From: homestead1@eoni.com [mailto:homestead1@eoni.com]
Sent: Wednesday, April 08, 2015 12:57 AM
To: LaBar James
Subject: SB 417

The Honorable Chair Lee Beyer and members of Senate Committee on Business and Transportation

I am writing in opposition to SB 417 as written as it wraps tobacco and vaping together. Vaping is not smoking and is much healthier than smoking. HB 2546 regulates vaping under Oregon Health Authority. This bill would regulate vaping under two agencies. This bill would also demonize a much safer and healthier alternative to combustible cigarettes. E liquid does not contain tobacco. It contains nicotine as do NRT patches, gum and inhalers.

I urge you to save lives! NO on SB 417!

Jack Morton
501 W Park St.
Enterprise, OR.

(http://thevitalityinstitute.org)

In The News (http://thevitalityinstitute.org/news-type/in-the-news/)

'Smoking Kills, Nicotine Doesn't': A Huge Boost for Campaigners who say E-Cigs Save Lives

The Spectator Blog (http://blogs.spectator.co.uk/damian-thompson/2015/02/smoking-kills-nicotines-doesnt-a-huge-boost-for-the-campaign-to-promote-e-cigarettes/) | Feb 19, 2015

By Damian Thompson

Dr Derek Yach has done more than any man alive to eradicate smoking. A former professor of global health at Yale, he developed the World Health Organisation's Framework Convention on Tobacco Control, now in effect in almost 180 countries. He has relentlessly drawn attention to the slippery tactics of the tobacco industry, which promotes its products while ostensibly lending its support to anti-smoking campaigns.

But his article in today's *Spectator Health* (http://www.spectator.co.uk/health/features-health/cover-feature/9442271/e-cigarettes-save-lives/) breaks ranks with former colleagues in the WHO, which

disapproves of e-cigarettes and other vaping products. Their 'intransigence' threatens the lives of millions, he argues. As matters stand, a billion people will die from smoking-related diseases by 2100. If that happens, the WHO will bear some of the responsibility.

But Dr Yach goes further. His article accuses the WHO of allowing anti-vaping lobbyists to twist its arm. Here's the paragraph that will have anti-vapers hyperventilating this morning (my emphasis in bold):

> Why are we in this position? One reason is that governments have become addicted to tobacco excise tax and may fear that, as e-cigs take off, they will lose a valuable source of revenue. **Many leading NGOs and academics exert strong influence at WHO, within governments, in the media and among the general public.** In the past, they helped bring tobacco control out of the shadows and into the mainstream of health policy. Now, alas, their intransigence threatens more profound progress.

Full disclosure: Dr Yach is executive director of the Vitality Institute for Health Promotion, and Vitality (https://www.vitality.co.uk/)are the *Spectator's* partners in producing today's*Spectator Health* supplement. None of us has any commercial interest in promoting e-cigarettes; indeed, the article demands far greater transparency from e-cig maufacturers. In more than 30 years of doing battle with tobacco companies, Dr Yach – who advises the Clinton Global Initiative and the World Economic Forum – has learned to distrust assurances from *every* producer of nicotine products.

His support for electronic cigarettes and vaping products rests on what he regards as the stark truth: that they help people quit smoking more effectively than other remedies. It is therefore not just unfortunate but scary that the World Health Organisation persists in treating them as if they were almost as dangerous as cigarettes.

Many medical professionals endorse this view – that vaping hooks young people on nicotine and create new addicts. Dr Yach's response? *Prove it*. Because, in his opinion, they haven't:

> Unsupported statements are accepted as truth by policymakers and are used as the basis for stringent regulation of e-cigs in many jurisdictions.

Derek Yach is not alone in his view. He quotes the Royal College of Physicians: 'Switching completely from tobacco to e-cigarettes achieves much the same in health terms as does quitting smoking and all nicotine use completely. Furthermore… risks associated with passive exposure to e-cigarette vapour are far less than those associated with passive exposure to tobacco smoke.'

Today's article raises troubling questions. One immediately springs to mind. What, precisely, is the relationship between Big Pharma and regulatory bodies that stubbornly refuse to deploy e-cigarettes as a devastatingly effective anti-smoking weapon?

Let's be clear about this: hundreds of millions of pounds have been invested in smoking-reduction products such as nicotine patches and chewing gum that help some people give up, but don't work in the long term for countless cigarette smokers whose habit is more stubborn. Nothing like the same investment

is going in to producing e-cigs and vaping that meet the requirement of public health authorities that they should deliver a precisely measured dose of nicotine (a pointlessly high bar to set, one might argue).

