

Title: How to Think – Not Feel – about Tobacco Harm Reduction

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ABSTRACT

Introduction

The debate over tobacco harm reduction (THR) has divided the tobacco control community into two camps, one expressing serious reservations about THR while the other believes that reduced-risk products like e-cigarettes will disrupt the cigarette market. The often emotional debate would benefit from dispassionate data-based evaluation of evidence.

Methods

After briefly discussing harm reduction in public health and specifically in tobacco control, this paper identifies major issues concerning e-cigarettes and reviews relevant evidence. Issues include: e-
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cigarettes' risks compared to cigarette smoking; the effect of vaping on youth smoking; vaping's impact on adult smoking cessation; the net long-term public health implications of vaping; and differences in views on policy issues. The intent is to provide a broad overview of issues and evidence, directing readers to more detailed reviews of specific issues.

Findings

Principal findings include the following: (i) While longitudinal studies suggest that vaping increases never-smoking young people's odds of trying smoking, national survey data indicate that adolescents' 30-day smoking prevalence decreased at an unprecedented rate precisely while vaping increased. Use of all other tobacco products also declined. (ii) Recent population-level studies add evidence that vaping is increasing adult smoking cessation. (iii) Vaping is likely to make a positive contribution to public health.

Conclusions

THR can be a complement to, not a substitute for, evidenced-based tobacco control interventions. Tobacco control professionals need to focus on objective assessment of and discussion about the potential costs and benefits of THR.

IMPLICATIONS

Participants on both sides of the divisive THR debate need to examine the complicated issues and evidence more objectively. That entails considering both the potential benefits and costs associated with reduced-risk products like e-cigarettes. Further, it requires examining different kinds of evidence when considering specific issues. For example, those concerned by longitudinal study findings that vaping increases students' trial of cigarettes should consider US national survey evidence that youth

smoking has decreased at an unprecedented rate. A review of the major issues suggests that the potential of vaping to assist adult smokers to quit outweighs the potential negatives.

INTRODUCTION

Taken literally, tobacco harm reduction – reducing the harms created by tobacco – is what everyone in tobacco control wants to accomplish. But the term “tobacco harm reduction” (THR) has become the source of one of the most divisive, often acrimonious debates in tobacco control history. Intense emotions, on both sides, have obstructed objective consideration of complicated THR issues. This paper examines data underlying several of those issues with the goal of improving rational, civil discussion about THR. The paper provides a broad overview, with readers directed to more detailed reviews of specific issues. While much of what follows is relevant for countries worldwide, the review focuses on issues and evidence pertaining to the United States. Different cultural and political contexts might influence interpretations of what constitute the most important issues and evidence.

Defining tobacco harm reduction

THR refers to substituting lower-risk nicotine and tobacco products, like nicotine replacement therapy pharmaceuticals, low-nitrosamine smokeless tobacco products, and e-cigarettes, for the highest risk tobacco products – cigarettes and other combusted products – for smokers who otherwise cannot or will not quit using nicotine, or will not do so soon. This is consistent with the general concept of harm reduction in public health. Harm Reduction International defines harm reduction with regard to illicit drugs as follows.

Harm reduction refers to policies, programmes and practices that aim to reduce the harms associated with the use of psychoactive drugs in people unable or unwilling to stop. The defining feature [is] the focus on the prevention of harm, rather than on the prevention of drug use

itself...Harm reduction complements approaches that seek to prevent or reduce the overall level of drug consumption.¹

Each of the three sentences applies to THR: The objective is to reduce harms to health for smokers unable or unwilling to stop. The focus is on preventing harm and not on preventing the use of nicotine itself. Importantly, THR complements – it does not replace – evidence-based approaches to preventing smoking initiation, assisting smokers to quit, and protecting nonsmokers from second-hand smoke.

Recently some scholars have adopted the term harm *minimization* instead of reduction.² They believe “minimization” more effectively connotes the objective’s importance, emphasizing the goal of getting harm down to zero. In contrast, “reduction” covers minor to major improvements. Because harm reduction is the term used throughout the field of public health, it is the term used in the present paper.

Harm reduction history in public health and tobacco control

Harm reduction has a long and successful history in public health.³ Examples include:

- Needle exchange to minimize the spread of HIV/AIDS;
- Sex education for adolescents, and condom distribution in schools, to reduce teen pregnancies and sexually transmitted infections;
- Methadone as a substitute for heroin;
- Motorcycle helmet laws to reduce the severity of head injuries;
- Designated driver programs to reduce drunk driving.

Such policies confront fervent public opposition, with a strong underlying tone of moralism.

Nevertheless, the field of public health has often embraced harm reduction policies, always with a pragmatic focus on what works.

In tobacco control, experience with the principal early examples of alleged “harm reduction” – filtered and low-tar-and-nicotine cigarettes – provides ample reason for skepticism about THR. Both were tobacco industry public relations ploys, moves to reassure smokers that, instead of quitting, they could switch to ostensibly “safer” cigarettes.^{4,5}

One of the earliest filtered cigarettes, Kent, explicitly advertised itself as “the one cigarette that can show you proof of greater health protection”. Ironically, its “exclusive Micronite filter” contained asbestos.⁶ Two decades later, a prominent low-tar-and-nicotine brand, True, ran a series of ads showing intelligent-looking models with the tagline, “Considering all I’d heard, I decided I’d either quit or smoke True. I smoke True”. Ads like these conveyed the message that the novel cigarettes were safe enough, compared to conventional “full-strength” cigarettes, to permit smokers to smoke them instead of quitting. The campaigns worked. Millions of Americans switched to filters and then to low-tar-and-nicotine cigarettes. Both categories dominated the market within a decade of their introduction. Both were eventually demonstrated to be no less hazardous than their predecessors,⁷ and both were therefore responsible for millions of premature deaths.

These experiences, and the industry’s behavior more generally, have created within public health a profound hostility toward the industry, manifested for many in wanting to see the industry driven out of business, a desire expressed by former WHO Director-General Margaret Chan.⁸ This attitude constitutes a barrier to the acceptance of harm reduction because THR necessarily involves companies’ manufacturing and profiting from sale of nicotine and tobacco products, some marketed by the mainstream tobacco companies.

If the experiences with filtered and low-tar-and-nicotine cigarettes warrant skepticism about a new generation of purported harm reduction products, another experience offers reason to believe that THR

might genuinely reduce harm. For decades large proportions of Swedish males have substituted snus, a low-nitrosamine smokeless tobacco, for smoking. Swedish males have the lowest male smoking rate in Europe: 8% in 2016. However, including snus, males' total tobacco use prevalence, 25%, is not especially low.⁹ Yet Swedish males have by far the lowest tobacco-related mortality risks of men in all European Union countries. In all 4 disease categories in [Table 1](#), Swedish males' death rate is lower than that of the lowest of all other EU countries. In contrast, Swedish women, few of whom use snus, have average smoking rates among European women and average to high rates of tobacco-related death rates.¹⁰ Extensive research has found few health risks associated with snus.¹¹ Swedish males' use of snus thus serves as an impressive natural experiment in successful tobacco harm reduction.

THR ISSUES DIVIDING THE FIELD

[Table 2](#) lists a dozen issues that divide the tobacco control community concerning today's principal THR product, e-cigarettes, treated as representative of reduced-risk alternative nicotine delivery systems (ANDS) throughout this paper. The table is illustrative rather than comprehensive and definitive. Likely relatively few members of the tobacco control community fit the table's characterization of the e-cigarette enthusiast or skeptic across the board. But many, perhaps most, would see themselves as leaning more in one direction than the other.

