

Good Afternoon,

March 4, 2020

I first want to start off by saying thank you for accepting my request to speak on behalf of my company, FOV Labs Inc, and the thousands of customers who rely on us every day to supply them with high quality, ISO7 lab made and tested e-liquid.

I founded FOV Labs in 2016 after being a 10yr smoker. I grew up my entire life watching my mother struggle with addiction to combustible tobacco. That addiction took a major toll on her health at the ripe young age of 42yrs old when she had the first of her many strokes. My mother is now 59yrs old and just last month, I had to convince her to move into an assisted living home. She's been thru 2 heart attacks, 1 quadruple by-pass open heart surgery and 7 strokes. She is now legally blind in her left eye and can no longer walk by herself without a walker due to the paralysis from her most recent stroke.

Even after watching her struggles, I too became addicted to combustible tobacco and scaled my addiction to 2 packs of cigarettes a day. I knew it was bad for me but did so anyway. My 20's were spent with a cigarette hanging from my lips. When I tried to quit I chose nicotine patches which gave me severe mood swings and Champix, to which the side effects were worse than smoking. Suicidal thoughts and severe stomach pains were nearly unbearable, so I chose the lesser of two evils and continued to smoke.

On my 30th birthday I decided to give this vaping thing a try. I started with what most started out with, an AIO pen style vape and 24mg of blue raspberry mango flavoured e-liquid. The first few weeks I kept a pack with me at all times because I didn't believe that vaping would help. I found myself reaching for my vape after every cigarette to change the taste of dirty ash in my mouth and replace it with the blue raspberry mango that I had grown to love. Finally, after two weeks I asked myself why I was continuing to spend money on cigarettes if I preferred the taste of the e-liquid. That was my first day completely off cigarettes and where I finally broke the chains of addiction. I had done something that my mother tried doing for 45yrs. Within a few months I felt like a brand-new man. My energy levels were up again and the shortness of breath I once had was gone. Don't let this image fool you, I may be a bit overweight and stressed to the max, but I feel a million times better than when I smoked!

After a year of vaping I discovered how to make e-liquid and ran with the idea. My mission was now to help every single adult smoker I could find. I wanted, and still do, to help people quit smoking and experience its liberating effects much as I did. It's my passion, just like many business owners and vapers who spoke here today. My business flourished because of its business model and its core values.

You see, vaping in its entirety was built by people like myself and my colleagues here today who are better known as the grass roots industry. We poured our hearts and souls into our businesses. We sacrificed everything to help others avoid the fate my mother and many like her have faced. Long hours, doubt, financial burdens and more stress than a human being should have to endure... All in the name of helping others quit combustible tobacco and its death sentence. 48000 Canadians die each year from combustible tobacco. 1 in 2 of its users will suffer the same fate my mother has and that's why we are here today.

The sad reality is that our industry is in jeopardy right now. Its facing some of the most stringent regulations the world has ever seen. To compile a 0.50 cent per ml tax on top of a flavour ban is to completely burry the market. A juice bottle that normally cost 40\$ will now cost 100\$. Increasing its price by 150%. Something that is completely unheard of in any other market in the world. A pack of cigarettes is roughly 20\$ and last you a day. A 30ml bottle of e-liquid which will last the same amount of time, will now cost 30\$. With this model cigarettes now become more attractive and completely undermines the harm reduction values of vaping.

The projections on this new tax are 2.3 million dollars in revenue. I stand here today to tell you that if this structure of banning flavours and adding a per mL tax is allowed to go thru, there will be no tax revenue coming from it because the entire market will be wiped out completely. I ask you, why would a current smoker even consider vaping if the product is more expensive and taste as bad, if not worse than cigarettes due to its bitter taste.

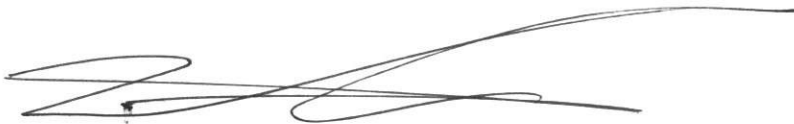
The flavours are what kept me off cigarettes much like so many adult vapers right this minute. Of all the vapers present in this room today less than 5% of them are vaping a tobacco flavour and even less are vaping flavourless. Roughly 4% of our sales come from tobacco and flavourless. The vast majority of vapours choose fruity flavour. In fact, the vast majority represents 56%. The rest choose creams, custards and bakery flavours. Taste is subjective and part of what makes Vaping such an effective tool for adults is the ability to find a flavour you like and stick with it. That's what makes vaping 3x more effective than any other NRT on the market. Banning flavours in this province will only help a massive flavoured e-liquid black-market flourish and if you've been following the news in the states you would know that the entire Evali scare was a product of Black Market THC Carts. This was confirmed by the CDC months ago. It seems counterproductive to set these stringent regulations to only create an entire un regulated black market that will work against your efforts.

Many moons ago we saw the United States apply a parental advisory sticker to all explicit CD's to hit the market. That sticker was like a billboard for teenagers saying listen to me!!! Those artists exploded in popularity. Their music became glorified. The same is true about vaping in its entirety. If we treat vaping as a taboo subject and keep pushing a narrative that its bad for you it will only increases its appeal. We should be enforcing the TVPA and being stricter on offenders. Vaping should be marketed like it is in the UK who push fact-based science on its population and educates their teens about its harm reduction value to smokers. We should be constantly repeating. If you don't smoke don't vape. If you don't vape don't start.

I agree that youth uptake should be addressed and there needs to be clear regulations on that subject. All I ask is that we are consulted so that we can help you solve the problem. If we had agricultural problems, we would talk to farmers wouldn't we. Let us help you create balanced regulations that keep our products out of the hands of youth and allows adults smokers to have access to a harm reduction product that is 95% safer than combustible tobacco according to the Royal College of Physicians and Public Health England. Let's keep the small business owners operational and squash youth vaping.

To summarise, if this is allowed to go thru many businesses will shut down in NS and it's a crying shame to think of, due to the sheer passion this industry was founded on. Current vapers and current smokers will be left with no option other than returning or continuing to use combustible tobacco because of its high price and lack of palatable taste. Nova Scotians will be forced to choose a product that is a death sentence. Lastly, with this structure a massive flavoured e-liquid black market will grow exponentially creating untested products. I implore you to do the right thing and please take the time to read the documents that I have provided. In them you will find our manufacturing processes, E-Liquid test results, a study on flavour variability by Dr, Farsalinos and a study on Harm Minimization and Tobacco Control by Dr. Abrams.

I thank you for your time and look forward to possibly working with you in order to resolve the issues.

A handwritten signature in black ink, appearing to read 'Charles Byram', with a long horizontal flourish extending to the right.

Charles Byram
CEO & Founder
FOV Labs Inc.
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Fogged Out Vapes

144 Edinburgh Dr., Door 12, Moncton, NB E1E 2K7

e-Liquid Samples

Summary Report
(FV06-26-18)



Dvine Laboratories, Inc

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I certify that to the best of my knowledge all analytical data presented in this report:

- Has been reviewed for completeness and accuracy
- Is legible and free of errors
- Has been conducted in conformity with approved agreement

Prepared in PDF format by Dvine Laboratories



Signature

Review Performed by:

Rachel Longwell

Report issued:

June 26, 2018

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Summary of Results

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Test Results

Report For: Fogged Out Vapes
Job #: FV06-26-18
Sample Type: E-Liquid

Project Start Date: See original reports
Analysis Methods: GC/FID
Method Deviations: None

Dvine Code	Client Code	Diacetyl (ug/mL)	2,3 Pentanedione (ug/mL)	Original Report ID
1220-001	Bliss	ND	ND	FV12-20-17
1220-001	Blue Rancher	ND	ND	FV12-20-17
1220-001	Cookie Monster	ND	ND	FV12-20-17
1220-001	Desserted	ND	ND	FV12-20-17
1220-001	Fundy Fog	ND	ND	FV12-20-17
1220-001	Grapple	ND	ND	FV12-20-17
1220-001	Green Rancher	ND	ND	FV12-20-17
1220-001	Jacked Up	ND	ND	FV12-20-17
1220-001	Lady B's Lemonade	ND	ND	FV12-20-17
041218-002	Lust	ND	ND	FV04-12-18
1220-001	Mrs. Perry Roll	ND	ND	FV12-20-17
1220-001	Salty Sea Dog	ND	ND	FV12-20-17
041218-004	Serenity	ND	ND	FV04-12-18
1220-001	Sinful	ND	ND	FV12-20-17
062118-001	'Stachio	ND	ND	FV06-21-18
1220-001	Winters Passion	ND	ND	FV12-20-17
1220-001	WTF!?	ND	ND	FV12-20-17

These results only apply to the samples tested

Notes: NA - Non-Applicable, ND - Non-Detected

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Narrative Summary

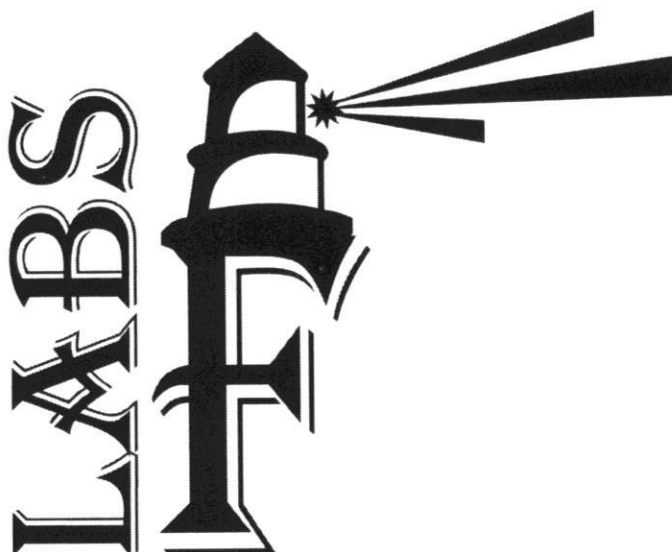
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Dvine Laboratories Narrative Summary

Client	Fogged Out Vapes
Analyst(s)	RL
Parameters	GC/FID Analysis
Job #	FV06-26-18
# Samples	17
Analysis	<p>The samples were analyzed for diacetyl and 2,3-pentanedione (aka acetyl propionyl) following the following procedures:</p> <ul style="list-style-type: none">- WI-004 preparation of E-Liquids for GC/FID Analysis- WI-007 Test Sampling Plan, Procedure, and Handling- WI-019 Method for Detection of Diketones in E-Liquid
Reporting Notes	<p>This report is a summary of the total reports created for Fogged Out Vapes. Original Reports are available upon request.</p> <p>The results presented in this report are representative of the samples and/or sample recipes as provided to the laboratory.</p>

This Is the Last Page of Report FV06-26-18
by Dvine Laboratories

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Receiving Inspection #370

Generated by Charles Byram on March 4th,
2020 8:00 pm UTC

Status

Closed

Requested Arrival Date

February 27th, 2020

Actual Arrival Date

February 27th, 2020

Supplier

The Flavor
Apprentice

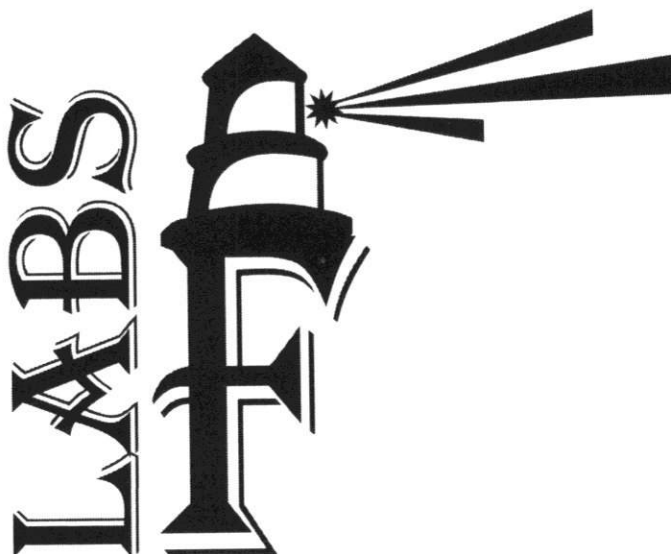
PO #

Lot Serial #

Notes

There were no notes for this receiving inspection.