Vested interests stand in the way, though the public is mostly unaware of just how entrenched and opaque these interests are. For example, do we know how much money flows by circuitous routes from tobacco companies to anti-vaping researchers?

It's a cruel irony that many impassioned anti-smoking advocates and Big Tobacco share the same agenda of restricting access to products that unshackle smokers from their deadly habit and which have, within the past decade, rendered obsolete the old template for fighting smoking. And I use the word 'cruel' advisedly. By sticking with the status quo, we are – even if unintentionally – shrugging off the prospect of a billion early deaths this century. That's an awful lot of widows.

To access original post, click here (http://blogs.spectator.co.uk/damian-thompson/2015/02/smoking-kills-nicotines-doesnt-a-huge-boost-for-the-campaign-to-promote-e-cigarettes/).

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VIEWPOINT

Promise and Peril of e-Cigarettes
Can Disruptive Technology Make Cigarettes Obsolete?

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Despite extraordinary success, progress has stalled in reducing premature deaths from tobacco (primarily caused by cigarettes or other combusting tobacco products and not by nicotine per se). The dominance of cigarettes over the past 100 years (the cigarette century) threatens to persist for another century.

Two philosophies have dominated tobacco control: abstinence and harm reduction. Abstinence implies avoiding all tobacco use behavior because there is no safe tobacco or nicotine level. If avoidance is not practical or realistic, harm reduction sets a goal that minimizes the harm caused by the behavior. Tension between reduction and abstinence advocates can be divisive. The rapid rise in the use and popularity of e-cigarettes has substantially increased this tension because of their potential for harm reduction. Although still variable in quality, appeal, and efficient nicotine delivery, e-cigarettes represent an evolving frontier, filled with promise and peril for tobacco control practitioners, policy makers, and regulators.

This Viewpoint examines the promise, from a harm reduction perspective, and the peril, from an abstinence perspective—represented by e-cigarettes and asks the question "Do e-cigarettes represent a breakthrough disruptive technology, able to render the combustion of tobacco obsolete, potentially ending the combustion-related morbidity and mortality that has been characterized by the cigarette century?"

The Advent of e-Cigarettes

Whether e-cigarettes deliver promise or peril depends on a complex dynamic interplay among the industries marketing e-cigarettes (independent makers and tobacco companies), consumers, regulators, policy makers, practitioners, scientists, and advocates. The public health standard for evaluating e-cigarettes is a critical yardstick because it considers both individual (safety and efficacy) and public health outcomes in terms of the likelihood of harms vs benefits to the population. Although there is insufficient scientific evidence to fully inform the standard, the increasing evidence to date points to an opportunity of a new class of safer, but very appealing, nicotine delivery technologies that could favor the speedy obsolescence of conventional cigarettes.[1-3]

The popularity of e-cigarettes is obvious. e-Cigarette revenues have doubled every year since 2008 and are projected to reach $2 billion in 2013.[4] Adult use among smokers doubled to 20% from 2010 to 2011; experimental use among teens increased from 1.1% to 2.1% in 2011-2012.[5,6] Even without clear evidence of efficacy, use of e-cigarettes for cessation or harm reduction purposes in England has exceeded nicotine replacement therapy (NRT).[7] The free market suggests there is pent-up interest in products that deliver cleaner nicotine in a safe, appealing mode. Whether this can be translated into a sustained disruptive technology depends on factors including innovation of better products, enhanced labeling and marketing, and appropriate regulation and policy implementation.

US Food and Drug Administration Regulation

Product regulation is essential to minimize unintended consequences and to appropriately reassure consumers. However, regulations should not be so burdensome as to stifle innovation and independent manufacturers.[3,8-10] A comprehensive nicotine regulatory policy is needed from the US Food and Drug Administration (FDA). Embracing harm reduction, the director of the FDA's Center for Tobacco Products (CTP) proposed a continuum of risk, with combustible products (eg, cigarettes, cigars, and hookahs) posing the most hazard and NRTs posing the least.[9,10] Tobacco control should be based on proportional risk that strongly discourages combusting tobacco and encourages smokers who cannot quit to use safer forms of nicotine including more flexible uses of over-the-counter NRTs.