This paper focuses on 2 sets of issues described in the table. Most attention is devoted to important elements of what motivates each side of the e-cigarette divide. The paper concludes with brief consideration of each side's position on select policy issues.

Principal issues motivating the e-cigarette debate

Vaping's risk compared to cigarette smoking

The table's first three rows identify issues that motivate enthusiasm for and opposition to e-cigarettes. First is the question of how risky e-cigarettes are relative to cigarette smoking. Everyone agrees that e-cigarettes are less dangerous than smoking. The question is how much.

E-cigarette enthusiasts point to reports of Public Health England¹² and the Royal College of Physicians¹³ concluding that e-cigarettes are at least 95% less dangerous than smoking, an estimate first reported in 2014 by Nutt et al.¹⁴ Few scientists have published specific estimates of the relative risk of vaping, with this the lowest. In part, the conclusion that vaping is far less dangerous than smoking derives from the fact that e-cigarettes emit few of the 7,000 chemicals in cigarette smoke. For toxins found in both smoke and e-cigarette vapor, e-cigarettes' emissions are typically a small fraction of the levels in cigarette smoke.¹⁵ Compared to cigarette smokers, e-cigarette users who have quit smoking have significantly lower levels of tobacco-related toxicants in saliva and urine samples.¹⁶ Further, switching from cigarettes to e-cigarettes lowers blood pressure¹⁷ and improves lung function.¹⁸

E-cigarette skeptics emphasize research that leads them to conclude that vaping poses real risks of cardiovascular and non-cancer lung disease.¹⁹ Observing that these conditions are responsible for two-thirds of smoking-related mortality, and noting "similarities between the effects of e-cigarettes and those of conventional cigarettes on determinants of cardiovascular and lung disease," vaping's leading opponent has conjectured that vaping might be responsible for half (or more) of the mortality risk of smoking.¹⁹ This is the highest published estimate of the relative risk of vaping.

The amount of risk reduction matters. Given the multiple types of ANDS, and those to come, and multiple patterns of use, scientists likely will be unable to develop a precise estimate of risk reduction for decades, if ever. However, a simple heuristic, the risk/use equilibrium, helps to put the relative risk in perspective.²⁰ (See [Figure 1.](#)) Each point on the curve shows how many users of a novel product would produce the same population disease risk as one cigarette smoker (the ordinate on the graph), given specific levels of decreased risk per user for the alternative product (the abscissa). For example, if a product is half as risky as cigarette smoking, 2 people would have to use it to generate the same aggregate risk as 1 person smoking. If the product was 90% less risky than smoking, 10 people would have to use it to create the population risk of 1 person's smoking. The risk/use equilibrium demonstrates that to negate the potential benefits of e-cigarettes, their uptake, in lieu of cigarettes, would have to be quite substantial for virtually the entire range of plausible relative risks of e-cigarettes. Readers interested in learning about the e-cigarette health consequences literature are encouraged to consult recent detailed reviews.^{2,12,15,19,21,22}

The precautionary principle

Lacking knowledge of the degree of risk reduction, many skeptics likely oppose e-cigarettes because they adhere to the precautionary principle, "the principle that the introduction of a new product or process whose ultimate effects are disputed or unknown should be resisted."²³ The principle has often been applied to environmental and occupational exposures and more recently to genetically modified foods. The THR application would recommend avoiding novel ANDS unless and until they are definitively proven to be substantially less risky than regular cigarettes and that they will not start youth on a path to cigarette smoking nor prevent adult smoking cessation.²⁴

The precautionary principle is generally applied in cases in which the at-risk population is otherwise healthy, with the objective being to avoid the risk of damaging their health. With smoking, however, while that interpretation holds for children and non-smoking adults, it does not apply to smokers. Their health is already greatly at risk and the value of e-cigarettes is their potential to reduce that risk. E-cigarette enthusiasts interpret the precautionary principle as supporting novel products like e-cigarettes for harm reduction for smokers because their principal danger lies in *not* accepting uncertainty about the products' risk profile.²⁴

Smoking thus poses the complexity for the precautionary principle that the uncertainties associated with e-cigarettes can be a cause of concern for one population (children and non-smoking adults) but hope for another (smokers). This said, many e-cigarette skeptics apply the precautionary principle to the case of adult smokers too, wary that vaping might decrease smoking cessation. This is discussed later.

An extreme variation of the precautionary principle holds that nicotine dependence in any form poses too great a health risk to tolerate. For adherents to this view, the only acceptable form of nicotine is medicinal products with little to no addiction potential, such as nicotine "gum" and patches. WHO has suggested that this position is embedded in Article 5.2(b) of the Framework Convention on Tobacco Control.²⁵

Primary concerns of enthusiasts and skeptics

The third issue motivating interest in e-cigarettes reflects enthusiasts' and skeptics' principal concerns other than direct health effects. Enthusiasts believe that e-cigarettes, and future ANDS, will help millions of smokers to quit smoking. They are not especially concerned about adverse effects on adolescents, some believing that e-cigarettes help some to avoid or quit smoking.

In contrast, many e-cigarette skeptics focus laser-like on their fear that e-cigarettes endanger children. Skeptics devote relatively little consideration to the potential benefits of e-cigarettes in helping adults quit smoking. Some believe that e-cigarettes may impede smoking cessation.

We turn now to the evidence pertaining to these two sets of issues.

EFFECTS OF E-CIGARETTES ON YOUNG PEOPLE

E-cigarettes' opponents have 3 principal concerns regarding e-cigarettes' effects on young people, seen in the right-hand column of the fourth row of [Table 2](#).

Are e-cigarettes a gateway to smoking?

Longitudinal studies

The first-listed concern is that vaping acts as a causal gateway²⁶ to smoking for otherwise never-smoking young people. A controlled trial, randomly assigning some youth to vape and others not, is not an ethically possible means of testing this concern.

The second-best methodological approach is a longitudinal study. Longitudinal studies survey young people about their prior use of e-cigarettes, conventional cigarettes, and often other substances (including other tobacco products, alcohol, marijuana), various attitudes and beliefs, and their socioeconomic and demographic backgrounds. In a follow-up survey 6-18 months later the investigators ask the same respondents similar questions.

The gateway hypothesis is supported by longitudinal studies that have found that, compared to never-smoking young people who had not vaped, those who had were more likely to have tried cigarette smoking at follow-up.¹⁵ A meta-analysis concluded that, controlling for a number of variables, the

adjusted odds ratio of smoking by the follow-up period was 3.50 for the never-smokers who had vaped at the time of the original survey.^{27,28}

These studies are beset by challenges.²⁹ First, it is difficult, although critical, to control for what makes some never-smoking youth try vaping and others not. That some vape and others do not means that these two groups of young people are inherently different.

Most of the studies include controls but miss important ones, generally including use of other psychoactive substances. While several studies ask questions assessing the respondents' "sensation seeking" or "rebelliousness,"³⁰⁻³² actual substance use may be a better measure of that phenomenon. A few studies include superficial measures of other drug use that do not discriminate effectively. For example, one asked whether respondents had ever used any of 14 different substances.³³ This measure treats the adolescent who has consumed alcohol once identically to an adolescent who smokes marijuana multiple days per week. Ironically, only three of the studies controlled for use of other tobacco products^{31,34} (one not including smokeless tobacco³⁵), unacceptable in an era of poly-tobacco use.^{36,37}

In one study in which marijuana use was included as one of 4 "mediating" variables, the authors found no statistically significant direct relationship between vaping and smoking at follow-up.³⁸ Earlier, using the same data but omitting these mediators, the authors reported the standard statistically significant relationship between vaping and subsequent smoking.³² Thus, the inclusion of the mediators eliminated the direct link between vaping and smoking.