<u>Part</u>	<u>Serial #</u>	<u>Juice Inspection Criteria</u>	<u>Qty Accepted</u>	<u>Qty Rejected</u>
TFA- Jack Fruit	56977	Receiving Inspection - Flavour Concentrates 0	3785.00000000 ml	0.00000000 ml
TFA- Dragon Fruit	A55554	Receiving Inspection - Flavour Concentrates 0	3785.00000000 ml	0.00000000 ml
TFA- Strawberry Ripe	B56225	Receiving Inspection - Flavour Concentrates 0	3785.00000000 ml	0.00000000 ml
TFA- Sour 20%	A55593	Receiving Inspection - Flavour Concentrates 0	3785.00000000 ml	0.00000000 ml
TFA- Watermelon	A55754	Receiving Inspection - Flavour Concentrates 0	3785.00000000 ml	0.00000000 ml



Inspection #11415

Generated by Charles Byram on March 4th, 2020 8:32 pm

UTC

Acceptance Threshold

100%

Part

Jacked Up 3mg

Status

Passed

Lot Serial #

0228201ANC

Quantity Accepted

19200.00000000 ml

Defect Summary

There were no defects logged for this inspection.

Batch Records

Jacked Up 3mg	0228201ANC	
Jacked Stone	022720ST2	3840 ml
Nicotine	011020-PG100	576 ml
PG	71128	960 ml
VG	G180318-1W	13824 ml

Notes

There were no notes for this inspection.

Sample #1 - 0228201ANC

Passed

Inspected by

CB

Inspected on

February 28th, 2020

8:27 am

Results

<u>Characteristic</u>	<u>Operation</u>	<u>Criteria</u>	<u>Value</u>	<u>Signatures</u>	<u>Method / Equipment</u>
Label Quality	Straight, Art, Mg Strength	(Pass/Fail)	Passed		
Product Characteristics	Smell, Look, Debris	(Pass/Fail)	Passed		
Retain Sample Kept	Retain Sample	(Pass/Fail)	Passed		
Cross Referencing	Scale Reading to Recipe	(Pass/Fail)	Passed		
Batch # Assigned	Label Applied to Container	(Pass/Fail)	Passed		
Inspection Label	Applied to Container	(Pass/Fail)	Passed		
Storage	In proper Location	(Pass/Fail)	Passed		



Inspection #11607

Generated by Charles Byram on March 4th, 2020 8:28 pm
UTC

Acceptance Threshold

100%

Part

OHW 30mL 10mg Salts

Status

Passed

Lot Serial #

0127201FZS

Quantity Accepted

6.00000000 units

Defect Summary

There were no defects logged for this inspection.

Batch Records

#FS-OHW030-10 - OHW 30mL 10mg Salts - 0127201FZS

White Label#50-10mg Salts

0127201FZS

180 ml

#BTL-CHBB-BK-030 - Chubby 30 Black CA

6 units

Notes

There were no notes for this inspection.

Sample #1 - 0127201FZS

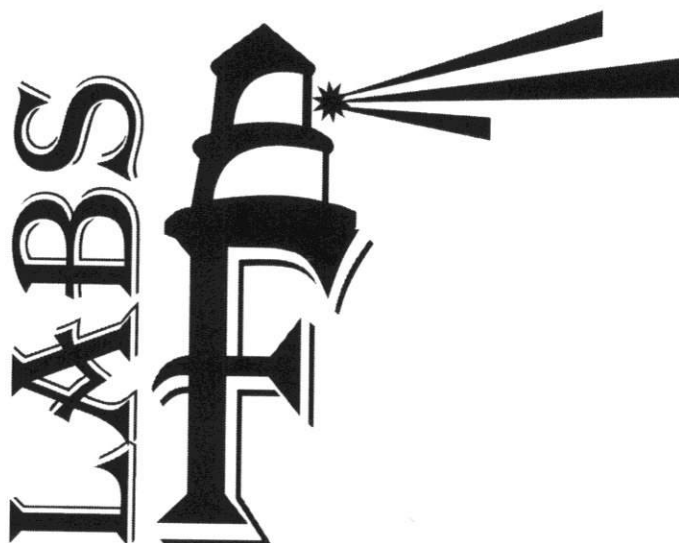
Passed

Inspected by
MThibodeau

Inspected on
March 4th, 2020
10:58 am

Results

<u>Characteristic</u>	<u>Operation</u>	<u>Criteria</u>	<u>Value</u>	<u>Signatures</u>	<u>Method / Equipment</u>
Inner Cap	Clean, Seated, Cracks	(Pass/Fail)	Passed		
Bottle	Clean, Leaks, Tightened	(Pass/Fail)	Passed		
Outer Cap	Clean, Seated, Tightened	(Pass/Fail)	Passed		
Leaks	***BOTTOM***, Cap	(Pass/Fail)	Passed		
Labels	Straight, Centred, Art, Mg Strength	(Pass/Fail)	Passed		
Amount	Filled to Correct Amount	(Pass/Fail)	Passed		



Shipment #FL5663

Generated by Charles Byram on March 4th, 2020 8:08 pm
UTC

Status

Closed

Requested Ship Date

March 4th, 2020

Actual Ship Date

March 6th, 2020

Customer

Tyler Homans

PO #

FL5663

Notes

There were no notes for this shipment.

<u>Part</u>	<u>Serial #</u>	<u>Juice Inspection</u> <u>Criteria</u>	<u>Qty</u>
asylum 30ml 48mg salts	0219201SKS	Bottling QA 2	2.00000000 units
sanitarium 30ml 48mg salts	0210201SKS	Bottling QA 2	1.00000000 units
straight jacket 30ml 50mg salts	0211202SKS	Bottling QA 2	1.00000000 units
Unhinged 30ml 48mg salts	1113195SKS	Bottling QA 2	1.00000000 units

Article

Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey

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Received: 19 November 2013; in revised form: 11 December 2013 / Accepted: 12 December 2013 /
Published: 17 December 2013

Abstract: *Background:* A major characteristic of the electronic cigarette (EC) market is the availability of a large number of different flavours. This has been criticised by the public health authorities, some of whom believe that diverse flavours will attract young users and that ECs are a gateway to smoking. At the same time, several reports in the news media mention that the main purpose of flavour marketing is to attract youngsters. The importance of flavourings and their patterns of use by EC consumers have not been adequately evaluated, therefore, the purpose of this survey was to examine and understand the impact of flavourings in the EC experience of dedicated users. *Methods:* A questionnaire was prepared and uploaded in an online survey tool. EC users were asked to participate irrespective of their current smoking status. Participants were divided according to their smoking status at the time of participation in two subgroups: former smokers and current smokers. *Results:* In total, 4,618 participants were included in the analysis, with 4,515 reporting current smoking status. The vast majority (91.1%) were former smokers, while current smokers had reduced smoking consumption from 20 to 4 cigarettes per day. Both subgroups had a median smoking history of 22 years and had been using ECs for 12 months. On average they were using three different types of liquid flavours on a regular basis, with former smokers switching between flavours more

frequently compared to current smokers; 69.2% of the former subgroup reported doing so on a daily basis or within the day. Fruit flavours were more popular at the time of participation, while tobacco flavours were more popular at initiation of EC use. On a scale from 1 (not at all important) to 5 (extremely important) participants answered that variability of flavours was “very important” (score = 4) in their effort to reduce or quit smoking. The majority reported that restricting variability will make ECs less enjoyable and more boring, while 48.5% mentioned that it would increase craving for cigarettes and 39.7% said that it would have been less likely for them to reduce or quit smoking. The number of flavours used was independently associated with smoking cessation. *Conclusions:* The results of this survey of dedicated users indicate that flavours are marketed in order to satisfy vapers’ demand. They appear to contribute to both perceived pleasure and the effort to reduce cigarette consumption or quit smoking. Due to the fact that adoption of ECs by youngsters is currently minimal, it seems that implementing regulatory restrictions to flavours could cause harm to current vapers while no public health benefits would be observed in youngsters. Therefore, flavours variability should be maintained; any potential future risk for youngsters being attracted to ECs can be sufficiently minimized by strictly prohibiting EC sales in this population group.

Keywords: electronic cigarette; flavours; smoking; tobacco; nicotine; smoking cessation; public health

1. Introduction

Cigarette smoking is considered the single most preventable cause of disease, affecting several systems in the human body and causing premature death [1]. The World Health Organisation predicts more than 1 billion deaths within the 21st century related to tobacco cigarettes [2]. Although there is overwhelming evidence for the benefits of smoking cessation [3], it is a very difficult addiction to break. Currently available nicotine replacement therapy have low long-term success rate, which may be attributed solely to psychological support [4], while oral medications are more effective [5] but are hindered by reports of adverse neuropsychiatric effects [6]. In this context, the tobacco harm reduction strategy has been developed, with a goal of providing nicotine through alternative methods in order to reduce the amount of harmful substances obtained by the user [7].

Electronic cigarettes (ECs) have been marketed in recent years as alternative to smoking products. They consist mainly of a battery and an atomiser where liquid is stored and gets evaporated by energy supplied to an electrical resistance. The liquid contains mainly propylene glycol and glycerol, with the option to include nicotine. A major characteristic of the EC liquid market is the availability of a variety of flavourings. Besides tobacco-like flavours, the consumer can choose flavours consisting of fruits, sweets, drinks and beverages and many more. The availability of so many flavours has been criticized by authorities such as the Food and Drug Administration (FDA), stating that there is a potential to attract youngsters [8]. Such a concern was probably raised by the experience with tobacco products, with studies showing that flavoured cigarettes were more appealing to young users [9]. A recent survey

of electronic cigarette users found that almost half of participants were using non-tobacco flavours [10]. However, no survey was specifically designed to detect the impact of flavourings on EC experience by users. Therefore, the purpose of this survey was to evaluate the patterns of flavourings use and determine their popularity in a sample of dedicated adult EC users.

2. Methods

A questionnaire was prepared by the research team in two languages (English and Greek) and was uploaded in an online survey tool (www.surveymonkey.com). A brief presentation of the survey was uploaded in the website of a non-profit EC advocates group (www.ecigarette-research.com) together with informed consents in English and Greek. If the participant agreed with the informed consent, he was redirected to the questionnaire in the respective language by pressing the “I agree” button. The survey was available online for 15 days. The protocol was approved by the ethics committee of our institution.

EC users of any age, irrespective of current or previous smoking status, were asked to participate to the survey. The survey was communicated in internet social media and several EC users’ forums and advocate groups worldwide. The IP address of the participants was recorded in order to remove double entries. There was an option for participants to report their email address for participation in future projects; unwillingness to report the email address was not a criterion for exclusion from the survey. Information about age, gender, country of residence and education level was requested. Past and present smoking status was asked and, based on the latter, participants were divided into two groups for the analysis: former smokers who had completely quit smoking and smokers who were still smoking after initiation of EC use. The questionnaire included questions about the type of flavours used regularly by the participants, whether the variety of flavourings was important in reducing or completely substituting smoking and defining the reasons for using multiple flavours. To assess difficulty in finding flavours of their preference at EC use initiation, the following question was asked: “Was it difficult to find the flavourings of your preference at initiation of EC use?”. The answers were scored as: 1, “not at all difficult”; 2, “slightly difficult”; 3, “difficult”; 4, “very difficult”; and 5, “extremely difficult”. To examine the importance of flavours variability in reducing or quitting smoking, the following question was asked: “Was the variability of flavourings important in your effort to reduce or completely substitute smoking?”. The answer was scored as: 1, “not at all important”; 2, “slightly important”; 3, “important”; 4, “very important”; and 5, “extremely important”.

3. Statistical Analysis

Participants were categorised into current smokers and former-smokers according to their reported status at the time of participation to the survey. Results are reported for the whole sample and for each of the subgroups. The sample size varied by variable because of missing data. In some questions, responders were allowed to choose more than one option; in these cases, each answer is presented separately and the sum of responses may exceed 100%. Kolmogorov-Smirnoff tests were performed to assess normality of distribution of variables. Continuous variables are reported as median (interquartile range [IQR]). Categorical variables are reported as number (percentage). Mann Whitney U test was used to compare continuous variables between current and former smokers, while cross tabulations with χ^2 test were used for categorical variables. Finally, a stepwise binary logistic regression analysis

was performed, with smoking status (former vs. current smoker) as the independent variable and age, gender, education level, smoking duration, number of flavourings used regularly, and EC consumption (ml liquid or number of prefilled cartomisers) as covariates. A two-tailed P value of <0.05 was considered statistically significant, and all analyses were performed with commercially available statistical software (SPSS v. 18, Chicago, IL, USA).