Assuming appropriate scientific studies are completed (to validate degree of harm reduction, cessation efficacy, craving reduction, and relapse prevention), e-cigarettes could be approved under the Center for Drug Evaluation and Research (CDER) and by CTP to maximize the promise and minimize potential risk of these products, but preferably with premarket requirements that are not overly burdensome for provisional approval by either the CTP or by the CDER. Simultaneously CTP regulation can also be used to make conventional cigarettes less appealing and satisfying using product standards to reduce the nicotine levels in these cigarettes to nonaddictive, nonzero levels, as permitted by law.

A balance between underregulation and overregulation is achieved by flexible and discretionary use of product standard, modified risk, and cessation regulations. Aggressive postmarketing surveillance should be used to detect unintended consequences.[1-3,8-10] Applying overly burdensome, expensive regulatory hurdles to e-cigarettes could stifle innovation and favor the market domination of tobacco companies, which potentially promote dual use of cigarettes and e-cigarettes to minimize losing market share for their primary cigarette products. Independent e-cigarette companies (ie, not subsidiaries of tobacco companies) are more likely to have the goal of eliminating combusted cigarettes.[8]

Federal and State Tobacco Control Policy and Practice

Other approaches to achieve maximal benefit of e-cigarettes would follow the proportional risk frame-

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work. e-Cigarettes and some noncombustible nicotine delivery products can be used as part of a harm reduction strategy, as a reduce-to-eventually-quit strategy, as a cessation strategy, or to prevent relapse back to smoking.

Federal and State Taxation

Taxes should be proportional to harms and should include, for example, health care subsidies and full insurance coverage for long-term NRT (even for a lifetime); no or minimal tax on e-cigarettes or Swedish-type snus, and a doubling or tripling of the current tax on all combustible tobacco products.

Indoor Air and Public Restrictions

At present there is little research basis for or against restrictions. Studies of secondhand vapor from e-cigarettes show minimal known harmful exposure compared with conventional cigarettes and reasonable indoor air standards.[8] The potential concern is that e-cigarettes undermine denormalization of smoking. Harm reduction advocates point out that people can readily see these products are not conventional cigarettes and that e-cigarettes are a mechanism to quit smoking rather than prolonging it. Thus, e-cigarettes are a gateway out of smoking and may further denormalize smoking and normalize safer alternatives.[8] The risk of unintended consequences must be monitored. The concern is if most smokers use e-cigarettes as a "bridge" to alleviate craving only when they cannot smoke or to delay cessation, then net population harms might possibly exceed benefits even if some individual users benefit.

Practitioners in Health Care and Public Health

Clinicians counseling patients about smoking cessation should first recommend FDA-approved, evidence-based treatments for cessation. However, for smokers who cannot quit, clinicians could point out the reduced harms associated with noncombusted nicotine products. Assuming FDA regulation, exclusive use of noncombusted, nicotine-containing products like e-cigarettes and Swedish snus with low nitrosamines[10] is preferable to any combusted tobacco use (eg, cigarettes, cigars, pipes, and hookahs).

The Appeal to Youth

Tobacco products of any kind should not be sold to persons younger than 18 years. Young people should not be targets of marketing for any tobacco products. Products should not be made attractive to youth. Advertising should not resemble in any way the old approach of tobacco companies (eg, the use of cartoon characters like Joe Camel). Aggressive surveillance and enforcement at every level of tobacco control and at point-of-sale by the FDA is clearly warranted. According to the public health standard, restriction of sales and advertising to minors minimizes the potential harms of potential use by minors, offsetting the net benefits of having minimal restrictions on adults so that e-cigarettes remain attractive, accessible, and appealing to cigarette users to accelerate making conventional cigarettes obsolete.

Conclusions

The more appealing e-cigarette innovations become, the more likely they will be a disruptive technology. Although the science is insufficient to reach firm conclusions on some issues, e-cigarettes, with prudent tobacco control regulations, do have the potential to make the combusting of tobacco obsolete. Strong regulatory science research is needed to inform policy. If e-cigarettes represent the new frontier, tobacco control experts must be open to new strategies. Statements based on ideology and insufficient evidence could prevent the use of this opportunity before it becomes established as part of harm reduction strategy. Overly restrictive policies by either the FDA, the states, and tobacco control advocates might support the established tobacco industry, whose rapid entry into the marketplace and history of making potentially misleading claims of harm reduction could promote poly-use of all their tobacco products, and thus perpetuate sales of conventional cigarettes well into the next century rather than speed their obsolescence.