With a few exceptions, the longitudinal studies fail to evaluate the length or intensity of vaping upon initial surveying and of subsequent experimentation with cigarette smoking.^{32,39} In one study, the few vaping young people who went on to smoke all said that they had smoked no more than 2 cigarettes in

the subsequent 12 months.⁴⁰ Most cigarette use by adolescents is experimental, leading to regular smoking relatively infrequently.^{41,42} Thus this study provides no evidence that the subsequent smoking was anything more than one-time experimentation with cigarettes.^{36,37}

Finally, some of the studies are remarkably small. One study had only 14 never-smoking respondents who vaped, among whom 11 tried smoking before the follow-up.³⁰ A second one had only 4 previously never-smoking respondents whose vaping was associated with subsequent smoking.⁴⁰

While the longitudinal studies link e-cigarette experimentation with subsequent experimentation with cigarettes, they have not established causality. Further, this body of research has not connected smoking during the follow-up period to later dependent smoking. Subsequent research should examine this important issue.

Population studies of vaping and smoking by young people

Nationally representative population surveys of youth provide context for interpreting the longitudinal studies. An examination of 5 large-scale surveys of vaping and smoking behaviors among 11-16 year-olds in the UK, covering more than 60,000 young people, found that most experimentation with e-cigarettes has not resulted in subsequent regular use. Among never-smokers fewer than 0.5% vaped weekly. The study concluded that “there is no evidence of e-cigarettes driving smoking prevalence upwards. This...suggests that fears about e-cigarettes as a gateway to more youth becoming smokers are not currently justified, at least in the UK.”⁴³

US surveys provide similar evidence. High school and middle school students’ smoking rates fell, at an unprecedented rate, precisely when vaping rates escalated. [Figure 2](#) shows data from the 2011-16 National Youth Tobacco Surveys (NYTS) for high school students.⁴⁴ The data indicate the following:

- 30-day e-cigarette prevalence escalated rapidly, primarily from 2013-14, but declined 29% from 2015-16.
- Hookah use increased 2011-14 but decreased the past 2 years.
- Use of all other tobacco products decreased.
- That includes cigarettes, which dropped by fully 50% over the five years.

Another national survey, Monitoring the Future (MTF), recorded nearly identical declines.⁴⁵ The year of the largest increase in e-cigarette use, 2013-14, saw the largest one-year percentage decline in high school seniors' cigarette smoking prevalence (16.6%) in the survey's 40+ year history. That was followed by a nearly identical decline (16.2%) the following year. Smoking continued to fall significantly from 2015-16, when MTF recorded a 23% decrease in e-cigarette use, and again from 2016-17, when vaping increased modestly.

Thus, examining 6 years of data in two US national surveys, there is no evidence that e-cigarette use is associated with increased smoking by adolescents. To the contrary, there is a strong negative correlation. The sequential annual surveys imply that even if vaping by never-smoking adolescents increases their risk of trying smoking, that effect is swamped by the far larger trend of decreasing cigarette smoking.

With smoking among adults decreasing as well, there is no evidence to support the concern that vaping might be "renormalizing smoking."⁴⁶

Effects of nicotine on the developing brains of adolescents

Evidence suggests that exposure to nicotine can harm adolescents' developing brains.⁴⁷ The relevance of this regarding e-cigarettes is not self-evident, however, for several reasons.

First, adolescents who use other tobacco products are already exposed to nicotine, especially the very small percentage who smoke regularly. They are the only heavy e-cigarette users,⁴⁸ and the numbers of regular smokers are dwindling. Since the first year that students' e-cigarette use was measured in the US (2011), the percentage of high school seniors who smoke daily has fallen from 10.3% to 4.8%.⁴⁵

Second, proportionately few never-smoking adolescents try vaping, and for most it is just short-term experimentation. In 2016, while a majority of high school seniors who were regular smokers had vaped in the past 30 days, only 5.6% of never-smokers did so. Of those, fewer than half (45.6%) vaped more than 2 times.⁴⁹

Third, it is not clear how many never-smokers who vape are being exposed to nicotine at all. In 2016, three-quarters of never-smoking 12th graders in MTF said they vaped only flavors; just 14.3% said they vaped nicotine. By contrast, among current smokers over 60% reported vaping nicotine, with only 31% responding that they vaped just flavors.⁵⁰ Some of the adolescents, especially the never-smokers, likely were mistaken; i.e., they were vaping nicotine as well as flavors. But the data suggest that many never-smoking adolescents who have vaped have not vaped nicotine.

2016 MTF data can be combined to develop a crude estimate about nicotine brain exposure through e-cigarette use for never-smoking adolescents: Based on their self-reports, 0.4% of never-smoking high school seniors were exposed to nicotine from e-cigarettes more than twice in the past month (= 5.6% [never-smokers who vaped] x 45.6% [vaped >2 times] x 14.3% [vaped nicotine]). If half of the never-smoking adolescents who claimed to vape only flavors had actually vaped nicotine as well, that figure rises to 1.5%.

Thus, it is unlikely that e-cigarettes are creating significant nicotine brain exposure for more than a very small fraction of young people. Indeed, given the substantial decrease in smoking and other tobacco use

during the e-cigarette era, the brains of young people are likely being exposed to far less nicotine than they were prior to the emergence of e-cigarettes.

Policy studies

Conventional wisdom holds that young people's access to nicotine and tobacco products should be minimized. This includes prohibiting sale of e-cigarettes to anyone under a minimum age, typically 18. Two analyses, however, question whether this policy might inadvertently produce an unintended opposite effect. Friedman⁵¹ and Pesko et al.⁵² found that states that prohibited e-cigarette sales to minors experienced a nearly 1 percentage point increase in cigarette smoking by youth, compared to states that did not restrict youth access. 1 percentage point represents a substantial proportion of the very low rate of youth smoking.

These studies do not constitute a definitive conclusion about the effects of age restrictions. However, they indicate that even "obvious" policies need to be subjected to careful analysis.

Effects of e-cigarettes on young people: concluding thoughts

Collectively, the evidence examined above suggests that concerns about the effects of e-cigarettes on young people likely exaggerate actual risks. Although they have problems,²⁹ the longitudinal studies linking vaping to subsequent trial of cigarettes^{15,27} warrant serious consideration. Even so, the implicit notion that a gateway effect will increase smoking by young people and renormalize smoking is inconsistent with findings from population-level surveys that cigarette smoking, and other tobacco product use, declined significantly precisely during the years in which e-cigarette use became popular.^{44,45} The infrequent use of e-cigarettes by most students who vape, combined with a substantial decline in students' use of e-cigarettes in 2016, raises the possibility that e-cigarette use by adolescents

may ultimately prove to have been a relatively short-lived fad. Data on students' vaping prevalence over the next several years will provide the answer.

VAPING AND ADULT SMOKING CESSATION

Reviews of the evidence

To date, empirical studies on the effects of vaping on smoking cessation have been limited in number, with the quality of many questioned. A 2016 Cochrane review⁵³ identified a handful of studies, including two randomized trials, that support the conclusion that e-cigarettes aid in cessation, and that they may be as effective as and possibly more effective than nicotine patches. The authors considered the overall evidence weak, however, reflecting the limited number of studies and weak methods of some. Other recent reviews have also concluded that e-cigarettes likely help some smokers to quit.^{15,21,54,55} But all of them caution that few studies meet the criteria to be considered scientifically strong. Another review concluded that the overall effect of e-cigarettes on cessation was negative.⁵⁶ However, this study suffered from selection problems regarding the studies included.⁵⁵

Recent population-level studies

Over the past two years, new population-level studies have reported that e-cigarettes have increased smoking cessation in the UK^{57,58} and the US⁵⁹⁻⁶¹. The UK studies imply that vaping increased smoking cessation by at least 8% (personal communication with Robert West, November 17, 2016.) The lead author of Zhu et al.⁵⁹ concluded that vaping increased smoking cessation in the US in 2014-15 by at least 12% (personal conversation with Zhu, July 30, 2017).