4. Results

4.1. Baseline Characteristics

After excluding double entries, 4,618 participants were included to the analysis, with 4,515 reporting current smoking status (current vs. former smokers). The baseline characteristics of the study group and subgroups are displayed in Table 1. More than 90% were former smokers. The mean age was 40 years, with male predominance. No difference between former and current smokers was observed in age, while more males were former smokers. The vast majority were from America and Europe, with a small proportion residing in Asia and Australia. More than half of participants were educated to the level of university/college. Smoking duration was similar between subgroups. Interestingly, former smokers reported higher daily cigarette consumption before initiation of EC use, although the difference was not statistically significant. Current smokers reported a substantial reduction in cigarette consumption, from 20 to 4 cigarettes per day. The median duration of EC use was 12 months, with higher consumption (ml liquid or number of cartridges) reported by former smokers. Higher nicotine concentration liquids were used by current smokers ($P = 0.005$). In total, 140 participants (3.0%) reported using non-nicotine liquids, 2.8% of former and 1% of current smokers ($\chi^2 = 4.5$, $P = 0.033$); 21 users of non-nicotine liquids did not mention their current smoking status. Finally, more current smokers were using first (cigarette-like) and second generation (eGo-type) devices while more former smokers were using third generation devices (also called “Mods”, variable voltage or wattage devices).

4.2. Perceptions in Relation to Flavours

Responses to questions related to flavours are displayed in Table 2. At the time of participation, most commonly used flavours were fruits, followed by sweets and tobacco. Significant differences were observed between subgroups. Characteristically, more current smokers were using tobacco flavours compared to former smokers, while more of the latter were using fruit and sweet flavours. On a regular basis, participants reported using 3 (IQR: 2–4) different types of flavours. At initiation of EC use, most popular flavours were tobacco followed by fruit and sweet flavours. The median score for difficulty to find the flavours of their preference at EC initiation was 2 (IQR: 1–3), with no difference between subgroups. Most participants (68.3%) were switching between flavours on a daily basis or within the day, with former smokers switching more frequently. More than half of the study sample mentioned that they like the variety of flavours and that the taste gets blunt from long-term use of the same flavour. The average score for importance of flavours variability in reducing or quitting smoking was 4 (“very important”). Finally, the majority of participants stated that restricting variability of flavours would make the EC experience less enjoyable while almost half of them answered that it

would increase craving for tobacco cigarettes and would make reducing or completely substituting smoking less likely.

Table 1. Baseline characteristics of the study population and subgroups.

Characteristic	Total	Former Smokers	Current Smokers	Statistic	P
Participants, n (%)	4,618	4,117 (91.2)	398 (8.8)		
English translation	4,386 (95.0)	3,915 (95.1)	369 (92.7)		
Greek translation	232 (5.0)	202 (4.9)	29 (7.3)		
Region of residence, n (%)					
America	2,220 (48.5)	2,007 (48.7)	157 (39.4)		
Asia	76 (1.7)	58 (1.4)	16 (4.0)		
Australia	80 (1.7)	75 (1.8)	4 (1.0)		
Europe	2,197 (48.0)	1,939 (47.1)	217 (54.5)		
Education, n (%)					
High school or less	1,037 (22.7)	917 (22.3)	98 (24.6)		
Technical Education	1,099 (24.1)	993 (24.1)	86 (21.6)		
University/College	2,425 (53.2)	2,170 (52.7)	206 (51.8)		
Age (years)	40 (32–49)	40 (32–49)	40 (32–49)	U = 754,278	0.624
Gender (male)	3,229 (71.8)	2,922 (72.7)	246 (62.5)	$\chi^2 = 18.0$	<0.001
Smoking duration (years)	22 (15–30)	22 (15–30)	22 (14–30)	U = 816,534	0.924
Cigarette consumption before EC use (/d)	24 (20–30)	25 (20–30)	20 (19–30)	U = 768,398	0.189
Cigarettes consumption after EC use (/d)			4 (2–6)		
EC use duration (months)	12 (6–23)	12 (6–23)	12 (5–23)	U = 790,219	0.373
EC consumption (ml or cartridges/d)	4 (3–5)	4 (3–5)	3 (2–5)	U = 677,862	<0.001
Nicotine levels in EC (mg/ml)	12 (6–18)	12 (6–18)	12 (8–18)	U = 722,563	0.005
EC devices used, n (%)					
Cigarette-like	84 (1.8)	61 (1.5)	20 (5.0)	$\chi^2 = 25.9$	<0.001
eGo-type	1,123 (24.7)	966 (23.5)	133 (33.4)	$\chi^2 = 19.5$	<0.001
“Mods” ^a	3,348 (73.5)	3,047 (74.0)	237 (59.5)	$\chi^2 = 38.3$	<0.001

Notes: Values presented as median (interquartile range) or number (percentage). Abbreviations: EC, electronic cigarette. ^a New generation devices, usually hand-made or with the ability to manually set the voltage or wattage delivery.

Table 2. Patterns of flavourings use in the study population and subgroups.

Characteristic	Total	Former Smokers	Current Smokers	Statistic	P
Flavours used now, n (%) ^a					
Tobacco	1,984 (43.9)	1,773 (43.1)	211 (53.0)	$\chi^2 = 14.6$	<0.001
Mint/menthol	1,468 (31.8)	1,339 (32.5)	129 (32.4)	$\chi^2 = 0.0$	0.964
Sweet	2,836 (61.4)	2,629 (63.9)	207 (52.0)	$\chi^2 = 21.8$	<0.001
Nuts	691 (15.0)	643 (15.6)	48 (12.1)	$\chi^2 = 3.5$	0.060
Fruits	3,203 (69.4)	2,953 (71.7)	250 (62.8)	$\chi^2 = 14.0$	<0.001
Drinks/beverages	1,699 (36.8)	1,562 (37.9)	137 (34.4)	$\chi^2 = 1.9$	0.167
Other	1,028 (22.3)	946 (23.0)	82 (20.6)	$\chi^2 = 1.2$	0.281

Table 2. Cont.

Flavours used at EC initiation, n (%) ^a					
Tobacco	3,118 (69.1)	2,846 (69.1)	272 (68.3)	$\chi^2 = 0.1$	0.746
Mint/menthol	1,086 (24.1)	1,004 (24.4)	82 (20.6)	$\chi^2 = 2.8$	0.092
Sweet	1,347 (29.8)	1,251 (30.4)	96 (24.1)	$\chi^2 = 6.8$	0.009
Nuts	203 (4.5)	186 (4.5)	17 (4.3)	$\chi^2 = 0.1$	0.821
Fruits	1,743 (38.6)	1,606 (39.0)	137 (34.4)	$\chi^2 = 3.2$	0.073
Drinks/beverages	808 (17.9)	748 (16.8)	60 (15.1)	$\chi^2 = 2.4$	0.124
Other	302 (6.7)	282 (6.8)	20 (5.0)	$\chi^2 = 1.9$	0.164
Switching between flavours, n (%)					
Daily/within the day	3,083 (68.3)	2,851 (69.2)	232 (58.3)	$\chi^2 = 20.1$	<0.001
Weekly	718 (15.9)	636 (15.4)	82 (20.6)	$\chi^2 = 7.2$	0.007
Less than weekly	465 (10.3)	412 (10.0)	53 (13.3)	$\chi^2 = 4.3$	0.038
At EC initiation, was it difficult to find the flavours of your preference? ^b	2 (1–3)	2 (1–3)	2 (1–3)	U = 760,068	0.054
Why do you feel the need to choose different flavours? n (%) ^a					
Like variety of choices	3,300 (73.1)	3,041 (73.9)	259 (65.1)	$\chi^2 = 14.3$	<0.001
They get “blunt” from long-term use	2,325 (51.5)	2,131 (51.8)	194 (48.7)	$\chi^2 = 1.3$	0.250
Other reasons	342 (7.6)	318 (7.7)	24 (6)	$\chi^2 = 1.5$	0.223
Was flavours variability important in reducing/quitting smoking? ^b	4 (3–5)	4 (3–5)	4 (3–5)	U = 731,547	0.455
How would your experience with EC change if flavours variability was limited? n (%) ^a					
Less enjoyable	3,111 (68.9)	2,886 (70.1)	225 (56.5)	$\chi^2 = 31.2$	<0.001
More boring	2,063 (45.7)	1,901 (46.2)	236 (40.7)	$\chi^2 = 4.4$	0.036
Increase craving for cigarettes	2,188 (48.5)	1,982 (48.1)	206 (51.8)	$\chi^2 = 1.9$	0.168
Less likely to reduce or quit smoking	1,793 (39.7)	1,617 (39.3)	176 (44.2)	$\chi^2 = 3.7$	0.054
No difference	285 (6.3)	253 (6.1)	32 (8.0)	$\chi^2 = 2.2$	0.138

Notes: Values presented as median (interquartile range) or number (percentage). Abbreviations: EC, electronic cigarette. ^a Participants were allowed to choose more than one answers. ^b Score reported (see text for details).

Binary logistic regression analysis showed that male gender ($B = 0.373$, $P = 0.001$), EC consumption ($B = 0.046$, $P = 0.044$) and number of flavours regularly used ($B = 0.089$, $P = 0.038$) were associated with complete smoking abstinence in this population of dedicated long-term vapers, while age, education level and smoking duration were not associated with smoking abstinence.

5. Discussion

This is the first survey that specifically focused on the issue of flavours and their impact in EC use. A substantial number of dedicated EC consumers participated; they reported that flavours play an important role in their EC use experience and in reducing cigarette consumption and craving, while the number of flavours regularly used was independently associated with complete smoking abstinence in this population.

The availability of a variety of flavours has been a controversial issue since the initial appearance of ECs to the market. Most companies offer a variety of flavours, from those resembling tobacco to a large

number commonly used in the food industry. Public health authorities have raised concerns about this issue, and several statements have been released suggesting flavours could attract youngsters [8,11,12]. Such concerns are probably rooted back to the marketing of the tobacco industry for flavoured tobacco cigarettes. Internal industry documents and published surveys indicated that flavoured tobacco products are more appealing to youngsters and may be a gateway to maintaining smoking as a long term habit, while use by adults was quite low [13–16]. This is the main reason why the FDA decided to implement a ban on characteristic flavours in tobacco cigarettes [17]. It was expected that such concerns would be raised for ECs, although current vapers are overwhelmingly adults. Anecdotal evidence from EC consumers' internet forums and results from surveys [10] have shown that different flavours are very popular among dedicated users. The results of this survey confirm previous observations by finding that dedicated users switch between flavours frequently and the variability of flavours plays an important role both in reducing cigarette craving and in perceived pleasure. Moreover, the number of flavours used was associated with smoking cessation. Therefore, flavours variability is needed to support the demand by current vapers, who are in their vast majority adults. This survey also indicated that there is a switch in flavours preference of EC consumers; tobacco is the preferred flavour when initiating EC use, probably because smokers are used to this flavour and feel the need to use something that resembles their experience from smoking. However, different choices are made as time of use progresses. This may be a way to distract them from the tobacco flavour in order to reduce smoking craving; alternatively, it could indicate that they just don't need the tobacco flavour any more, but feel the desire to experiment with new flavours. In some cases, tobacco flavour may even become unpleasant, especially in those who have completely quit smoking. The improvement in olfactory and gustatory senses in these people can lead to both more pleasure perceived from different flavours and an aversion to tobacco flavour (in a similar way that it is unpleasant for a non-smoker); the latter has been reported in EC consumers' forums (<http://www.e-cigarette-forum.com/forum/polls/209041-do-you-vape-tobacco-flavors.html>). Such a phenomenon may contribute to lower relapse to smoking and may prevent the EC from being a gateway to smoking; however, this should be specifically studied before making any conclusions. Finally, the issue of taste buds "tolerance", which is anecdotally mentioned by vapers, was reported by almost half of the sample as a reason to switch between flavours, although it is most probably a type of olfactory rather than gustatory tolerance.