Independent manufacturers of e-cigarettes could compete with tobacco companies and make the cigarette obsolete, just as digital cameras made film obsolete. Use of noncombusted nicotine products is preferable to perpetuating the use of combustible cigarettes and a second cigarette century. The stakes are high, with an estimated 430 000 premature deaths associated with tobacco use per year in the United States and more than 1 billion expected deaths associated primarily with combusted tobacco use worldwide by the next century.[11] The central question is whether e-cigarettes should be aggressively supported by tobacco control in what already appears to be its free market significant rise as a disruptive technology—an extraordinary opportunity to end the cigarette century well before the 100th anniversary of the surgeon general's report on smoking and health in 2064.

ARTICLE INFORMATION

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Promise vs perils of electronic cigarettes

BMC Medicine

COMMENTARY Open Access

Electronic cigarettes have a potential for huge public health benefit

Peter Hajek

Abstract

Although there is no doubt that smokers switching to electronic cigarettes (EC) substantially reduce the risk to their health, some tobacco control activists and health organisations discourage smokers from using EC and lobby policy makers to reduce EC use by draconian regulation.

The hostility to EC may be related to a moral belief that nicotine use should be eradicated rather than allowed to morph into a relatively harmless activity. If EC are allowed to compete with cigarettes and develop further, smoking is likely to all but disappear. Discouraging smokers from making the switch and reducing EC competitiveness with cigarettes by unwarranted regulation will delay this opportunity or squander it altogether.

In fact, there is now sufficient evidence available for health professionals to recommend to smokers who cannot stop smoking with existing treatments or do not want to do so, to try several types of e-cigarettes to see if they can find one meeting their needs.

Keywords: E-cigarettes, Nicotine, Public health, Controversy

Introduction

Electronic cigarettes controversy

Electronic cigarettes (EC) are a consumer product appealing to smokers looking for a safer way to obtain what they want from their cigarettes. From what we know about EC ingredients, toxicology and the chemical and physical processes involved, they can be expected, outside pregnancy, to be at least 95% less harmful than cigarettes [1]. There is now a sufficient body of evidence available on several aspects and effects of EC for recent reviews to conclude that health care professionals and public health bodies should encourage smokers who cannot stop smoking using available treatments, or do not want to do so, to switch to EC [2,3].

Yet at the same time, the World Health Organisation (WHO) have labelled EC a threat to public health, issued a strong advice to smokers not to use them [4], and urges policy makers to limit their use by prohibition or strict regulation [5]. This and other negative campaigns are starting to have an alarming effect of persuading smokers that EC are as harmful as cigarettes [6] and discouraging them from making the switch [7,8].

This commentary argues that EC have a potential to generate substantial public health benefits and that discouraging smokers from using them and regulating EC as severely as cigarettes, or even more severely, is detrimental to public health.

There are manifest humane and logical reasons to encourage smokers who cannot or do not want to stop smoking but want to limit the damage smoking may do to their health to switch to EC. Here is the straightforward case:

There are currently two main products competing for smokers' custom. One, the conventional cigarette, is responsible for disease and premature death in a substantial proportion of its users. It also continues to recruit new customers from among non-smoking children who try it. The other, EC, is orders of magnitude safer. On current evidence it only appeals to smokers and generates negligible rates of regular use among non-smoking children who try it. Which one would you prefer your nicotine addicted father to use? And if your children were to try a nicotine product, which of these two would you prefer that they lay their hands on?

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Evidence and agendas

For the past few years, scientific journals have been publishing a large volume of commentaries on the EC phenomenon. Most of these focus on hypothetical concerns. Although all commentators now acknowledge that EC are safer than cigarettes, EC are typically presented as a competitor to smoking cessation medications that is possibly less safe and that can somehow increase cigarette use, rather than as a consumer product that competes with cigarettes, and that can make its deadly competitor obsolete.

