced product
- It is based upon a belief that a 20 mg/ml concentration will not generate dependence
- It is based upon a belief that lower nicotine will not make youth believe that vaping is safer
- A cornerstone for the proposal is a set of interviews with a group of 36 youths, an unspecified number of whom primarily vaped for the buzz
- The impact on youth initiation is indeterminate
- Youth vaping is not an epidemic; today's youth are consuming a miniscule fraction of the tobacco-related toxins consumed by their parents
- The economic model is unconvincing in multiple dimensions
- A cap will not be effective for youth unless proper access controls are put in place
- Better alternative policies are available, such as messaging and access control.

References

Bates, C., 2020. <https://www.clivebates.com/twenty-reasons-to-be-sceptical-about-rules-lowering-nicotine-levels-in-cigarettes-and-what-to-do-instead/>

Chan, G., Stjepanovic D, Lim C, Sun T, Shanmuga, A., Connor, J. et al., 2020. "Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation." *Addiction*. 2020 Sep 4.

Cummings, K. M., S. Ballin and D. Sweanor, 2020. "The past is not the future in tobacco control." *Prev Med (Baltim)*. <https://doi.org/10.1016/j.ypmed.2020.106183>

Dawkins, L, S. Cox and Kimber, 2021. "Response to the Canadian Consultation on Proposed Concentration of Nicotine in Vaping Products Regulation." Mimeo London South Bank University.

Etter, J. F., et al 2014. "Scientific errors in the Tobacco Products Directive." A letter sent by scientists to the European Union." <http://www.ecigarette-research.org/research/index.php/whats-new/whatsnew-2014/149-tpd-errors>

Farsalinos, K. and G. Gillman, 2017. "carbonyl emissions in e-cigarette aerosol: A systematic review and methodological considerations." *Frontiers in Physiology*, 8(1119). doi: 10.3389/fphys.2017.01119.

Food and Drug Administration, 2019. "PMTA Scientific Review: Technical Project Lead (TPL)." <https://www.fda.gov/media/133633/download> (22nd Century Application)

Hackshaw A, Morris J, Boniface S, Tang J, and D. Milenkovic, 2018. "Low cigarette consumption and risk of coronary heart disease." *British Medical Journal*, 360(5855). <https://www.bmj.com/content/BMJ/360/BMJ.j5855.Full.pdf>

Hajek, P., A. Phillips-Walker, D. Przulj, F. Pesola, K. M. Smith, N. Bisal, J. Li, S. Parrott, P. Sasieni, L. Dawkins, L. Ross and M. Goniewicz, 2019. "A Randomized trial of e-cigarettes versus nicotine-replacement therapy." *The New England Journal of Medicine*, February 2019. <https://www.nejm.org/doi/10.1056/NEJMoa1808779>

Hartmann-Boyce, J., H. McRobbie, N. Lindson, S. Freeman, A. Sutton, C. Bullen, R. Begh, A. Theodoulou, C. Notley, N. Rigotti, T. Turner, A. Butler, P. Hajek., 2020. "Electronic cigarettes for smoking cessation." *The Cochrane Library*, 14 October 2020. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>

Industrial Economics, 2017. "Elicitation of expert judgements on the behavioural Impacts of a nicotine standard." Prepared for Health Canada.

Jackson, S., J. Brown and M. Jarvis, 2020. "Dependence on nicotine in US high-school students in the context of changing patterns of tobacco product use." Doi:10.1111/add.15403

Kosminder, L., S. Cox, M. Zacier, J. Kurek, M. Goniewicz, H. McRobbie, C. Kimber and L. Dawkins. "Daily exposure to formaldehyde and acetaldehyde and potential health risk associated with use of high and low nicotine e-liquid concentrations." *Scientific Reports*. 10:6546 <https://doi.org/10.1038/s41598-020-63292-1>

Lee PN et al. 2019. "Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review." <https://dx.doi.org/10.12688%2Ff1000research.16928.3>

Levy, D., R. Borland, Lindblom, E. et al., 2018. "Potential deaths averted in USA by replacing cigarettes with e-cigarettes." *Tobacco Control*, 27(1), 18-25.

Levy, D., M. Cummings, A. Villanti et al., 2017. « A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products." *Addiction*, 112(1), 8-17.

Liber, A., Z. Cahn, A. Larsen and J. Drope, 2021. "Flavored e-cigarette sales in the United States under self-regulation from January 2015 through October 2019." *American Journal of Public Health*, June. <https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2020.305667>

McNeill A., L. Brose, R. Calder, P. Hajek, S. Hitchman and H. McRobbie, 2015. "E-cigarettes: an evidence update. A report commissioned by Public Health England." PHE publications gateway number: 2015260

O'Riordan, F., 2020. "The impact of COVID-19 on contraband tobacco and provincial tax revenues in Canada: March August 2020." Report commissioned from Ernst and Young by the Convenience Industry Council of Canada.

Phillips C V. 2015. "Gateway Effects: Why the Cited Evidence Does Not Support Their Existence for Low-Risk Tobacco Products (and What Evidence Would)." *Int J Environ Res Public Health*;12:5439–64.

Quoros Consulting Group, 2020. "Exploratory Research on Youth Vaping." Prepared for Health Canada, Final Report May 2020. http://publications.gc.ca/collections/collection_2020/sc-hc/H14-347-2020-eng.pdf

Remen T, Pintos J, Abramowicz M, Siemiatycki J. "Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal." *BMC Cancer*. 2018 December 19. <https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-5144-5>

Royal College of Physicians, 2016. "Nicotine Without Smoke: Tobacco Harm Reduction." London: Royal College of Physicians.

Son, Y., C. Bhattarai, V. Sam burova and A. Khlysto, 2020. "Carbonyls and Carbon Monoxide emissions from electronic cigarettes affected by device type and use patterns." *International Journal of Environmental Research and Public Health*, 17, 2767; doi:10.3390/ijerph17082767

Son, Y., C. Weisel, O. Wackowski, S. Schwander, C. Delnevo and Q. Meng, 2020. "The impact of device settings, use patterns, and flavorings on carbonyl emissions from electronic cigarettes." *International Journal Environmental Reserch Public Health*, vol. 17. Doi:10.3390/ijerph17165650

Stern, N., 2007. "The Economics of Climate Change: The Stern Review." Her Majesty's Treasury of the UK Government.

Talih, S., R. Salman, R. el-Hage, E. Karam, N. Karaoghlanian, A. El-Hellani, N. Saliba, T. Eissenberg, A. Shihadeh, 2020. "Might limiting liquid nicotine concentration result in more toxic electronic cigarette aerosols?" *Tobacco Control*, 0:1-3, doi:10.1136/tobaccocontrol-2019-055523.

Voos, N., M. Goniewicz and T. Eissenberg, 2019 "What is the nicotine profile of electronic cigarettes?" *Expert Opinion Drug Delivery*. 16(11):1193-1203. doi: 10.1080/17425247.2019.1665647.

Warner, K. and D. Mendez, 2019. "Comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation." *Tobacco Research*, 21(1), 41-47.