Besides information on the use of flavourings, this survey provides information on other issues related to EC use. A small minority of participants were using first generation cigarette-like devices. This has been observed in other surveys [10]. There was a higher prevalence of third-generation devices used in the subgroup of former smokers compared to current smokers. Such devices have the ability to provide higher energy to the atomiser, thus producing more vapour and delivering more pleasure to the user [18,19]. Until now, two randomised studies evaluating the efficacy of EC use in smoking cessation have used first-generation cigarette-like devices [20,21]. It is possible that newer generation devices may be more effective in substituting smoking, and this should be evaluated in future studies. Additionally, former smokers were using lower nicotine-concentration liquids compared to current smokers. It has been observed from previous studies that EC users who have completely substituted smoking try to gradually reduce their nicotine use [18]. Despite that, only 2.8% of former smokers were using 0-nicotine liquids at the time of survey participation, indicating that nicotine is

important in smoking abstinence and that EC consumers remain long-term nicotine users. However, the possibility that several vapers may quit EC use shortly after switching to non-nicotine liquids cannot be excluded; such users would not participate to this survey, therefore overestimating the significance of nicotine on EC use. Finally, we observed a male predominance in participation to this survey, which is in line with previous studies [10,18]. In this survey, males were more likely to have completely quit smoking. Further studies are needed to explore this phenomenon and define whether females are less successful in smoking cessation with EC use, are less motivated long-term users or use ECs in the short term as smoking substitutes.

There are some limitations applicable to this study. The survey was announced and promoted in popular EC websites. Therefore, it is expected that dedicated users with positive experience with ECs would mainly participate, and the high proportion of former smokers confirms this. However, it is important to evaluate the patterns of use in smokers who have successfully quit smoking, since this can provide health officials with information on how to educate smokers into using ECs, especially during the initial period of use. Although a significant proportion stated that flavours play a major role in reducing or quitting smoking, this study was not designed to evaluate whether variability of flavours may promote smoking cessation in the general population; moreover our sample is not representative of the general population of smokers, who are generally less educated compared to the population evaluated here [22]. This should be evaluated in a randomised study. Finally, although the fact that flavours are important for existing EC users provides sufficient explanation for their current marketing, it does not exclude the possibility that they may also attract youngsters. However, currently available evidence indicates that regular use of ECs by non-smoking adults or youngsters is very limited [23–25]; thus, any restriction of flavours for the reason of protecting youngsters is currently not substantiated by evidence and no public health benefit would be derived. On the contrary, such a measure could have a negative impact and cause harm in current vapers, who are reporting that they enjoy flavours and that restrictions would make smoking reduction or cessation more difficult and would increase cigarette craving. Therefore, it would be more realistic and valuable to promote restrictions to the use of ECs by youngsters and to properly inform the public that ECs should be used only by smokers as a method to reduce cigarette consumption or completely substitute smoking.

6. Conclusions

The results of this survey indicate that EC liquid flavourings play a major role in the overall experience of dedicated users and support the hypothesis that they are important contributors in reducing or eliminating smoking consumption. This should be considered by the health authorities; based on the current minimal adoption of ECs by youngsters, it is reasonable to support that any proposed regulation should ensure that flavourings are available to EC consumers while at the same time restrictions to the use by youngsters (especially non-smokers) should be imposed in order to avoid future penetration of EC use to this population.

Acknowledgements

We would like to thank E-Cigarette Research Advocates Group for promoting the survey in their website (www.ecigarette-research.com). This is a non-profit group of electronic cigarette users with no

relation to the electronic cigarette or other industry. The website does not promote or present any electronic cigarette product and do not accept any advertisements. The sole purpose of the group is to inform about research conducted on electronic cigarettes. Konstantinos E. Farsalinos has been allowed to present studies and post comments concerning electronic cigarette research on this website, without providing or receiving any form of payment. We would also like to thank all other websites and internet forums for promoting the survey and encouraging electronic cigarette users to participate. None of the websites promoting the survey had any access to the data collected from participants. No funding was received for this study.

Conflicts of Interest

The authors declare no conflict of interest.

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Annual Review of Public Health

Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives

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Annu. Rev. Public Health 2018. 39:193–213

First published as a Review in Advance on January 11, 2018

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

<https://doi.org/10.1146/annurev-publhealth-040617-013849>

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Keywords

harm minimization, nicotine, e-cigarettes, smoking, tobacco

Abstract

Inhalation of the toxic smoke produced by combusting tobacco products, primarily cigarettes, is the overwhelming cause of tobacco-related disease and death in the United States and globally. A diverse class of alternative nicotine delivery systems (ANDS) has recently been developed that do not combust tobacco and are substantially less harmful than cigarettes. ANDS have the potential to disrupt the 120-year dominance of the cigarette and challenge the field on how the tobacco pandemic could be reversed if nicotine is decoupled from lethal inhaled smoke. ANDS may provide a means to compete with, and even replace, combusted cigarette use, saving more lives more rapidly than previously possible. On the basis of the scientific evidence on ANDS, we explore benefits and harms to public health to guide practice, policy, and regulation. A reframing of societal nicotine use through the lens of harm minimization is an extraordinary opportunity to enhance the impact of tobacco control efforts.

Smoking:

the inhalation of the smoke from any combustible tobacco product

Alternative nicotine delivery systems (ANDS):

noncombusted refined nicotine (e.g., e-cigarettes, heat-not-burn and other emerging products, as well as smokeless and NRT)

E-cigarettes:

also called vape pens, personal vaporizers, e-hookahs, e-pipes, and e-cigars, among other names, are battery-operated and produce an aerosol instead of smoke

Combusted/combustible tobacco:

products that burn tobacco resulting in inhalation of the resultant smoke (e.g., cigarettes, cigars, pipes, roll-your-own products, and hookah)

Harm minimization:

Reducing harm as much as possible with the ideal being zero harm

Noncombusted/

noncombustible tobacco: nonburning tobacco products (smokeless tobacco, snus)

1. INTRODUCTION

The fiftieth-anniversary US Surgeon General's Report, in 2014, concluded, "The burden of death and disease from tobacco use in the U.S. is overwhelmingly caused by cigarette and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden" (117, p. 7). Globally, smoking-caused annual deaths will rise to 8 million by 2030 if current trends continue (137, 139). It is imperative to find additional ways to accelerate the decline in smoking because, if nothing changes, a billion lives will be lost prematurely by 2100 (136). Despite declines over the last 50 years, ~520,000 Americans annually die prematurely from smoking-related causes (116, 117). The Surgeon General stated, "The current rate of progress in tobacco control is not fast enough. More needs to be done" (117, p. 875). The US Food and Drug Administration (FDA) Commissioner endorsed the need for striking an appropriate balance between regulation and encouragement of the development of innovative nicotine or noncombustible tobacco products that are less dangerous than cigarettes (119). It is past time to add new and even radical approaches (13, 132).

The term alternative nicotine delivery systems (ANDS) encompasses a diverse class of noncombustible smokeless tobacco products or nicotine-containing products, primarily exemplified by e-cigarettes that are vaped not smoked (**Figure 1**). ANDS raise fundamental questions for society: Could ANDS be leveraged to effectively compete with cigarettes, eventually making smoking obsolete sooner than would otherwise be possible (2, 29, 57)? Can many types of ANDS, when decoupled from deadly toxins in combusted tobacco smoke, be accepted by the public and by its health, regulatory, and advocacy bodies as an extraordinary opportunity to save lives rather than as a threat to the success of past tobacco control efforts? These questions are contentious, and their answers are complicated. Addressing opportunities for ANDS requires reexamination of the role that nicotine plays in sustaining smoking and the role that nicotine can play in reducing smoking when delivered in a safer, yet appealing manner (36, 77, 85). In a major shift in FDA policy following the FDA Commissioner's announcement (119), a new national comprehensive nicotine management strategy was proposed (44): "The agency's new tobacco strategy has two primary parts: reducing the addictiveness of combustible cigarettes while recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public health. . . .Reducing cigarettes' addictiveness could help users quit more easily and help keep those who are experimenting—young people, in particular—from becoming regular smokers. . . .The availability of potentially less harmful tobacco products could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it" (p. 1).

Reexamination of nicotine's role in society requires reconsidering the harm minimization perspective within tobacco control (13, 46) (see the sidebar titled Harm Reduction or Harm Minimization). The primary goal of harm minimization is to prevent the use of nicotine-containing products among nonusers, while pragmatically acknowledging that less harmful noncombusted nicotine products either with tobacco (e.g., snus) or without tobacco (e.g., e-cigarettes) can dramatically reduce risk compared with smoking combusted products (1, 2, 13, 46, 57). Harm minimization is wholly consistent with tobacco control goals to prevent any use by underage youth (1) and encourage complete smoking cessation in both youth and adults and is responsive to the Surgeon General's admonition that more must be done to eliminate smoking tobacco (117).

We suggest a science-based reframing of nicotine use to inform current and future US and global tobacco control strategies. We use e-cigarettes as exemplars of ANDS, but newer types of ANDS products (e.g., that heat and do not burn tobacco) (102, 113) and accumulating scientific evidence will require continued discussions about managing nicotine's changing role in society. At times, our use of the term ANDS may also encompass classes of substantially less harmful

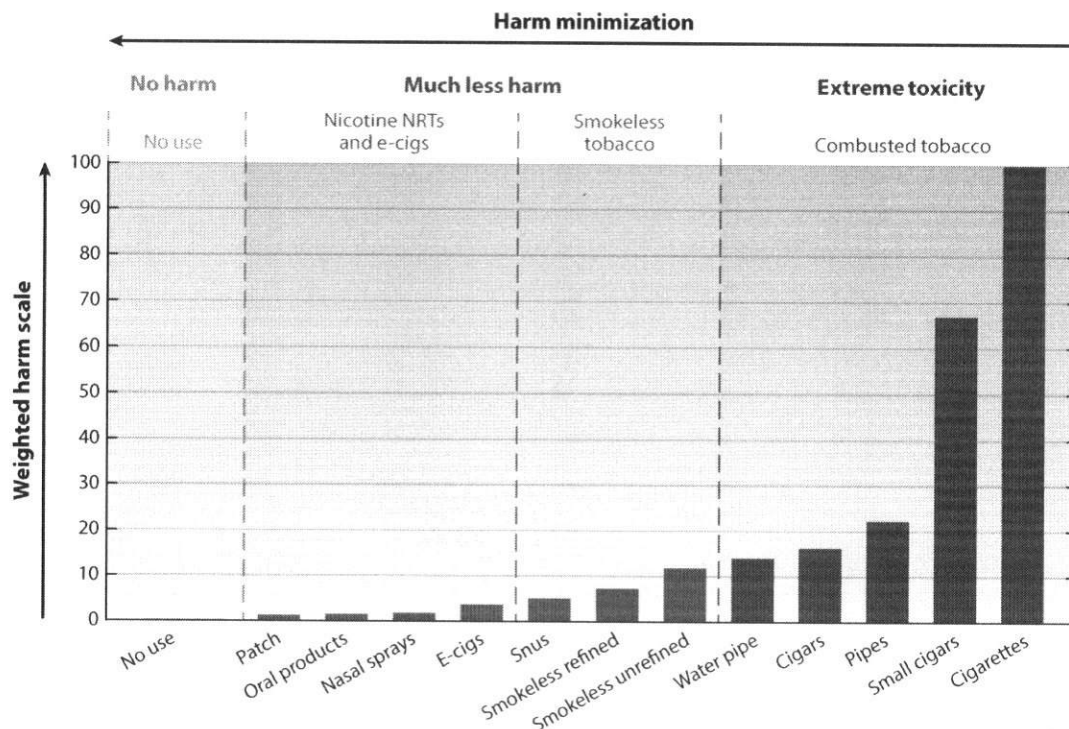


Figure 1

Products along the harm minimization continuum. Adapted with permission from Nutt et al. 2014 (89). The harm minimization continuum posits that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm (e.g., NRT) to exceptionally high harm (e.g., combusted tobacco such as cigarettes, cigars, hookah, pipe). The figure depicts four panels representing classes of products. Products containing tobacco are depicted as combusted or smoked (panel 1, *right*) and noncombusted or smokeless (panel 2, *right middle*). Smokeless products are far less harmful than smoked tobacco, but there is variation in the smokeless tobacco category; low nitrosamine Swedish-type snus is lower in relative harm than unrefined tobacco. Heat-not-burn tobacco products (e.g., heat sticks) would fall into this panel. Panel 3 (*left middle*) depicts the class of nicotine delivery products without any tobacco (e-cigs/e-vapor products and NRTs). Panel 4 (*left*) depicts no use and thus no exposure. Abbreviations: e-cigs/e-vapor, electronic cigarettes; NRTs, nicotine replacement therapies.

noncombustible modes of nicotine delivery [i.e., medicinal nicotine replacement therapy (NRT), low nitrosamine Swedish snus, any smokeless tobacco, e-cigarettes] (30, 36, 38, 58, 60, 65).