Some medical organisations which are supposed to protect public health, such as WHO, go further and actively discourage smokers from using EC while lobbying for restricting EC use by regulation. The WHO stance is underpinned by a review they commissioned [9] that has been criticised for an unorthodox use of evidence [10] and illustrates well the anti-EC arguments. Findings that EC vapour contains traces of toxicants is interpreted as a sign of danger and even as a threat to bystanders, even if the levels of these chemicals are well within limits considered safe in the air we breathe [2,11]. Surveys showing that a small proportion of children experiment with EC are presented as a sign of the 'gateway' risk despite the fact that virtually no non-smokers progress to daily EC use and that smoking in youth is declining [12]. Where it fits with the negative agenda, trying EC once in the past month is labelled as 'current use' which by analogy with 'current smoking' is typically interpreted as daily use. Surveys which include only smokers who did not find EC helpful and exclude EC users who stopped smoking are presented as a proof that EC are unhelpful. 'Dual use' is presented as a sign of danger despite the fact that it leads to reduced toxin intake [2]. The toxicity of nicotine is exaggerated [13] and the evidence that it makes little if any contribution to smoking related disease and death [14,15] is ignored. Concerns about the twisting of evidence for ideological ends have generated an exchange of letters by large groups of researchers and activists [16-18]. Given the visibility and influence of the activists and medical organisations opposing EC use, there is a risk that these campaigns will discourage or even bar large numbers of smokers around the world from the unquestionable benefits of switching from smoking to vaping. Indeed, alarming signs are emerging that smokers who could benefit from switching to EC now increasingly believe EC are dangerous and they might as well stick to the conventional cigarettes [6-8].

Why is there a controversy?

EC are a disruptive technology, threatening sales of tobacco products as well as sales of stop smoking medications and so commercially motivated opposition can be expected. The hostility to EC from some tobacco control activists, however, is puzzling. Future textbooks are likely to discuss this phenomenon at length. Here is one hypothesis.

The field of public health is not always rational. Ideology and morality can play at least as big a role as evidence and logic. Public health policies struggle with ideology in areas ranging from abortion to harm reduction strategies in drug addiction and sexually transmitted diseases. One of the possible explanations of the EC controversy is that for some tobacco control activists, any nicotine use is 'drug abuse' and abhorrent even if it were to carry no physical health risk. When encountering evidence that EC are much safer than cigarettes, do not attract non-smokers, and promise to reduce smoking-related morbidity, people with this 'moral stance' look for objections and counterarguments. Evidence is not needed to discover the truth as the truth is 'self-evident' and there is a higher purpose. Evidence is just a tool to gain converts. Nicotine use should be eradicated, not allowed to morph into an activity akin to drinking coffee. An earlier version of the WHO Report to the Framework Convention on Tobacco Control (FCTC), now off-line, betrayed its missionary ethos when it stated that the group's target is nicotine addiction (that is, nicotine use) 'independently from its source' (that is, whether it impacts physical health or not).

Nicotine use, of course, can have negative consequences even if it does not affect physical health. A proportion of users become dependent. However, compared with disease and death caused by combustible non-nicotine chemicals in tobacco smoke, this is a minor consideration. Worries about nicotine use stripped of the health risks of smoking are on par with worries about drinking coffee. Some coffee drinkers do become dependent and spend a fair amount of money and time on their habit, but this does not constitute a major public health issue. It definitely does not justify denying smokers health benefits of stopping smoking just because they would continue to use nicotine and so their conversion to the true virtue would be incomplete.

How best to appraise the impact of EC?

Negative expectations and concerns can ultimately prove to be correct, even if they were generated by irrational or commercial motives. How should we determine objectively what impact EC are having on public health? For a negative impact, EC use would have to generate an increase in use of cigarettes.

Where commentators worry about gateway effects, undermining tobacco control achievements or renormalisation of smoking, they should be understood as saying that in their opinion, EC use is generating or is likely to generate an increase in cigarette consumption. When put like this, it appears a highly improbable concern. There is no precedent for a safer technology to

increase the use of the less safe competitor. However, hard data on this issue are needed.

Emerging trends are as expected. In the UK where EC are available and taken up by sufficient numbers of smokers, quit rates are increasing and decline in smoking, especially among young people, is accelerating [19-21]. The same is happening in the US [12]. In France and Italy the decline in cigarette sales has been accelerating [22,23]. Such data, of course, cannot determine the cause of these trends. The sales of EC have so far been too low compared to sales of cigarettes for their impact to be clearly visible. More comprehensive studies of the relationship between sales of cigarettes and sales of EC are currently the number one research priority. Comparisons are needed of time trends in sales of cigarettes in countries that allow and that prohibit EC sales, and sales of cigarettes need to be plotted against sales of EC over time. This is needed urgently, before the drastic regulation of EC advocated by the tobacco and pharmaceutical industries and misguided medical organisations stops the effects of EC sales on cigarette sales unfolding and hard data emerging which could provide a rational guidance to policy.