Levy et al.,⁶⁰ Giovenco and Delnevo,⁶¹ and Berry et al.⁶² produced a potentially very important finding: more frequent users of e-cigarettes have a higher likelihood of quitting smoking than do smokers not using e-cigarettes. In contrast, less frequent vapers have lower quit rates than do non-vaping smokers.

These studies cannot prove that e-cigarettes increase quitting. For example, the finding regarding the importance of vaping frequency may reflect more intensive vapers being more committed to quitting. Nevertheless, the consistency of findings across multiple studies using different data and methods adds important evidence that vaping does increase smoking cessation.

In addition to these formal studies, recent data indicate that in some countries a growing majority of vapers are former smokers; until recently most were dual users.⁶³ Further, 36% of British former smokers who are also former vapers report that they used e-cigarettes during their quit attempt.⁶³ In both the UK and the US, e-cigarettes are now the most widely used aid to quitting smoking, exceeding government-approved pharmaceuticals.^{64,65}

Future studies will offer further insights into vaping's potential to increase smoking cessation.

Interpreting both the existing evidence and future research will require awareness that the technology itself is evolving rapidly. Much of the research to date reflects the impact on smoking cessation of vaping earlier generations of e-cigarettes. If newer generations prove to be superior, in terms of their delivery of nicotine or simply their appeal to smokers, their ability to help smokers quit may be enhanced.

THE IMPACTS OF NATIONAL ATTITUDES TOWARD ALTERNATIVE NICOTINE DELIVERY SYSTEMS

Different countries approach e-cigarettes with different attitudes and policies. For example, the British support the use of e-cigarettes for cessation for smokers who have not succeeded in quitting through more conventional means. Public Health England,¹² the Royal College of Physicians,¹³ the British Psychological Society,⁶⁶ and the British Medical Association⁶⁷ have endorsed this position.

In contrast, US government agencies^{47,68} have heavily emphasized e-cigarettes' potential risks for both children and adults. So too have mainstream non-governmental tobacco control organizations.⁶⁹ The same has been true of the treatment of smokeless tobacco products. Communications about the risks of both e-cigarettes and smokeless tobacco focus on the products' potential dangers, failing to provide information on their harms relative to smoking. The communications may contribute to consumers' misperceptions of the alternative products' dangers.⁷⁰

Campaigns embodying such themes work. American consumers significantly overestimate the actual dangers of both smokeless tobacco and e-cigarettes compared to the dangers of smoking. For example, nearly two-thirds of respondents to a 2017 US National Cancer Institute survey did not believe that some smokeless tobacco products are less harmful than cigarettes. Only 12% knew the right answer.⁷¹ Yet smokeless tobacco's health risks pale in comparison with those of smoking.^{14,70} The most heavily publicized and most widely recognized smokeless tobacco risk is oral cancer. But the risk of oral cancer appears to be far greater from smoking⁷² than from smokeless.⁷³ More generally, and especially referring to the newer low-nitrosamine forms of smokeless, the overall mortality risk of smokeless is no more, and quite likely less, than 10% that of cigarette smoking.^{14,74} The cancer risk associated with the low-nitrosamine products may be statistically indistinguishable from zero, as appears to be the case with Swedish snus.¹¹ Yet two-thirds of American adults do not understand that smokeless is at all less dangerous than smoking.

The situation is similar for e-cigarettes. Over time, continual emphasis on the possible dangers of e-cigarettes has increased adults' perception that e-cigarettes are more hazardous relative to smoking than they are in fact. In 2012, early in e-cigarette popularity, 11.5% of adult respondents to a national survey considered the harm associated with e-cigarettes "about the same" as that of smoking. Three

years later 35.7% held that erroneous belief. By 2015, those who responded “less harmful” – the correct answer – had declined by nearly a quarter.⁷⁵

Smokers who perceive e-cigarettes or smokeless tobacco as being as harmful as smoking are less likely to use them in attempts to quit smoking.⁷⁶

COMPARING THE POTENTIAL RISKS OF E-CIGARETTES WITH THEIR POTENTIAL BENEFITS

The fundamental conundrum remains: E-cigarettes’ opponents believe they pose a serious risk to the health and wellbeing of children, and possibly to adults as well. E-cigarettes’ supporters perceive an opportunity to significantly reduce smoking and its enormous toll of disease and death.

With definitive evidence on these beliefs possibly years into the future, several researchers have turned to simulation modeling as a method of developing quick insights into the likely implications of e-cigarettes (and other ANDS).^{15,77-88} Most find the benefits of e-cigarettes considerably exceeding the costs. A couple of studies have demonstrated, however, that relatively modest risk reductions of vaping relative to smoking (e.g., half the risk of smoking) and significant uptake of the new product could shift simulation findings from positive to negative.^{77,79} So too can assuming that vaping has little to no benefit to smoking cessation.⁸⁷ The modeling chapter in the recent report of the National Academies of Science, Engineering, and Medicine¹⁵ covered a wide range of alternative assumptions that correspondingly led to a wide range of outcomes. However, the committee ultimately concluded that under the most plausible scenarios, vaping likely represents a net positive contribution to public health.⁸⁹

In a new study,⁸⁸ David Mendez and I assessed the public health implications in the US over 50 years if the principal beliefs of *both* e-cigarette enthusiasts and skeptics held. That is, vaping increased both smoking cessation and initiation. The study also evaluated the implication of vaping posing significant health risks for individuals who quit smoking with e-cigarettes. Under a variety of assumptions, including

several that were intentionally unfavorable to e-cigarettes, the analysis found that the potential life-years saved due to increased smoking cessation substantially outweigh the possible life-years lost due to increased smoking initiation. Only if e-cigarettes did not increase smoking cessation, or decreased it, would e-cigarettes represent a net public health loss. The best evidence is not consistent with that outcome.

As with most of the previous simulation analyses, we interpreted our findings as indicating that e-cigarettes likely represent an excellent THR opportunity. We noted as well that the public health benefit of e-cigarettes could be considerably higher than estimated if vaping increased smoking cessation by more than assumed in the analysis. That could occur as products improve, as knowledge about how they can assist in cessation increases, and as new communications effectively explain how best to use the products for cessation.

The upside potential of e-cigarettes would benefit from public health organizations focusing on the positives of e-cigarette use by adult smokers, rather than concentrating narrowly on the risks, as in the US today. As we observed in our paper, “[P]ublic messaging and policy should strive to reduce [young people’s] exposure to all nicotine and tobacco products. But they should not do so at the expense of limiting such products’ potential to help adult smokers to quit...[T]hat cost is too high.”⁸⁸

POLICY AND REGULATION

E-cigarette enthusiasts and skeptics advocate different directions for policy and regulation. A few central differences are identified below. Space precludes a more detailed analysis.^{21,47,90}

Vaping in public places

E-cigarette skeptics want vaping banned wherever smoking is banned, to protect people from “second-hand vapor” and to protect adolescents from exposure to the practice of vaping. Enthusiasts want decisions about vaping left to individual proprietors. Enthusiasts perceive little to no risk associated with second-hand vapor and believe that the ability to vape in public places might encourage smokers to switch. Skeptics respond that permitting vaping where smoking is prohibited could allow smokers to sustain their smoking addiction instead of quitting.