The changing landscape of innovative reduced-harm products calls for a refocusing of tobacco control strategies, concentrating specifically on smoking control (57). Some traditional strategies will continue to be effective, whereas others may become ineffective or possibly iatrogenic (57) if

NRT: nicotine replacement therapy

HARM REDUCTION OR HARM MINIMIZATION

The term harm reduction implies any reduction in relative harm from a prior level, even a small reduction such as reducing smoking by one or two cigarettes per day. Harm minimization strives to reduce harms to zero (i.e., ideally to no use and thus no harmful exposure). When a consumer does not want to stop all nicotine use, then harm minimization implies striving for the complete elimination of smoked tobacco exposure by substituting it with the use of less harmful noncombusted forms of nicotine instead of smoking.

TCA (or FSPTCA):
The Family Smoking
Prevention and
Tobacco Control Act

CDER: FDA Center
for Drug Evaluation
Research

CTP: FDA Center for
Tobacco Products

Vaping: the inhalation
of e-cigarette aerosol

they slow rather than speed the demise of smoking (2, 77). Herein, we integrate science and policy analysis to address the critical questions that underpin public health practice, policy, regulation, advocacy, and communication on nicotine-containing products (128).

2. REFRAMING TOBACCO CONTROL AND NICOTINE USE

Decades of tobacco control interventions (e.g., age purchasing restrictions, taxation, media campaigns, cessation services) have significantly decreased smoking prevalence in the United States (20, 35, 54). The 2009 Tobacco Control Act (TCA) (120) and the newly promulgated nicotine management strategy (44) complement tobacco control efforts by giving the FDA statutory authority to regulate tobacco and ANDS products. The TCA includes a public health standard that requires regulators to consider the net impact of tobacco products on the population as a whole, including smokers and nonsmokers (1, 2, 41, 117, 128). Adding to the FDA's prior role [via the Center for Drug Evaluation Research (CDER)] of approving medicinal products (e.g., NRT) for smoking cessation, the FDA established the Center for Tobacco Products (CTP) to regulate the manufacture, distribution, and marketing of tobacco and emerging nicotine products for consumer use (i.e., recreational rather than medicinal) (2, 13, 57, 130).

Whereas the CTP's authorities seek to protect the public from products that could harm public health, the CTP can also promote public health by supporting products (e.g., using product standards) and encouraging behaviors that maximize net population benefits by displacing smoking (2, 44, 119, 120, 128). Public education by the CTP can change behavior by informing smokers about the harms of different classes of refined nicotine products (**Figure 1**), compared with both smoking (relative risk) and no use (absolute risk) (2, 13, 57, 103).

Both the emergence of ANDS products and the TCA provide an opportunity to enrich tobacco control with a harm minimization framework (2, 13, 44, 57, 119). The following sections use e-cigarettes as the main case example of the individual health and the population health potential of selected harm minimization strategies.

2.1. Decoupling Nicotine from Inhaled Smoke for Harm Minimization

The logic of smoking harm minimization is simple and compelling. As Michael Russell, a pioneer in the field, put it, "People smoke for nicotine but they die from the tar" (105, p. 1431). In getting the nicotine they seek, smokers are exposed to enormous harm, including from cardiovascular disease, cancer, and pulmonary diseases, due to the inhalation of toxic smoke from tobacco combustion products (117). For most smokers, there is little evidence that nicotine itself causes any of these classes of disease when decoupled from smoke [see details in Niaura et al. (85)]. Although nicotine use poses some risk for vulnerable groups (e.g., with cardiovascular disease or during pregnancy), this risk is substantially lower than the risk posed by continuing to smoke cigarettes (10, 29, 30, 85). Nicotine itself does not appear to cause cancer, even in former smokers who use low nitrosamine snus for decades (10, 30, 58, 60, 64–66, 85). Evidence also indicates that nicotine itself is relatively safe when obtained from FDA-approved NRT (85), which is widely used for smoking cessation (36, 38). E-cigarettes deliver nicotine without any tobacco in aerosol form (known as vapor) (30, 57, 103). Smokers switching to vaping have experienced improved lung capacity and less frequent asthma events (96–98). At the doses that smokers experience, nicotine itself carries minimal harm (38, 85). Thus, if smokers could be shifted from smoking to consuming clean nicotine (i.e., without smoke), many lives would be saved (24, 30). The safest course is to stop smoking or, better, never to start. But a harm minimization approach recognizes that demanding absolute perfection is often counterproductive and that, when a harmful behavior cannot be eliminated, it is necessary

to reduce its adverse health consequences (46). For those who are smoking and are unwilling or unable to quit nicotine use, moving to cleaner ANDS, including e-cigarettes, NRTs, or low nitrosamine snus, would reduce harm relative to smoking.

2.2. ANDS and the Harm Continuum: How Harmful Are E-Cigarettes?

The harm minimization continuum (**Figure 1**) posits that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm (e.g., NRT) to exceptionally high harm (e.g., cigarettes, cigars, hookah) (41–43, 48, 61, 85, 90, 103). Smokeless tobacco is much lower on the risk continuum than combusted products but varies in risk within that class of products (e.g., low nitrosamine Swedish-type snus versus other smokeless tobacco with high nitrosamine levels) (30).

When nicotine is decoupled from the deadly toxins in inhaled smoke, it is substantially less harmful (10, 85, 103, 117). Most of the harm is due to the inhalation of combustion products [about 70 human carcinogens and other toxins in particulate matter (sometimes called “tars”) and carbon monoxide] (121). E-cigarette aerosol is very different. E-cigarettes do not contain any tobacco and do not produce carbon monoxide (103). The harm continuum (**Figure 1**) emphasizes a key point: It is not that e-cigarettes are completely safe, or even the safest nicotine-containing product available, but that they are much safer than smoking. NRTs are safe enough that CDER approved them for over-the-counter consumer use more than two decades ago. Long-term use of NRT has been endorsed as an acceptable strategy to reduce morbidity and mortality from smoking (23, 36, 122). CDER updated NRT labeling in 2013 to permit NRT use while smoking (also known as dual use) as part of the journey to cessation and permits sustained use for relapse prevention for a lifetime if need be (38).

Most reviews of toxicological, clinical, and epidemiological evidence indicate that the chemicals found in e-cigarettes, when used as intended, are far fewer and well below levels seen in cigarette smoke (10, 41, 42, 48, 85). According to the Royal College of Physicians in the United Kingdom, “[T]he available data suggest that they are unlikely to exceed 5% of those associated with combusted tobacco products” (103, p. 87). Studies in humans have also documented improved physiological outcomes, including reduced blood pressure, improved lung function, and lower disease symptoms, among smokers who switched to e-cigarettes (96, 97, 98). E-cigarettes are much less dependence-producing than are cigarettes (73, 109). Thus, the potential harm of e-cigarettes falls in the low range on the continuum. Harm levels do differ among e-cigarettes. Lab studies have documented some potentially toxic constituents in some devices, e-liquids, and flavors, especially when overheated to produce aldehydes (such as acrolein and formaldehyde) and an acrid “dry puff condition” unlikely to be tolerated by actual users (34). Nonetheless, prudent product standards can readily eliminate these unnecessary risks and ensure quality control over devices and liquids (2, 7, 30, 44, 119). In summary, the FDA’s Gottlieb & Zeller state: “Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease and heart disease that kill hundreds of thousands of Americans each year” (44, p. 1).

Dry puff: conditions when vaping with a high wattage, too much airflow, old coils, or no liquid; not normally used

2.3. Rethinking Nicotine: A Three-Dimensional Framework for Harm Minimization

Nicotine and tobacco products can fit into a three-dimensional conceptual space (**Figure 2**): (a) harmfulness, (b) appeal, and (c) satisfaction including dependence. **Figure 2** provides a road map with which to envision how to optimize ANDS product use to successfully compete with and

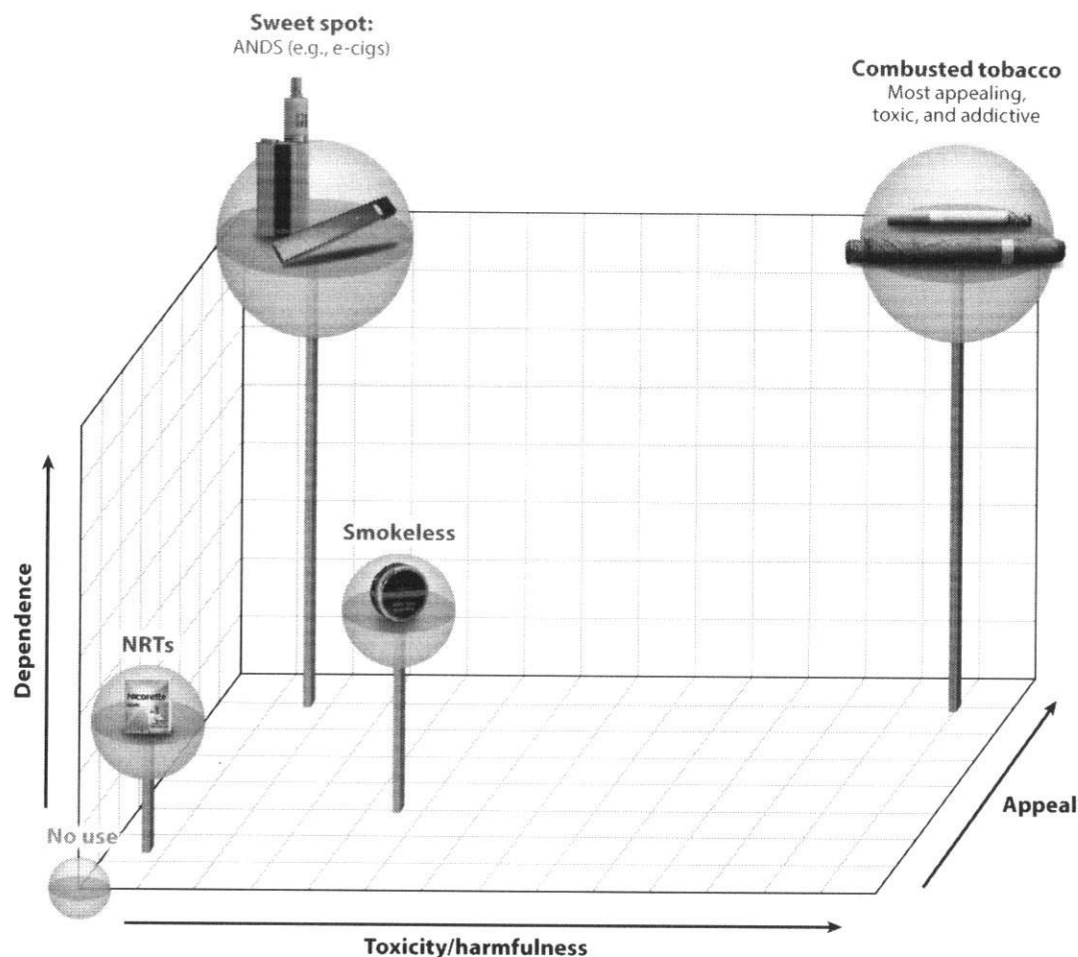


Figure 2

Multidimensional framework for nicotine-containing products. Nicotine and tobacco products can be depicted within a three-dimensional conceptual space: harmfulness (x -axis), appeal or popularity (z -axis), and satisfaction, which includes degree of dependence (y -axis). Appeal is a complex function of attractiveness, as well as cost, accessibility, and marketing practices, and appeal is related to satisfaction, including factors such as nicotine levels, taste, flavors, sensory characteristics, and dependence liability. This figure provides a roadmap with which to envision where a specific class of products can be placed. The top, back, right corner depicts the most popular (appealing), highly satisfying (dependence), and toxic space, whereas no use at all is zero on all three axes. Combusted products are, by far, the most appealing, satisfying, and toxic. The bottom, front, left space depicts products that have low toxicity but little appeal or satisfaction. NRTs are not used by many and are thus not appealing or satisfying and unlikely to displace cigarettes at a population level. Minimizing risk while making a net population health impact requires products to successfully compete with and replace smoking. Thus, the sweet spot, where ANDS products fall, is depicted by high appeal and satisfaction but low toxicity along with intermediate products such as Swedish-type snus, which has successfully displaced cigarettes in Sweden. Abbreviations: ANDS, alternative nicotine delivery systems; e-cigs/e-vapor, electronic cigarettes; NRTs, nicotine replacement therapies.

replace smoking, minimizing risk and making both an individual and a net population beneficial health impact.