Conclusions

Today's e-cigarettes appeal to only a fraction of the smoking population, but if they are allowed to carry on competing with cigarettes as a consumer product and innovate and evolve, there is a good chance that they will continue to improve in offering smokers what they want, cigarette sales will continue to fall, and over the next 10 years, in countries where EC are available and competitively priced, the use of combustible tobacco will virtually disappear. The public health benefit would be huge, even if recreational use of nicotine carries on. If, on the other hand, misleading public health messages discourage smokers from switching and drastic regulations stop EC evolution and make them uncompetitive, the opportunity for a dramatic reduction in smoking related disease and death will be postponed by many years or even missed altogether. Future commentators are likely to consider attempts to remove safer alternatives to cigarettes from the market unethical, however virtuous the missionaries of the nicotine eradication gospel may feel. In the meantime, clinicians facing smokers who cannot or do not want to stop smoking and who follow evidence and common sense rather than ideologically and commercially driven agendas should recommend that their patients try several types of e-cigarettes to see if they can find one meeting their needs.

Abbreviations

EC: electronic cigarettes; FCTC: Framework Convention on Tobacco Control; WHO: World Health Organisation.

Competing interests

PH received research funding from and provided consultancy to manufacturers of stop-smoking medications. He has no links with any tobacco or e-cigarette manufacturers.

Author's information

PH is Director of Health and Lifestyle Research Unit at Wolfson Institute of Preventive Medicine and of the QM branch of the UK Centre for Tobacco and Alcohol studies. His research focuses on tobacco dependence and its treatment, including studies of EC funded by MHRA, UKCTAS and NIHR.

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Contemporary Review

Do Electronic Cigarettes Impart a Lower Potential Disease Burden Than Conventional Tobacco Cigarettes?: Review on E-Cigarette Vapor Versus Tobacco Smoke

Anne Y. Oh, MS; Ashutosh Kacker, MD

Objectives/Hypothesis: Development and utilization of electronic cigarettes (ECs) resulted from the search for healthier alternatives to conventional tobacco cigarettes (TCs) and the search for alternative methods for quitting TCs. This review compares the potential disease burden presented by TC smoke to that of EC vapor.

Methods: Potential disease burden of EC vapor versus TC smoke was assessed by reviewing clinical studies that measured inhaled components. Chemicals and carcinogens produced by vapor versus smoke were compared.

Results: Studies show that EC vapors contain far less carcinogenic particles than TC smoke. Whereas ECs have the ability to reach peak serum cotinine/nicotine levels comparable to that of TCs, ECs do not cause an increase in total white blood cell count; thus, ECs have the potential to lower the risk of atherosclerosis and systemic inflammation. Use of ECs has been shown to improve indoor air quality in a home exposed to TC smoke. This reduces secondhand smoke exposure, thus having the potential to decrease respiratory illness/asthma, middle-ear disease, sudden infant death syndrome, and more. However, some studies claim that propylene glycol (PG) vapor can induce respiratory irritation and increase chances for asthma. To minimize risks, EC manufacturers are replacing PG with distilled water and glycerin for vapor production.

Conclusion: Based on the comparison of the chemical analysis of EC and TC carcinogenic profiles and association with health-indicating parameters, ECs impart a lower potential disease burden than conventional TCs.

Key Words: Electronic cigarette; vapor; vaping; tobacco cigarette; smoke; carcinogen; disease burden; second-hand smoke exposure.

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INTRODUCTION

Introduced to U.S. markets in 2007, electronic cigarettes (ECs) are a fairly new concept lacking set regulations for manufacturing and use.[1] Although this new nicotine-delivery device offers solutions to some of the health problems associated with the conventional tobacco cigarette (TC), there remains great caution and hesitation concerning its approval by the U.S. Food and Drug Administration (FDA) and the common public. EC use is novel and unfamiliar, making it difficult at this point and time to assess the long-term health effects on users (active vapers) and nonusers who are exposed to EC vapor (passive vapers). More uncertainty arises from the highly variable quality control and the lack of uniform manufacturing standards.[2,3] Finally, there is ongoing debate over the regulation of availability, purchase, and use in the United States, leaving the population conflicted about introducing a new drug delivery product that has the potential to attract young nonsmokers rather than to encourage current smokers to quit.

This review covers current research that focuses on the components and potential health risks associated with EC vapor and presents a thorough comparison of the components and known health problems of TC smoking. Acute (short-term) or chronic (long-term) and active or passive vaping on complete blood count, lung function, and myocardial function is investigated and reported to present potential disease burden.