Taxation

Both sides agree that tobacco cigarettes should be taxed heavily, given the enormity of their risk. E-cigarette skeptics want high taxes on e-cigarettes as well, primarily to discourage their use by adolescents. Enthusiasts advocate no taxes or much lower taxes, reflecting the large difference in risk. A big tax and hence price differential could move some smokers to vaping.⁹¹

Information dissemination

As discussed previously, in the US e-cigarette opponents have dominated public communications with their focus on vaping’s risks for adolescents and uncertainty about the risks to adult users. Supporters want much more information disseminated on the *relative* risks of e-cigarettes and other ANDS. They believe that emphasis on relative risks would encourage more adult smokers to use alternative products to quit smoking. They observe, as well, that public health authorities have a moral imperative to be honest with the public.⁷⁰

Product regulation

The task of determining the products permitted on the market, and their characteristics, falls to regulatory agencies. Since the signing of the Tobacco Control Act in 2009, the Food and Drug

Administration (FDA) has possessed the authority to regulate tobacco products in the US. To date it has exercised that authority only in minor ways that have likely contributed little to promoting public health.

Both sides of the e-cigarette divide want regulation of e-cigarettes and other ANDS. Some specific regulations are favored by all, for example requiring child-proof containers of e-juice and ensuring that vaping devices will not explode. More generally, however, THR advocates and opponents have stark differences about the desired nature of FDA regulation. E-cigarette skeptics support the current regulatory process, which requires lengthy, detailed submissions that prove novel products' safety and public health benefit. They believe the demanding standards and review process will ensure that undesirable novel products, which might introduce new risks, will be kept off the market. (For more on the FDA review requirements, see the agency's website.⁹²)

In contrast, e-cigarette supporters believe the agency has created enormous regulatory hurdles to the authorized marketing of novel ANDS, with e-cigarettes the poster child. They perceive the new product approval process as prohibitively expensive for all but the major tobacco companies. As such, they fear, regulation will stifle innovation, reducing the potential for novel ANDS to replace smoking in the future, thereby prolonging the smoking disease pandemic. E-cigarette supporters favor light-touch regulation of ANDS, including product standards to promote safety and far less onerous new product review procedures. THR supporters argue that regulations should impose the most substantial regulatory burdens on the most harmful products, cigarettes and other combustible tobacco products. Currently, those products are subject to little meaningful regulation.

A few product regulation issues have produced specific debates, for example whether flavors in e-cigarettes should be restricted. E-cigarette opponents have emphasized that flavors attract adolescents to vaping, much as adolescents were attracted to flavored tobacco products, now banned in the US

(except for menthol). E-cigarette supporters note that the most ardent adult vapers like to use a variety of flavors, many claiming that was essential to their quitting smoking with e-cigarettes.

Nicotine reduction in cigarettes to non-addicting levels

On July 28, 2017, FDA announced a new comprehensive nicotine and tobacco regulation plan.⁹³ The most controversial element concerns the idea of requiring the reduction of nicotine in cigarettes to levels not capable of sustaining addiction. While the Tobacco Control Act prohibited FDA from requiring the removal of all nicotine, it encouraged product standards and was silent on nicotine reduction. The commissioner called for an examination of this regulation.

Nicotine reduction would constitute the first cigarette product standard that might substantially reduce smoking and its enormous toll. Logically the regulation would have to be extended to all combustible tobacco products to avoid substitution of other smoked products for cigarettes. If adopted, nicotine regulation would reinforce the need for ANDS that could provide nicotine-dependent smokers with viable alternatives to smoking. FDA implicitly noted this in identifying the need to encourage innovation in nicotine delivery.

CONCLUSION

Harm reduction is not the answer to the devastation wrought by smoking. Rather, it holds the potential to complement tried-and-true evidence-based prevention and cessation interventions. Harm reduction, with all of its political and scientific complexity, will be with us for the foreseeable future. We need to examine all dimensions of the issues, consider both costs and benefits, and do so in a balanced, non-emotional manner.

As with previous examples of public health harm reduction we cannot know in advance, with absolute certainty, that e-cigarettes, or THR more generally, is unequivocally desirable. So we have to go with the best available evidence. Lives are at stake. What does that best evidence indicate?

- Adolescents are giving up tobacco, at an unprecedented rate;
- E-cigarettes appear to be increasing smoking cessation;
- And even if vaping causes some never-smoking adolescents to try smoking, a moderate rate of increased smoking cessation by adults makes e-cigarettes a net public health good.

We need more definitive understanding of the risks of e-cigarettes and other ANDS relative to cigarette smoking. We need stronger evidence on their effects on smoking initiation and cessation. Importantly, we need to assess that evidence in a fair and objective manner, and to move forward together toward the elimination of tobacco's harms.

That, after all, is the THR goal shared by every single tobacco control professional.

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DECLARATION OF INTERESTS

The author declares that he has no conflicts of interest relevant to this study.

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REFERENCES

1. Harm Reduction International. What is harm reduction? A position statement from Harm Reduction International. Available at <https://www.hri.global/what-is-harm-reduction>. Accessed November 11, 2017.
2. Abrams DB, Glasser AM, Pearson JL, Villanti AC, Collins LK, Niaura RS. Harm minimization and tobacco control: reframing societal views of nicotine use to rapidly save lives. *Ann Rev Public Health*. 2018;39:193-213.
3. Marlatt GA, Larimer ME, Witkiewitz K, eds. *Harm Reduction: Pragmatic Strategies for Managing High-risk Behaviors*, 2nd ed. New York: The Guilford Press, 2012.
4. Glantz SA, Slade J, Bero LA, Hanauer P, Barnes DA. *The Cigarette Papers*. Berkeley, CA: University of California Press, 1996.
5. Pollay RW, Dewhirst T. The dark side of marketing seemingly “Light” cigarettes: successful images and failed fact. *Tob Control*. 2002;11(Suppl I):i18–i31. doi:10.1136/tc.11.suppl_1.i18
6. Longo WE, Rigler MW, Slade J. Crocidolite asbestos fibers in smoke from original Kent cigarettes. *Cancer Research*. 1995;55(11):2232–2235.
7. Thun MJ, Burns D. Health impact of “reduced yield” cigarettes: a critical assessment of the epidemiological evidence. *Tob Control*. 2001;10(Suppl I):i4–i11.
8. Huet N. WHO’s strategy to put Big Tobacco ‘out of business’. *Politico*. May 13, 2016. Available at <https://www.politico.eu/article/the-whos-strategy-to-put-big-tobacco-out-of-business-margaret-chan-tax-cigarettes-labeling-rules-trade/>. Accessed December 6, 2017.
9. Public Health Agency of Sweden. Tobacco. Available at <https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/living-conditions->

and-lifestyle/alcohol-narcotics-doping-tobacco-and-gambling/tobacco/. Accessed December 5, 2017.

10. Ramström L, Wikmans T. Mortality attributable to tobacco among men in Sweden and other European countries: an analysis of data in a WHO report. *Tobacco Induced Diseases*. 2014;12:14. doi:10.1186/1617-9625-12-14
11. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control*. 2003;12(4):349-359. doi:10.1136/tc.12.4.349
12. McNeill A, Brose LS, Calder R, Bauld L & Robson D. Evidence review of ecigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf. Accessed April 8, 2018.
13. Royal College of Physicians. Nicotine without Smoke: Tobacco Harm Reduction. A Report by the Tobacco Advisory Group of The Royal College Of Physicians. London, April 2016. Available at <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>. Accessed December 5, 2017.
14. Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. *European Addiction Res*. 2014;20(5):218-225. doi:10.1159/000360220
15. National Academies of Sciences, Engineering, and Medicine. 2018. Public health consequences of e-cigarettes. Washington, DC: The National Academies Press. doi:10.17226/24952.

16. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Annals Int Med*. 2017;166(6):390-400. doi:10.7326/M16-1107
17. Farsalinos K, Cibella F, Caponnetto P, et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern Emerg Med*. 2016;11(1):85-94. doi:10.1007/s11739-015-1361-y
18. Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, Bruno CM. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir Res*. 2016;17(1):166. doi:10.1186/s12931-016-0481-x
19. Glantz SA, Bareham DW. E-cigarettes: use, effects on smoking, risks, and policy implications. *Ann Rev Public Health*. 2018;39:215-235.
20. Kozlowski LT, Strasser AA, Giovino GA, Erickson JA, Terza JV. Applying the risk/use equilibrium: use medicinal nicotine now for harm reduction. *Tob Control*. 2001;10(3):201-203. doi:10.1136/tc.10.3.201
21. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: a systematic review. *AJPM*. 2017;52(2):e33-e66. doi:10.1016/j.amepre.2016.10.036
22. Benowitz NL, Fraiman JB. Cardiovascular effects of electronic cigarettes. *Nat Rev Cardiol*. 2017;14(8):447-456. doi:10.1038/nrcardio.2017.36
23. English Oxford Living Dictionaries. Definition of precautionary principle. Available at https://en.oxforddictionaries.com/definition/us/precautionary_principle. Accessed December 5, 2017.
24. Chowkwanyun M, Wolfe D, Colgrove J, Bayer R, Fairchild AL. Beyond the precautionary principle: protecting public health and the environment in the face of uncertainty. In: Macpherson C, ed.

Bioethical Insights into Values and Policy. Public Health Ethics Analysis. 2016;4. Springer, Cham.
doi:10.1007/978-3-319-26167-6_11

25. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Electronic nicotine delivery systems: report by WHO (page 10, paragraph 33). September 1, 2014. Available at http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10Rev1-en.pdf. Accessed December 6, 2017.
26. Kandel DB, ed. Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis. Cambridge, England: Cambridge University Press, 2002.
27. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatr. 2017;171(8):788-797. doi:10.1001/jamapediatrics.2017.1488
28. Soneji S. Errors in data input in meta-analysis on association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults. JAMA Pediatr. 2018;172(1):92-93. doi:10.1001/jamapediatrics.2017.4200
29. Kozlowski LT, Warner KE. Adolescents and e-cigarettes: objects of concern may appear larger than they are. Drug Alcohol Dependence. 2017;174:209–214.
doi:10.1016/j.drugalcdep.2017.01.001
30. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatr. 2015;169(11):1018–1023. doi:10.1001/jamapediatrics.2015.1742
31. Spindle TR, Hiler MM, Cooke ME, Eissenberg T, Kendler KS, Dick DM. Electronic cigarette use and uptake of cigarette smoking: a longitudinal examination of U.S. college students. Addict Behav. 2017;67:66–72. doi:10.1016/j.addbeh.2016.12.009

32. Wills TA, Knight R, Sargent JD, Gibbons FX, Pagano I, Williams RJ. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tob Control*. 2016;(1):34–39. doi:10.1136/tobaccocontrol-2015-052705
33. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700–707. doi:10.1001/jama.2015.8950
34. Unger JB, Soto DW, Leventhal A. e-Cigarette use and subsequent cigarette and marijuana use among Hispanic young adults. *Drug Alcohol Depend*. 2016;163:261–264. doi:10.1016/j.drugalcdep.2016.04.027
35. Barrington-Trimis JL, Urman R, Berhane K, et al. e-Cigarettes and future cigarette use. *Pediatrics*. 2016;138(1):e20160379. doi:10.1542/peds.2016-0379
36. Villanti AC, Pearson JL, Glasser AM, et al. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: Measurement precision is critical to inform public health. *Nicotine Tob Res*. 2017;19(11):1345–1350. doi:10.1093/ntr/ntw388
37. Collins LK, Villanti AC, Pearson JL, et al. Frequency of youth e-cigarette, tobacco, and poly-use in the United States, 2015: Update to Villanti et al., ‘Frequency of youth e-cigarette and tobacco use patterns in the United States: Measurement precision is critical to inform public health’. *Nicotine Tob Res*. 2017;19(10):1253–1254. doi:10.1093/ntr/ntx073
38. Wills, T.A., Gibbons, F.X., Sargent, J.D., Schweitzer, R.J. How is the effect of adolescent e-cigarette use on smoking onset mediated: a longitudinal analysis. *Psychol. Addict. Behav*. 2016;30(8):876-886. doi:10.1037/adb0000213
39. Leventhal, A.M., Stone, M.D., Andrabi, et al. Association of e-cigarette vaping and progression to heavier patterns of cigarette smoking. *JAMA*. 2016;316,1918–1920. doi:10.1001/jama.2016.14649.

40. Miech R, Patrick ME, O'Malley PM, Johnston LD. e-Cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. *Tob Control*. Published online 2017. doi:10.1136/tobaccocontrol-2016-053291
41. Miech, R.A., Johnston, L.D., O'Malley, P.M., Bachman, J .G., Schulenberg, J.E, 2016. Vaping, hookah use by US teens declines for first time. University of Michigan News Service: Ann Arbor, MI. <http://www.monitoringthefuture.org>. Accessed on December 6, 2017.
42. Saddleson ML, Kozlowski LT, Giovino GA, Homish GG, Mahoney MC, Goniewicz ML. Assessing 30-day quantity-frequency of U.S. adolescent cigarette smoking as a predictor of adult smoking 14 years later. *Drug Alcohol Depend*. 2016;162:92–98. doi:10.1016/j.drugalcdep.2016.02.043
43. Bauld L, MacKintosh AM, Eastwood B, et al. Young people's use of e-cigarettes across the United Kingdom: findings from five surveys 2015–2017. *Int. J. Environ. Res. Public Health* 2017;14:973. doi:10.3390/ijerph14090973
44. Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students — United States, 2011–2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:597–603. DOI Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. *MMWR Morb Mortal Wkly Rep* 2017;66:597–603. doi:10.15585/mmwr.mm6623a1
45. Monitoring the Future. 2016 data from in-school surveys of 8th-, 10th-, and 12th-grade students. Tobacco press releases: text, figures, & tables. Tables 1 and 2. Available at <http://www.monitoringthefuture.org/data/16data.html#2016data-cigs>. Accessed December 7, 2017.
46. Fairchild AL, Bayer R, Colgrove J. The renormalization of smoking? E-cigarettes and the tobacco “endgame” *N Engl J Med*. 2014;370:293-295. doi:10.1056/NEJMp1313940
47. U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human

Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016. Available at https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/pdfs/2016_SGR_Chap_3_508.pdf. Accessed December 7, 2017.