As already depicted in **Figure 1** and described in Section 2.1, the toxicity of ANDS (e-cigarettes, smokeless nicotine, and NRTs) differs substantially from that of smoking (**Figure 2**, x -axis). The appeal or popularity of various types of ANDS also differs as does their degree of satisfaction

and thus their ability to displace smoking (**Figure 2**, *z*-axis), which contributes to the likelihood that ANDS will be adopted and its use sustained at a scale large enough to affect population-level outcomes (24). Appeal is a complex function of attractiveness, sensory characteristics, and subjective satisfaction (including nicotine level, taste, and flavors) as well as consumer beliefs about relative harm, cost, accessibility, and marketing practices (2, 30, 32, 33, 57, 106). A product with minimal satisfaction will not be appealing and is unlikely to be adopted or used extensively, which has proven to be the case with over-the-counter NRT (45, 134). Ideally, less harmful products must be sufficiently appealing. The ANDS product must also be believed to be much less harmful than smoking to encourage switching from the high- to the low-harm products.

Dependence (**Figure 2**, *y*-axis) refers to the potential for the product to provide satisfaction and, relatedly, its potential to induce addiction, which is a function of both its pharmacological and its subjective rewarding and sensory properties. Dependence can also reflect a response to negative consequences of stopping smoking (withdrawal) and to wanting the positive and desirable effects that nicotine can have for some users (e.g., the satisfaction related to improved alertness, attention, concentration, memory, or mood) (49, 86, 110). Some degree of satisfaction, benefit from, and even dependence on much less harmful ANDS may have to be acceptable to society (i.e., recreational use of clean nicotine similar to the societal acceptance of adult alcohol use and marijuana use, rather than prohibition of all forms of nicotine primarily because of its addiction liability) as a means of speeding the demise of smoking and its attendant massive harms (2, 57). The limited evidence available suggests relatively little harm in secondhand vapor, as compared with secondhand smoke (41). Society will need to develop separate policies for secondhand vapor as was done in the United Kingdom (103).

Cigarettes and combusted tobacco products are the most appealing, most addictive, and most toxic of all nicotine delivery products and thus have dominated use for more than a century (12, 100). They are the perfect storm, occupying the space at the highest level on all three dimensions (highest on all axes in **Figure 2**).

The question arises: Where do ANDS fit? The dimensional space depicted in **Figure 2** can be helpful in locating what may be the sweet spot of an ideal e-cigarette or a future innovation of an ANDS. This sweet spot is depicted by both ANDS and by the success of snus in displacing cigarettes in Sweden (64–66). Appealing flavors, efficient nicotine delivery, and lower cost compared with cigarettes all play an important role in improving the overall appeal of less harmful ANDS on a large-scale basis (32, 33). Smokers who have completely switched to e-cigarettes report that flavors other than tobacco helped them to sustain exclusive e-cigarette use (33, 104).

NRT products, while minimally harmful and dependence inducing, lack widespread appeal among smokers. NRT has demonstrated a weak ability to displace cigarettes, despite its evidence-based CDER approval as a cessation therapy and its strong support in tobacco control policy for more than 20 years (112). In contrast with NRT, some new innovations in e-cigarettes do begin to occupy the sweet spot in this three-dimensional space because some smokers have found an e-cigarette with sufficient appeal for them to sustain use and quit smoking (11, 15, 32, 33, 41, 51, 75). As evidence of their appeal, e-cigarettes are used by smokers more often than NRT in quit attempts in both the United States and the United Kingdom (19, 103).

The three-dimensional space provides a road map to help inform a harm minimization framework and to guide research, policy, and practice. Different products can be ordered in this space and be compared with one another. Classes of nicotine-containing products (e.g., combustible versus noncombustible; high versus low nitrosamine; fast versus slow nicotine delivery; flavored versus nonflavored) can be evaluated for comparative safety, appeal, and impact on smoking prevalence. One challenge is to identify products that move the largest proportion of nicotine users to a place along these three dimensions that minimizes net harm and maximizes net benefits.

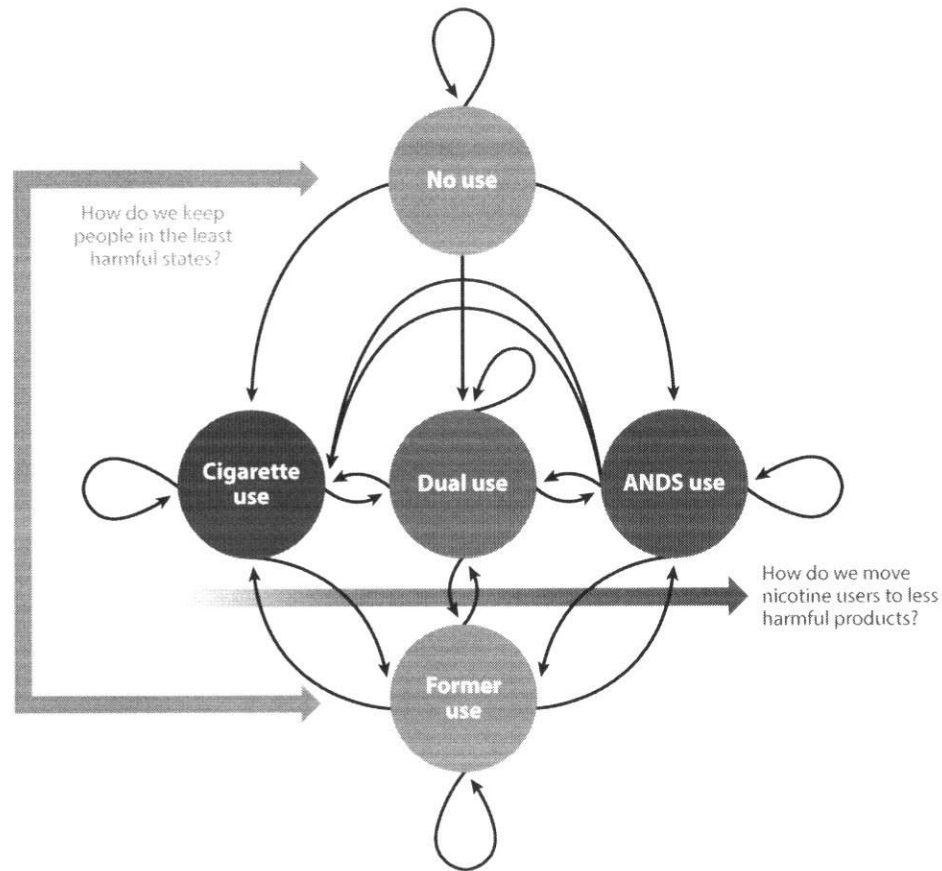


Figure 3

Markov state transition model of cigarette and e-cigarette use. This figure presents a state transition model using the example of cigarettes and ANDS to illustrate the possible states and pathways that must be considered to optimize a harm minimization strategy in tobacco control. Directed arrows represent transitions, whereas looped arrows at each state represent maintenance of that state. Youth prevention and smoking cessation strategies reinforce the states of noncurrent and former use depicted by green circles, and harm minimization strategies facilitate movement away from smoking to less harmful alternatives (*blue arrow*). Adapted with permission from Cobb et al. 2015 (23). Abbreviation: ANDS, alternative nicotine delivery systems.

Tobacco control strategy should be aligned so that less harmful ANDS are able to compete with, and ultimately completely replace, smoking for adults who want to use nicotine.

2.4. Systems Integration: Optimizing Population Benefits Over Harms

Population net exposure to harmful toxicants depends on the actual patterns and prevalence of product use, which vary along the continuum of harm (**Figures 1 and 2**). **Figure 3** presents a state transition model using the example of cigarettes and ANDS to illustrate the possible states and pathways that must be considered to optimize the benefits of a harm minimization strategy for smoking control (23, 57).

Individuals begin in the noncurrent use state (a variant of never use) and can either remain in that state or transition to current exclusive use of cigarettes or ANDS or to dual use. Once in a current use state, individuals can maintain use, transition to one of two alternative states, or cease use of both products. Former users may also maintain no use or relapse to current exclusive or dual

use. The CTP's public health standard implies an integrated consideration of product harms and benefits at the individual and population levels (including likelihoods of initiation and cessation). Population health could be improved by changes in nicotine-containing product use that result in transitions to less harmful use states (23). These changes include limiting movement from noncurrent use (i.e., preventing initiation of any nicotine product use by nonusers) and increasing movement away from cigarette use (perhaps via dual use) to exclusive use of less harmful ANDS and/or increased transition to former use and reduced relapse to smoking.

Each tobacco control strategy (e.g., taxes, media campaigns, treatment availability, accurate consumer knowledge of relative harms, regulations) will influence the flows from one state to another. Prevention of youth initiation and support for cessation will keep noncurrent and former users from starting or relapsing (depicted by green arrows and circles in **Figure 3**). Harm minimization strategies facilitate movement away from smoking (depicted by the blue arrow in **Figure 3**) by regulating and managing products according to their relative harms. Outcomes are determined empirically by estimating the prevalence rates within states and the transition rates between states based on population surveillance. Simulation modeling of the effects of policies and regulations on transition rates can indicate where harms might exceed benefits, given different scenarios of product use (70).

Three examples of these approaches could be (*a*) imposing a differential tax on nicotine-containing products that is proportional to their degree of harm, with less harmful products being minimally taxed and all combusted products being very highly taxed (22); (*b*) reducing the addiction liability of combusted tobacco via nicotine reduction while ensuring adequate and satisfying nicotine delivery in ANDS (9, 27); and (*c*) reducing the appeal of smoking by banning menthol and other flavors in smoked products (32, 33, 111, 124) but not in ANDS. Making combusted tobacco more expensive and less appealing while making ANDS more appealing, less harmful, and less costly are consistent with fully embracing harm minimization to speed users away from smoking as the primary end goal.

3. TWO MAJOR CHALLENGES TO ANDS AS A HARM MINIMIZATION STRATEGY

The concerns about a harm minimization strategy that relies on ANDS derive from two concerns about unintended harmful consequences and the fact that abstinence from all tobacco and nicotine products is safest. The concerns are that the availability of e-cigarettes or any other ANDS might lure some youth who would otherwise not smoke into smoking and that smokers who adopt e-cigarettes/ANDS, and who otherwise would have quit smoking altogether, might be led to continue smoking.

3.1. Do E-Cigarettes Attract Youth and Lead Them to Smoking and Lifelong Addiction?

Consistent with harm minimization, tobacco control should strive to prevent all youth initiation of nicotine, (e.g., prohibiting the sale of nicotine-containing products to those under legal purchase age, preventing predatory marketing to youth). This aspiration must be understood in the context of adolescent behavior. Risk-taking in adolescence is normative and results from competition between the strong socioemotional network in the brain and the immature cognitive-control network (108). Early risk-taking with any tobacco or nicotine product, such as an e-cigarette, may result from social or emotional rewards from trying a product, including peer approval or mood

Precautionary
principle: resisting a
new product with little
known effects

enhancement. Thus, eliminating all experimentation may not be a realistic goal, just as it has not been for cigarettes.

Existing studies show that current e-cigarette use by youth consists largely of experimentation, not long-term adoption (25, 127). As many as 70% of youth using e-cigarettes report only using flavors without nicotine (80). Poly-product use is common (25, 127). Findings are consistent with adolescent risk-taking (108) and shared vulnerabilities (25, 86, 123, 127). In the United States, whereas rates of past 30-day e-cigarette use in youth have risen between 2011 and 2014, these leveled off or dropped in 2015–2016 (25, 55, 81, 127, 133); contemporaneously, the prevalence of past 30-day cigarette smoking declined rapidly in youth to the lowest levels in history (41, 131). These patterns are consistent with data from the United Kingdom (8).