Positive Aspects

Advocates of ECs encourage EC development and use as an alternative and supplemental method for quitting TC use. Whether ECs are used to replace nicotine therapy or to supplement it, ECs offer another form of nicotine delivery without the known adversaries of TC combustion and the resulting smoke. Some studies have shown that EC use provides a more natural way to decrease TC smoking because the act of "smoking" an EC mimics the habits surrounding TC smoking; that is, taking cigarette breaks, having an actual object to puff and produce "smoke" (vapor), and carrying (cartridge) packs around.[4]

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This is a welcome alternative to current nicotine replacement therapies such as nicotine patches and gum, which offer no solution to the physical hand–mouth motion associated with TC smoking. Furthermore, ECs have been found to reduce TC cravings for smokers and those implementing nicotine replacement therapy.[4] In addition, EC use helps quitters avoid relapse.[5,6] Above all positives, ECs do not require the combustion of chemicals to attain a TC-comparable dose of nicotine. The single most harmful aspect of TC use is the combustion of chemicals. Upon burning, TCs release thousands of carcinogens in the form of smoke into the air, where it is exposed to smokers and nonsmokers. EC has the potential to diminish secondhand smoke exposure to nonsmokers and children of smokers while satisfying nicotine cravings.[4,7,8]

Negative Aspects

ECs have received negative attention for several valid reasons. A major concern is that current TC smokers will use ECs to cope in nonsmoking environments and will continue smoking TC in smoking-designated areas; something known as dual use.[4] Another concern is that ECs could become an attractive starter product for young nonsmokers who were initially turned off by the consequences of TC.[4] The claims made by EC could be the tipping factor for those sitting on the fence to start nicotine use and could cause a gateway effect. Furthermore, many criticize the fruit-flavored and other appetizing flavors of EC cartridges, claiming that this is an attractant for young nonsmokers. There is also concern that ECs may become the reason that many smokers forego traditional cessation methods that have a history of effectiveness.[4]

Furthermore, several studies have presented data indicating the challenge of effective EC vaping. This means that many users have difficulty extracting the nicotine from the EC device. Studies show that the reasons for this are three-fold: 1) EC and TC require different puffing techniques[9]; 2) EC use requires practice, so there is a learning curve for effective vaping[10]; and 3) users have preferences for different types and generations of ECs, indicative of inconsistent manufacturing and production.[11]

Finally, ECs receive the greatest criticism for the unknown effects on health and potential disease burden. Without the ability to study the long-term effects of ECs, it is difficult to measure the health risks associated with using ECs over conventional TCs. Current research is concerned with the excessive propylene glycol content in the vapor, and also the potential of accidental poisoning from liquid cartridge contents.[4]

Combustion Versus Vaporization

Combustion. It is well known that a TC delivers nicotine and produces smoke by way of heat and combustion. Combustion is the burning of chemicals that changes the properties of ingredients in a cigarette. The burning of a cigarette produces 4,000 chemicals, of which 100 have been identified as known carcinogens—cancer-causing agents.[12–14] Carcinogens are also agents that promote or aggravate the onset of cancer. The World Health Organization and the International Agency for Research on Cancer have evaluated 900 chemicals often found in the conventional TC that have cancer-causing potential. Although the bulk of these chemicals have been categorized as group 2A (probably carcinogenic to humans) and group 2B (possibly carcinogenic to humans), 100 chemicals have been classified as group 1 (carcinogenic to humans). An extensive list of these chemicals has shown that TCs contain everything from arsenic (rat poison) to polonium (radioactive, cancer-causing element).[14]

Vaporization. ECs do not require combustion to deliver TC-comparable doses of nicotine,[5] nor do they include many of the potentially carcinogenic additives that are found in TC. They are essentially electronic inhalers that work by way of vaporization—activation of a battery heats a cartridge liquid (usually containing humectants, nicotine, and flavoring) to a maximum temperature of 55°C to release aerosolized nicotine and smokeless vapor. Humectants are often propylene glycol or vegetable glycerin.[2] The aerosolized nicotine is readily delivered into the respiratory tract.

Carcinogenic content: smoke versus vapor. In order to compare the disease burden of TC versus EC, carcinogen and particle content in TC smoke is compared to that of EC vapor. Exhaled vapor composition is expected to differ from liquid composition.

Indoor air quality. One study, done by McAuley, et al. comparing the particles and components found in EC vapor and TC smoke in indoor air samples showed that EC vapor posed a significantly lower risk than TC smoke under identical experimental conditions and methods.[15] The analysis covered volatile organic compounds (VOCs), carbonyls, polyaromatic hydrocarbons, tobacco-specific nitrosamines (N′-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)), nicotine, and glycols (propylene glycols/PG, diethylene glycols/DEG). The findings of this studying were found to be in agreement with the findings of several other studies, including Schripp et al.,[1] Lauterbach et al.,[37] Laugeson et al.,[38] and FDA.[39] See Table I for a summary of the analyses.