48. Warner KE. Frequency of e-cigarette use and cigarette smoking by American students in 2014. *Am J Prev Med.* 2016;1(2):179–184. doi:10.1016/j.amepre.2015.12.004
49. Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the Future National Survey Results on Drug Use, 1975-2016: Volume I, Secondary School Students. Ann Arbor, MI: Institute for Social Research, The University of Michigan, 2017. Available at http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2016.pdf. Accessed December 7, 2017.
50. Tam J, Warner KE. Students' cigarette smoking and the perceived nicotine content of e-cigarettes they vape. *Amer J Prev Med.* In press.
51. Friedman AS. How does electronic cigarette access affect adolescent smoking? *J Health Econ.* 2015;44:300-308. doi:10.1016/j.jhealeco.2015.10.003
52. Pesko MF, Hughes JM, Faisal FS. The influence of electronic cigarette age purchasing restrictions on adolescent tobacco and marijuana use. *Prev Med.* 2016;87:207-212. doi:10.1016/j.ypmed.2016.02.001
53. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2016;Issue 9: Art. No.:CD010216. doi:10.1002/14651858.CD010216
54. Drope J, Cahn Z, Kennedy R, et al. Key issues surrounding the health impacts of electronic nicotine delivery systems (ends) and other sources of nicotine. *CA Cancer J Clin.* 2017;published online ahead of print. doi:10.3322/caac.21413

55. Villanti AC, Feirman SP, Niaura R, et al. How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. *Addiction*. 2017;published online ahead of print. doi:10.1111/add.14020
56. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *The Lancet Resp Med*. 2016;4(2):116-128. doi:10.1016/S2213-2600(15)00521-4
57. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: Time series analysis of population trends. *BMJ*. 2016;354:i4645. doi:10.1136/bmj.i4645
58. West R, Shahab L, Brown J. Estimating the population impact of e-cigarettes on smoking cessation in England. *Addiction*. 2016;111:1118-1119. doi:10.1111/add.13343
59. Zhu S-H, Zhuang Y-L, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ*. 2017;358:j3262. doi:10.1136/bmj.j3262
60. Levy D, Yuan Z, Luo Y, Abrams DB. The relationship of e-cigarette use to cigarette quit attempts and cessation: insights from a large, nationally representative U.S. survey. *Nicotine Tob Res*. 2017. Epub ahead of print. doi:10.1093/ntr/ntx166
61. Giovenco DP, Delnevo CD. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addictive Behaviors*. 2018;76:129-134. doi:10.1016/j.addbeh.2017.08.002

62. Berry KM, Reynolds LM, Collins JM, et al. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013–2015. *Tob Control*. 2018;online ahead of print. doi:10.1136/tobaccocontrol-2017-054108
63. Action on Smoking and Health (UK). Use of e-cigarettes (vapourisers) among adults in Great Britain. May 2017. Available at <file:///C:/Users/kwarner/Downloads/Use-of-e-cigarettes-vapourisers-among-adults-in-Great-Britain-May-2017-2.pdf>. Accessed December 7, 2017.
64. West R, Beard E, Brown J. Trends in electronic cigarette use in England. Smoking in England (the Smoking Toolkit). Reference no. STS140122. October 23, 2017. Available at <http://www.smokinginengland.info/latest-statistics/>. Accessed December 7, 2017.
65. Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. Quit methods used by US adult cigarette smokers, 2014–2016. *Prev Chronic Dis*. 2017;14:160600. doi:10.5888/pcd14.160600
66. Dawkins L, McRobbie H. Changing behavior: electronic cigarettes. British Psychological Society. 2017. Available at <https://www.bps.org.uk/sites/beta.bps.org.uk/files/Policy%20-%20Files/Changing%20behaviour%20-%20electronic%20cigarettes.pdf>. Accessed December 7, 2017.
67. British Medical Association. E-cigarettes: Balancing risks and opportunities. 2017. Available at <file:///C:/Users/kwarner/Downloads/E-cigarettes-position-paper-v3.pdf>. Accessed November 29, 2017.
68. Centers for Disease Control and Prevention. Transcript for CDC press briefing: E-cigarette use triples among middle and high school students in just one year. April 16, 2015. Available at <https://www.cdc.gov/media/releases/2015/t0416-e-cigarette-use.html>. Accessed December 7, 2017.

69. Bach L. Electronic Cigarettes and Youth. Washington, DC: Campaign for Tobacco-Free Adolescents. October 4, 2017. Available at <https://www.tobaccofreeadolescents.org/research/factsheets/pdf/0382.pdf>. Accessed November 6, 2017.
70. Kozlowski LT, Sweanor D. Withholding differential risk information on legal consumer nicotine/tobacco products: the public health ethics of health information quarantines. *International J Drug Pol.* 2016;32:17-23. doi:10.1016/j.drugpo.2016.03.014
71. National Cancer Institute. Health Information National Trends Survey. HINTS FDA Cycle 2, 2017. Available at https://hints.cancer.gov/view-questions-topics/question-details.aspx?PK_Cycle=9&qid=864. Accessed December 7, 2017.
72. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: A meta-analysis. *Int. J. Cancer.* 2008;122(1):155–164. doi:10.1002/ijc.23033
73. Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Medicine.* 2009;7:36. doi:10.1186/1741-7015-7-36
74. Levy DT, Mumford E, Cummings KM, et al. The relative risks of a low-nitrosamine smokeless tobacco product compared to smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol Biomarkers Prev.* 2004;13:2035-2042.
75. Majeed BA, Weaver SR, Gregory KR. Changing perceptions of harm of e-cigarettes among U.S. adults, 2012–2015. *Am J Prev Med.* 2017;52(3):331-338. doi:10.1016/j.amepre.2016.08.039
76. Brose LS, Brown J, Hitchman SC, McNeill A. Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug Alcohol Dependence.* 2015;157:106–111. doi:10.1016/j.drugalcdep.2015.10.014

77. Kalkhoran S, Glantz SA. Modeling the health effects of expanding e-cigarette sales in the United States and United Kingdom: a Monte Carlo analysis. *JAMA Int Med.* 2015;175(10):1671-80. doi: 10.1001/jamainternmed.2015.4209
78. Weitkunat R, Lee PN, Baker G, Sponsiello-Wang Z, González-Zuloeta Ladd AM, Lüdicke F. A novel approach to assess the population health impact of introducing a modified risk tobacco product. *Regul Toxicol Pharmacol* 2015;72:87-93. doi:10.1016/j.yrtph.2015.03.011
79. Vugrin ED, Rostron BL, Verzi SJ, et al. Modeling the potential effects of new tobacco products and policies: a dynamic population model for multiple product use and harm. *PLoS ONE.* 2015;10(3):e0121008. doi:10.1371/journal.pone.0121008
80. Cherg ST, Tam J, Christine PJ, Meza R. Modeling the effects of e-cigarettes on smoking behavior: implications for future adult smoking prevalence. *Epid.* 2016;27(6):819–826. doi:10.1097/EDE.0000000000000497
81. Levy D, Cummings K, Villanti A, et al. A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products. *Addiction.* 2017;112(1):8-17. doi:10.1111/add.13394
82. Hill A, Camacho OM. A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes. *Regul Toxicol Pharmacol.* 2017;86:265-278. doi:10.1016/j.yrtph.2017.03.012
83. Lee PN, Fry JS, Hamling JF, Sponsiello-Wang Z, Baker G, Weitkunat R. Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. *Regul Toxicol Pharmacol.* 2017;88:192-213. doi:10.1016/j.yrtph.2017.06.009

84. Poland B, Teischinger F. Population modeling of modified risk tobacco products accounting for smoking reduction and gradual transitions of relative risk. *Nicotine Tob Res.* 2017;19(11):1277-1283. doi:10.1093/ntr/ntx070
85. Bachand AM, Sulsky SI, Curtin GM. Assessing the likelihood and magnitude of a population health benefit following the market introduction of a modified-risk tobacco product: enhancements to the Dynamic Population Modeler, DPM(+1). *Risk Anal.* Published online. 2017. doi:10.1111/risa.12819
86. Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control.* 2017. Published Online First: 02 October 2017. doi:10.1136/tobaccocontrol-2017-053759
87. Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One.* 2018;online ahead of print. doi:10.1371/journal.pone.0193328
88. Warner KE, Mendez D. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine Tob Res.* 2018;online ahead of print. doi:10.1093/ntr/nty062
89. National Academies of Science, Engineering, and Medicine. Public health consequences of e-cigarettes. Webinar. January 23, 2018. Available at <http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx>. Accessed April 9, 2018.
90. Public Health Law Center. Regulating electronic cigarettes & similar devices. Tobacco Control Legal Consortium. January 2017. Available at

<http://www.publichealthlawcenter.org/sites/default/files/resources/tclc-guide-reg-ecigarettes-2016.pdf>. Accessed December 8, 2017.