Longitudinal studies of youth never-cigarette users show that some ever-e-cigarette users try cigarettes during a follow-up period (6, 53, 67, 68, 79, 99, 107, 140–142), which raises some concern about so-called gateway effects (i.e., e-cigarette use leading directly to smoking) (63). But few studies examine the opposite transition: from cigarette use to e-cigarette use, a move toward less harm (blue arrow in **Figure 3**). Recent data show that 87% of past 30-day e-cigarette users have previously used a tobacco product, and 63% used a tobacco product in the past 30 days (127). Kozlowski & Warner (63) concluded that although society must be vigilant in tracking youth use trends, fears of harms (118) due to gateway effects seem to be exaggerated and are unlikely to undermine the much larger potential benefits of discouraging smoking behavior in the whole population.

Jurisdictions have adopted bans on e-cigarette sales to youth. Studies comparing the rates of youth cigarette use in US states with and without bans on sales to minors found that the prevalence of smoking was higher when youth access to e-cigarettes was restricted (37, 94, 95). These data illustrate the potential for some well-intentioned precautionary policies to have harmful effects.

Simulation modeling with sensitivity analyses that examine all the state and transition pathways in the state transition model (**Figure 3**) shows that the gateway effect would have to be implausibly large to increase the net public health harm (23, 70). Overall, the strongest science to date does not support the concerns that e-cigarettes are such a dire threat as to undermine 50 years of tobacco control success, to renormalize smoking, and to set off the addiction cycle for another generation of youth.

3.2. Do E-Cigarettes Help Smokers Quit or Do They Inhibit Cessation?

The public health benefits of e-cigarettes are enhanced if they promote complete cessation of smoking. Four randomized controlled trials (RCTs) and well-designed observational studies show that e-cigarettes are effective in helping some adult smokers successfully quit smoking (4, 16, 18, 31, 39, 41, 72, 78, 91, 93, 114, 126, 144). Rates of cessation using e-cigarettes are similar to or higher than rates of cessation from previous clinical trials of NRT (103, 112, 126). Although some studies with loosely defined measures of use (e.g., ever use, not necessarily for cessation), inadequate or no appropriate comparison groups, or inability to rule out plausible confounders or selection bias have reported that e-cigarette use may be associated with no change or negative correlations with cessation (41, 126), those studies with more robust measures of how e-cigarettes were used (e.g., duration of use, type of device, use specifically for cessation) suggest that daily vaping can facilitate quit attempts and cessation (11, 15, 51, 75, 126). Weak observational studies that did not meet the minimum criteria for scientific rigor [see details in Villanti et al. (126)] were also excluded from two reviews (47, 78) that employed the Cochrane criteria for inclusion in systematic reviews and meta-analyses (50). One other meta-analysis did not employ Cochrane standards, included most of the weak studies (56), and reported a negative association among

e-cigarette use and smoking cessation, concluding that e-cigarettes inhibit cessation. The Cochrane Handbook warns: “Meta-analysis of studies that are at risk of bias may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce a ‘wrong’ result that may be interpreted as having more credibility” (50, p. 247). New innovations in e-cigarette models (e.g., tank, mod and pod systems) provide more effective nicotine delivery, so studies on earlier devices may not be as strong as recent evaluations of e-cigarettes’ positive public health effect (92, 126). Four recently published studies using large national US data sets add to the science that e-cigarettes are associated with smoking cessation (39, 72, 93, 144).

Smokers’ complete displacement of cigarettes can take time. For many, a period of dual use is expected and can be acceptable along the path to smoking cessation. A transitional period of dual use with e-cigarettes and cigarettes is consistent with CDER-approved dual use of NRT (38). We are not aware of any evidence indicating that vaping has contributed to reduced interest in quitting smoking, has slowed the rate of cessation, or has promoted relapse in large numbers of long-term former smokers who had been quit for 5 years or longer (41). Surveys of e-cigarette users consistently indicate that, for most smokers, quitting cigarettes is one major reason for ANDS use (41), even among youth (125). In the years when e-cigarette use increased the most, studies revealed a rise in quit attempts (5, 40), along with either a steady or faster drop in cigarette use among both youth and adults rather than a slowing of prevalence reduction (21, 82). Studies suggest that daily users of e-cigarettes for a month or more are six times more likely to have quit smoking cigarettes two years later (11); former smokers who quit less than one year prior are four times more likely to be daily e-cigarette users compared with current smokers (26); and studies from the United Kingdom suggest that e-cigarettes have increased quitting rates and therefore reduced smoking prevalence above what would have otherwise been expected (135). In 2014, more than six million smokers in the European Union quit smoking with e-cigarettes (31).

Available scientific evidence does not support the contention that e-cigarettes when used daily specifically to quit smoking either inhibit cessation or are undermining historical tobacco control cessation efforts (31, 41, 63, 70, 77, 103, 126). Much less harmful ANDS products such as e-cigarettes could help displace cigarettes on a larger scale than NRT has because of differential appeal such as the use of flavors while eliminating flavors from smoked products, lower cost due to differential taxation, and differential ease of access relative to smoked tobacco (22–24).

4. POLICY IMPLICATIONS

The harm minimization approach yields clear implications for tobacco control policies, which demands a reorientation of these policies starting with a return to their harm minimization roots (see the sidebar titled *Saving Smokers’ Lives Now While Simultaneously Protecting Youth*). A core harm minimization principle is that policy, regulation, and advocacy be science based and proportional to the degree of product harm, with the most restrictive strategies applying to the most harmful products (2, 7, 13, 57, 77, 103).

4.1. Reaffirming Harm Minimization in Tobacco Control

Harm minimization was an accepted strategy at the beginning of tobacco control efforts in the 1960s (57). It was and still is implicit in tobacco control support for CDER-approved over-the-counter use of NRT as a safe nicotine product (38). Public health advocates are now often skeptical of reduced harm products because of mistrust of the tobacco industry and commercial entities more generally, given the experience of the highly misleading promotion of low-tar “light” cigarettes

SAVING SMOKERS' LIVES NOW WHILE SIMULTANEOUSLY PROTECTING YOUTH

The key challenge is to implement policies that maximize the net flow away from smoking and toward the use of safer products or to no use. A balance can and must be found to protect youth without discouraging cleaner nicotine use by smokers unable or not wishing to stop their nicotine use (1, 2, 7, 13, 77, 103). Considerations include (a) devising a regulatory and policy framework that focuses on reducing smoking; (b) enabling the public to have accurate information about and incentives to adopt less harmful options of nicotine delivery; and (c) allowing product innovation and market forces, as well as regulation proportionate to product harms, to contribute to the speedy demise of smoking. Delays in harm minimization may impede the end of smoking rather than encourage smokers to switch to safer nicotine delivery products. Emergence and uptake of low-risk tobacco and nicotine products, including ANDS such as e-cigarettes, as alternatives to smoking create the possibility of deep and rapid public health gains through the substitution of high-risk products by low-risk products.

(57, 59) that were not, in fact, reduced-harm products (84). This skepticism has generalized, negating all harm minimization strategies and data, including the well-documented successful Swedish experience with snus. Smokeless tobacco is still viewed by the World Health Organization and most countries as “not a safe alternative to smoking” even if it is much less harmful (57, 58, 60, 76), and e-cigarettes are also being banned in many countries (13).

Harm minimization approaches have often been resisted in many areas of risky behavior because of fears of unintended harmful consequences. But when carefully implemented, these approaches have dramatically reduced harm at the individual and population levels [e.g., condom use (115) and needle-exchange programs for HIV prevention (17, 85, 116, 129, 138)].

4.2. Industry Considerations

In tobacco control, there is understandable trepidation in supporting alternatives that may risk undermining 50 years of tobacco control efforts, given past tobacco industry behavior [for details, see Royal College of Physicians (103, pp. 135–45)]. While holding the traditional tobacco industry and the newer ANDS industries strictly accountable, if, out of an abundance of caution, tobacco control strategies fail to fully embrace movement to less harmful products (or actively discourage such movement), the result could be detrimental for smokers who are unable to quit or who do not wish to quit nicotine use completely (143). A key question is whether the combination of technological advances (i.e., ANDS) and regulation can align makers of safer nicotine-containing products with public health advocates to eliminate combusted tobacco as a defective and unacceptable product for human use (12, 31, 77, 87, 88, 100, 101, 143).

4.3. Public Education and Communication

Accurate public information is a crucial part of tobacco control policy (28). The positive impact of e-cigarettes may have been slowed by exaggerated claims of their harms (62, 63) and the harms of nicotine in general (28). Only 5.3% of Americans correctly believe that e-cigarettes are “much less harmful” than cigarettes, 37% believe they are the same or worse than smoking, and 34% don’t know (74, 83). Misperceptions of the harms of nicotine and e-cigarettes have recently increased, undermining their full potential to displace smoking (14, 52, 62, 74). A misinformed public lacks the information required to take health-protective action (28, 60, 62). Accurate public education is needed to counteract misperceptions of harm from nicotine and ANDS, to communicate the

continuum of risk related to the use of different tobacco and ANDS products (**Figure 1**), and to emphasize the importance of smoking cessation. ANDS should always be compared with smoked tobacco products (relative harms), and the mistaken public beliefs that nicotine is the cause of disease risk and cancer, rather than the smoke from combustion, must be dispelled (44). Fears that nicotine causes cancer discourages use of FDA-approved NRTs as well as e-cigarettes and other ANDS as viable ways to stop smoking cigarettes (28).

5. CONCLUSIONS

Harm minimization is a pragmatic approach that can complement proven current tobacco control efforts of prevention and cessation (1, 2, 7, 13, 41, 57, 63, 77, 85, 103). Its primary goal is to move the whole population of smokers of toxic combusted tobacco products to exclusive use of much safer products as quickly and as early as possible in their individual smoking careers. If prudently regulated (2, 103), e-cigarettes and Swedish snus (64–66) provide a great opportunity to disrupt the US and global smoking-related disease pandemic and offer a proof-of-principle for the potential role of further innovations in ANDS in improving public health (7, 13, 28, 70, 71, 143, 144). This opportunity depends on encouraging increased technological innovation and finding the appropriate balance between product safety, consumer appeal, and regulations targeted specifically to decrease the use of conventional, combusted tobacco products.

Regulation, policy, practice, and advocacy for harm minimization approaches have the potential to realign market forces and economic incentives for those willing to responsibly manufacture and market much less harmful ANDS products to adult consumers (2, 22, 24, 28, 66, 143). Even if the risk of harm to some youth who otherwise would not have smoked is marginally increased, such risks must be weighed against the substantial and immediate benefits of displacing smoking with safer nicotine products among both youth and adults (2, 13, 22, 24, 57, 63, 77, 103). Under all but the most implausible scenarios, population simulation modeling estimates millions of life years saved by employing the principles of harm minimization and switching smokers to safer ANDS products (70, 71, 126). Replacement of most cigarette use by e-cigarette use over a 10-year period yields up to 6.6 million fewer premature deaths with 86.7 million fewer life years lost (69). America and the world need a candid smoking control champion—a figure like C. Everett Koop, Surgeon General during the first eight years of the AIDS epidemic—to get out the latest accurate information about reduced harm ANDS products that could save millions of smokers' lives (28). Ethics and integrity in responsibly interpreting the scientific evidence with rigor (3, 7, 13, 28, 41, 57, 62, 63, 77, 78, 103, 127, 126), and with common sense, demand it.

SUMMARY POINTS

1. Inhaled tobacco smoke remains the single biggest threat to public health; it is widely used, highly appealing, addictive, and extremely toxic.
2. There is a continuum of harm of nicotine-containing products, from the high harm of combusted tobacco to much lower harms of noncombustible nicotine delivery with or without tobacco, including NRT.
3. In considering how to maximize population benefit and minimize population harm, one must fully consider all three dimensions of nicotine products and locate the sweet spot (see **Figures 2 and 3**), which defines the characteristics of products most likely to displace smoking: (a) lower harm, (b) sufficient appeal, and (c) sufficiently satisfying nicotine delivery.