91. Chaloupka FJ, Swenor D, Warner KE. Differential taxes for differential risks – toward reduced harm from nicotine-yielding products. *New Engl J Med*. 2015;373:594-597.
doi:10.1056/NEJMp1505710
92. U.S. Food & Drug Administration. Tobacco Products. Products, guidance & regulations. Available at <https://www.fda.gov/TobaccoProducts/Labeling/default.htm>. Accessed December 8, 2017.
93. U.S. Food & Drug Administration. FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death. FDA news release. Available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm>. Accessed December 8, 2017.

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Table 1. Death rates (per 100,000 population) attributable to tobacco in Sweden and other European Union countries, 2004

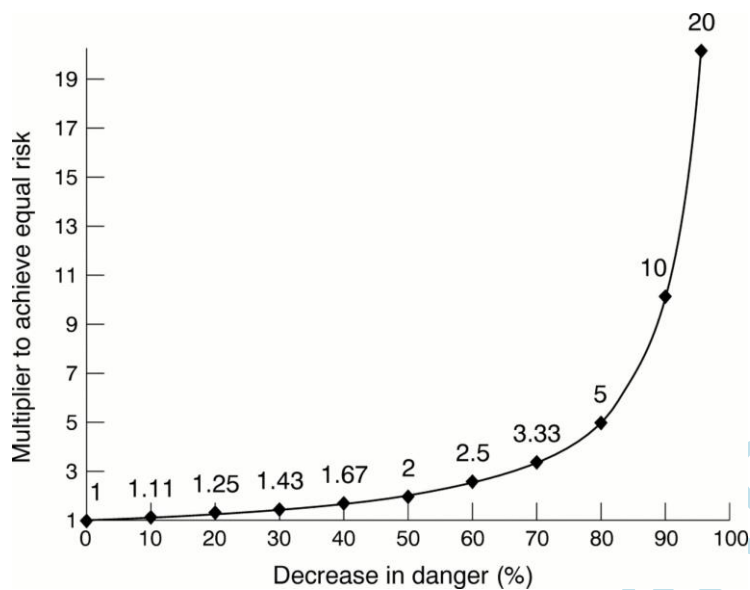
	Sweden	European Union Member States other than Sweden		
		Min	Median	Max
MEN				
Lung cancer	87	91	220	399
Other cancer	36	41	105	217
All cardiovascular	72	107	170	618
All causes	222	378	550	1388
WOMEN				
Lung cancer	61	5	39	127
Other cancer	17	1	10	39
All cardiovascular	63	5	50	222
All causes	173	14	115	690

Source: Ramstrom and Wikmans, *Tobacco Induced Diseases*, 2014¹⁰

Table 2. Areas of difference between e-cigarette enthusiasts and skeptics

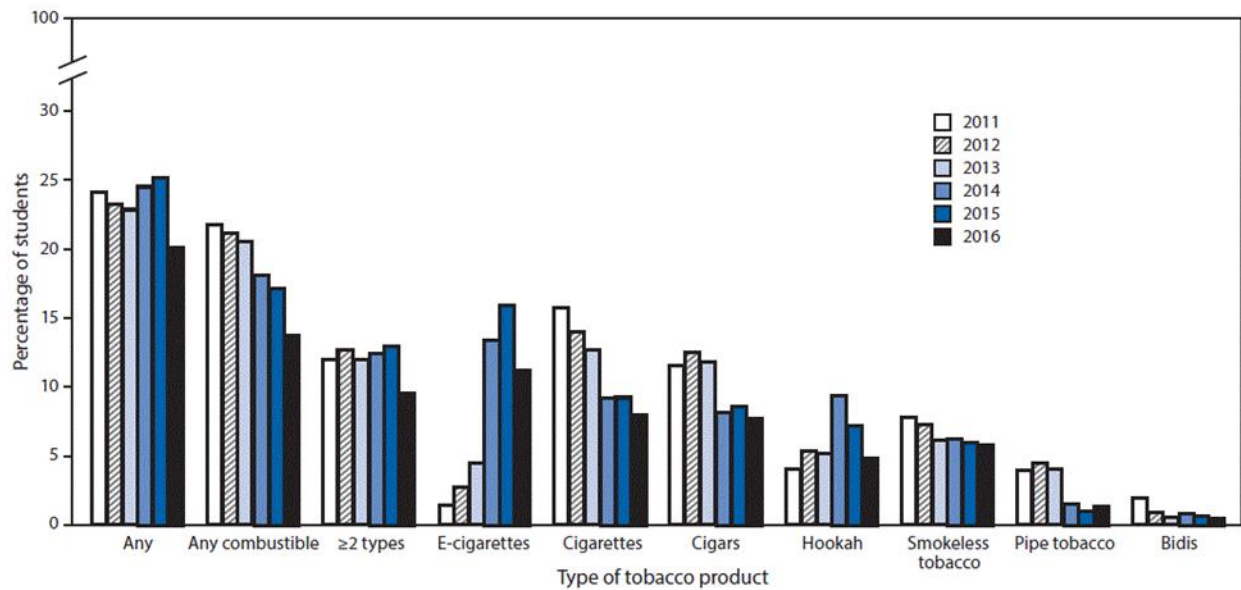
Issue	Enthusiasts	Skeptics
1. Degree of risk reduction	≥95%	Unknown; likely much <95%
2. Precautionary principle	Smoking toll requires support of novel products	Need to first prove (relative) safety & effectiveness
3. Primary articulated concern	Maximizing adults quitting smoking	Minimizing risks to adolescents
4. Nature/magnitude of risks to adolescents	Minimal; e-cigarettes may substitute for smoking	Feared substantial: gateway to smoking; renormalization; effects on developing brain
5. Impact on adult quitting	Potential to help millions	May reduce quitting
6. Long-term nicotine addiction	Acceptable if eliminates smoking	Not acceptable
7. Cigarette and e-cig companies	Open to working with them	Not to be trusted
8. Free market	Strongly support	Worry about “Wild West”
9. Scientific studies	Support/discredit	Support/discredit
10. Product regulation	Favor limited regulation that won’t disrupt innovation	Support strong regulation to ensure safety/effectiveness
11. Information dissemination	Emphasize harm reduction potential for adult smokers	Emphasize risks for adolescents and risks of dual use for adults
12. Policies, e.g., vaping where smoking prohibited; flavors; taxation	Oppose location restrictions; support flavors (to assist in adult quitting); no/low tax	Support location restrictions; oppose flavors (to reduce attractiveness to adolescents); tax

Figure 1. The risk/use equilibrium



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Figure 2. Percentage of high school students who currently use any tobacco products,* any combustible tobacco products, ≥ 2 tobacco products, and selected tobacco products — National Youth Tobacco Survey, United States, 2011–2016



* NYTS classifies e-cigarettes as tobacco products.

Source: Jamal et al.⁴⁴