4. Tobacco control strategies should adopt the concept of harm minimization in developing coordinated regulations, policies, and interventions to rapidly move smokers toward less harmful nicotine delivery products, while preventing the adoption of regular nicotine-containing or tobacco product use among youth.
5. The public must be accurately educated about the relative harms of nicotine-containing products relative to smoking.
6. A harm minimization approach implies proportionality of harm based on each product class. Policies and regulations must be aligned on the basis of proportionate harm.
7. Harm minimization is an evidence-based approach to tobacco control, which, when complemented by other, proven tobacco control interventions, can simultaneously prevent youth from starting to smoke and help current smokers stop, saving many lives more quickly than would otherwise be possible.

FUTURE ISSUES

1. Research is needed on the pathways by which ANDS can lead to the displacement of smoking. Traditional smoking cessation treatment designs may not be optimal because they focus on near-term outcomes of focused quit efforts, whereas the adoption of ANDS as an alternative to smoking may involve more of a gradual evolution in the smoker's goals and behaviors.
2. New and evolving ANDS products may raise new issues and data needs. For example, products that heat rather than burn tobacco, but still mimic smoking, may raise issues different from those raised by e-cigarettes.
3. Because not all effects of policies or products can be anticipated, frameworks for robust and responsive postmarket population surveillance and for modeling of likely outcomes of ANDS use need to be established.
4. A regulatory framework that aligns business goals with public health goals will need to be developed. Absent regulation, ANDS have evolved very quickly toward more effective nicotine delivery. Although regulation is necessary to ensure that product innovations are consistent with public health goals, it also has the potential to stifle innovation and thus undermine the potential of ANDS as a public health success.
5. A harm minimization strategy acknowledges that nicotine use and even dependence may be acceptable in the interest of reducing tobacco-caused death and disease. This approach will require a focused, objective, evidence-based dialogue that separates concerns about nicotine use and dependence from concerns about medical harm and implies a substantial shift in public, professional, and regulatory attitudes in the interest of eventually ending combusted tobacco use.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

All authors were supported by Truth Initiative. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the US Food and Drug Administration, or the Truth Initiative.

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The *Annual Review of Criminology* provides comprehensive reviews of significant developments in the multidisciplinary field of criminology, defined as the study of both the nature of criminal behavior and societal reactions to crime. International in scope, the journal examines variations in crime and punishment across time (e.g., why crime increases or decreases) and among individuals, communities, and societies (e.g., why certain individuals, groups, or nations are more likely than others to have high crime or victimization rates). The societal effects of crime and crime control, and why certain individuals or groups are more likely to be arrested, convicted, and sentenced to prison, will also be covered via topics relating to criminal justice agencies (e.g., police, courts, and corrections) and criminal law.

TABLE OF CONTENTS FOR VOLUME 1:

THE DISCIPLINE

- *Reflections on Disciplines and Fields, Problems, Policies, and Life*, James F. Short
- *Replication in Criminology and the Social Sciences*, William Alex Pridemore, Matthew C. Makel, Jonathan A. Plucker

CRIME AND VIOLENCE

- *Bringing Crime Trends Back into Criminology: A Critical Assessment of the Literature and a Blueprint for Future Inquiry*, Eric P. Baumer, María B. Vélez, Richard Rosenfeld
- *Immigration and Crime: Assessing a Contentious Issue*, Graham C. Ousey, Charis E. Kubrin
- *The Long Reach of Violence: A Broader Perspective on Data, Theory, and Evidence on the Prevalence and Consequences of Exposure to Violence*, Patrick Sharkey
- *Victimization Trends and Correlates: Macro- and Microinfluences and New Directions for Research*, Janet L. Lauritsen, Maribeth L. Rezey
- *Situational Opportunity Theories of Crime*, Pamela Wilcox, Francis T. Cullen
- *Schools and Crime*, Paul J. Hirschfield

PUNISHMENT AND POLICY

- *Collateral Consequences of Punishment: A Critical Review and Path Forward*, David S. Kirk, Sara Wakefield
- *Understanding the Determinants of Penal Policy: Crime, Culture, and Comparative Political Economy*, Nicola Lacey, David Soskice, David Hope

- *Varieties of Mass Incarceration: What We Learn from State Histories*, Michael C. Campbell
- *The Politics, Promise, and Peril of Criminal Justice Reform in the Context of Mass Incarceration*, Katherine Beckett

THE PRISON

- *Inmate Society in the Era of Mass Incarceration*, Derek A. Kreager, Candace Kruttschnitt
- *Restricting the Use of Solitary Confinement*, Craig Haney

DEVELOPMENTAL AND LIFE-COURSE CRIMINOLOGY

- *Desistance from Offending in the Twenty-First Century*, Bianca E. Bersani, Elaine Eggleston Doherty
- *On the Measurement and Identification of Turning Points in Criminology*, Holly Nguyen, Thomas A. Loughran

ECONOMICS OF CRIME

- *Gun Markets*, Philip J. Cook
- *Offender Decision-Making in Criminology: Contributions from Behavioral Economics*, Greg Pogarsky, Sean Patrick Roche, Justin T. Pickett

POLICE AND COURTS

- *Policing in the Era of Big Data*, Greg Ridgeway
- *Reducing Fatal Police Shootings as System Crashes: Research, Theory, and Practice*, Lawrence W. Sherman
- *The Problems With Prosecutors*, David Alan Sklansky
- *Monetary Sanctions: Legal Financial Obligations in US Systems of Justice*, Karin D. Martin, Bryan L. Sykes, Sarah Shannon, Frank Edwards, Alexes Harris
- *Forensic DNA Typing*, Erin Murphy



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Contents

Symposium

- Commentary: Increasing the Connectivity Between Implementation
Science and Public Health: Advancing Methodology, Evidence
Integration, and Sustainability
David A. Chambers 1
- Selecting and Improving Quasi-Experimental Designs in Effectiveness
and Implementation Research
*Margaret A. Handley, Courtney R. Lyles, Charles McCulloch,
and Adithya Cattamanchi* 5
- Building Capacity for Evidence-Based Public Health: Reconciling the
Pulls of Practice and the Push of Research
Ross C. Brownson, Jonathan E. Fielding, and Lawrence W. Green 27
- The Sustainability of Evidence-Based Interventions and Practices in
Public Health and Health Care
Rachel C. Shelton, Brittany Rhoades Cooper, and Shannon Wiltsey Stirman 55

Epidemiology and Biostatistics

- Selecting and Improving Quasi-Experimental Designs in Effectiveness
and Implementation Research
*Margaret A. Handley, Courtney R. Lyles, Charles McCulloch,
and Adithya Cattamanchi* 5
- Agent-Based Modeling in Public Health: Current Applications and
Future Directions
Melissa Tracy, Magdalena Cerdá, and Katherine M. Keyes 77
- Big Data in Public Health: Terminology, Machine Learning,
and Privacy
Stephen J. Mooney and Vikas Pejaver 95
- Environmental Determinants of Breast Cancer
Robert A. Hiatt and Julia Green Brody 113

Meta-Analysis of Complex Interventions <i>Emily E. Tanner-Smith and Sean Grant</i>	135
Precision Medicine from a Public Health Perspective <i>Ramya Ramaswami, Ronald Bayer, and Sandro Galea</i>	153
Relative Roles of Race Versus Socioeconomic Position in Studies of Health Inequalities: A Matter of Interpretation <i>Amani M. Nuru-Jeter, Elizabeth K. Michaels, Marilyn D. Thomas, Alexis N. Reeves, Roland J. Thorpe Jr., and Thomas A. LaVeist</i>	169

Social Environment and Behavior

The Debate About Electronic Cigarettes: Harm Minimization or the Precautionary Principle <i>Lawrence W. Green, Jonathan E. Fielding, and Ross C. Brownson</i>	189
Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives <i>David B. Abrams, Allison M. Glasser, Jennifer L. Pearson, Andrea C. Villanti, Lauren K. Collins, and Raymond S. Niaura</i>	193
E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications <i>Stanton A. Glantz and David W. Bareham</i>	215
Increasing Disparities in Mortality by Socioeconomic Status <i>Barry Bosworth</i>	237
Neighborhood Interventions to Reduce Violence <i>Michelle C. Kondo, Elena Andreyeva, Eugenia C. South, John M. MacDonald, and Charles C. Branas</i>	253
The Relationship Between Education and Health: Reducing Disparities Through a Contextual Approach <i>Anna Zajacova and Elizabeth M. Lawrence</i>	273

Environmental and Occupational Health

Building Evidence for Health: Green Buildings, Current Science, and Future Challenges <i>J.G. Cedeño-Laurent, A. Williams, P. MacNaughton, X. Cao, E. Eitland, J. Spengler, and J. Allen</i>	291
Environmental Influences on the Epigenome: Exposure-Associated DNA Methylation in Human Populations <i>Elizabeth M. Martin and Rebecca C. Fry</i>	309

From Crowdsourcing to Extreme Citizen Science: Participatory Research for Environmental Health <i>P.B. English, M.J. Richardson, and C. Garzón-Galvis</i>	335
Migrant Workers and Their Occupational Health and Safety <i>Sally C. Moyce and Marc Schenker</i>	351
Mobile Sensing in Environmental Health and Neighborhood Research <i>Basile Chaix</i>	367

Public Health Practice and Policy

Commentary: Increasing the Connectivity Between Implementation Science and Public Health: Advancing Methodology, Evidence Integration, and Sustainability <i>David A. Chambers</i>	1
Building Capacity for Evidence-Based Public Health: Reconciling the Pulls of Practice and the Push of Research <i>Ross C. Brownson, Jonathan E. Fielding, and Lawrence W. Green</i>	27
The Sustainability of Evidence-Based Interventions and Practices in Public Health and Health Care <i>Rachel C. Shelton, Brittany Rhoades Cooper, and Shannon Wiltsey Stirman</i>	55
The Debate About Electronic Cigarettes: Harm Minimization or the Precautionary Principle <i>Lawrence W. Green, Jonathan E. Fielding, and Ross C. Brownson</i>	189
Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives <i>David B. Abrams, Allison M. Glasser, Jennifer L. Pearson, Andrea C. Villanti, Lauren K. Collins, and Raymond S. Niaura</i>	193
E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications <i>Stanton A. Glantz and David W. Bareham</i>	215
Neighborhood Interventions to Reduce Violence <i>Michelle C. Kondo, Elena Andreyeva, Eugenia C. South, John M. MacDonald, and Charles C. Branas</i>	253
Mobile Sensing in Environmental Health and Neighborhood Research <i>Basile Chaix</i>	367
Policy Approaches for Regulating Alcohol Marketing in a Global Context: A Public Health Perspective <i>Marissa B. Esser and David H. Jernigan</i>	385

Problems and Prospects: Public Health Regulation of Dietary Supplements	
<i>Colin W. Binns, Mi Kyung Lee, and Andy H. Lee</i>	403

Health Services

Achieving Mental Health and Substance Use Disorder Treatment Parity: A Quarter Century of Policy Making and Research	
<i>Emma Peterson and Susan Busch</i>	421
Data Resources for Conducting Health Services and Policy Research	
<i>Lynn A. Blewett, Kathleen Thiede Call, Joanna Turner, and Robert Hest</i>	437
Designing Difference in Difference Studies: Best Practices for Public Health Policy Research	
<i>Coady Wing, Kosali Simon, and Ricardo A. Bello-Gomez</i>	453
How Much Do We Spend? Creating Historical Estimates of Public Health Expenditures in the United States at the Federal, State, and Local Levels	
<i>Jonathon P. Leider, Beth Resnick, David Bishai, and F. Douglas Scutchfield</i>	471
Modeling Health Care Expenditures and Use	
<i>Partha Deb and Edward C. Norton</i>	489
Promoting Prevention Under the Affordable Care Act	
<i>Nadia Chait and Sherry Glied</i>	507
Treatment and Prevention of Opioid Use Disorder: Challenges and Opportunities	
<i>Dennis McCarty, Kelsey C. Priest, and P. Todd Korthuis</i>	525

Indexes

Cumulative Index of Contributing Authors, Volumes 30–39	543
Cumulative Index of Article Titles, Volumes 30–39	549

Errata

An online log of corrections to *Annual Review of Public Health* articles may be found at <http://www.annualreviews.org/errata/publhealth>