Collected air quality data was presented to expert toxicologists, who determined the total cumulative hazard indices and excess lifetime cancer risks (ELCRs) values and translated the values to disease burden. The following summarizes the findings:

Child and adult exposure to noncancer and cancer analytes in vapor and smoke

- *Vapor*. Child and adult: no significant risk
- *Smoke*. Child: exceeded high-risk limit; adult: significant risk

Child and adult exposure to carcinogens in vapor and smoke

- *Vapor*. No cumulative ELCR exceeding cancer risk limit of 1×10^{-5}
- *Smoke*. Adult exposures approached ELCR risk limit of 1×10^{-5}

Overall, TC smoke contains significantly more carcinogens and carcinogenic analytes than EC vapor. This

TABLE I.
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Component	Detection in Vapor versus Smoke
VOC*	Vapor: Below LOD, except for ethylbenzene, benzene and toluene.
	Smoke: Orders of magnitude higher than found in vapor
Carbonyls*	Vapor: Low concentration, except for acetone, formaldehyde, acetaldehyde
	Smoke: Orders of magnitude higher than found in vapor
PAH†	Vapor: Below LOD, except for benzo(a)pyrene, which was found in same concentration as in smoke
	Smoke: Above LOD
TSNA*	Above LOD for both vapor and smoke, but significantly higher in smoke
Nicotine*	Above LOD for both vapor and smoke, but significantly higher in smoke
DEG*	Detected in some vapor and smoke samples, but below toxic levels
Glycols*	Significantly higher concentration in vapor than smoke
Particle count*	Vapor: Low particle count across all EC-liquids tested; significantly lower than smoke particle count

*Values found in McAuley et al.[15] in agreement with Schripp et al.,[1] Lauterbach et al.,[37] Laugesen et al.,[38] and FDA.[39]
†Lauterbach et al.[37] found benzo(a)pyrene below LOD for vapor and 40 times higher in smoke.
DEG = ; EC = electronic cigarettes; FDA = U.S. Food and Drug Administration; LOD = limit of detection; PAH = polyaromatic hydrocarbons; TSNA = tobacco-specific nitrosamines; VOC = volatile organic compounds.

study by McAuley et al. concludes that EC vapor poses significantly lower risk than TC smoke, and that there are no recognizable health impacts from the vapor produced by any of the four EC liquids tested in this study.[15]

Secondhand Exposure

EC vaping results in second hand vapor exposure. Upon exhalation, VOCs and ultrafine particulates are released into the indoor air resulting in potential passive vaping by non-vaping individuals inhaling the same air.[1] Some studies claim that heat alone causes formation of formaldehyde, acetaldehyde, and methylglyoxal.[16] However, continuous monitoring of the indoor air environment during EC vaping did not detect any significant increase in formaldehyde concentration.[1] Thorough comparison to emissions from conventional TC shows that EC vapor and consequent passive vaping is safer than TC smoke and subsequent SHSe. Although everything from 1,2-propanediol to benzene to formaldehyde was detected in EC vapor, the levels were close to the limit of detection (LOD). Some studies show that the presence of those particles is no different than what would be produced simply from the physiological metabolism and exhalation of an individual who does not use TC or EC products.[1,17]

The FDA has expressed concern about ECs due to the high propylene glycol (PG) content in EC vapor. However, PG has been safely used in numerous consumer and household products from food to cosmetics to pharmaceuticals. At worst, PG was found to be irritating to the throat upon constant inhalation. Some users reported upper airway irritation following short-term use of EC, claiming this was due to excessive exposure to propylene glycol.[18] Current FDA-approved Nicotrol Inhalers[1] also have this side effect on users. Furthermore, in response to PG concerns, most EC manufacturers have begun to eliminate this potential risk by replacing PG with glycerol and water vapors, thereby increasing EC safety.

Meanwhile, it has been well established that TC smoking and secondhand smoke exposure (SHSe) increases the risks of tuberculosis, cardiovascular risk, lung cancer mortality, emphysema, laryngitis, cancer of the throat and lung, and other fatal health implications.[19–21] The impact of smoke from conventional TCs on indoor air quality has been extensively studied and shows that hundreds of ingredients form carcinogenic and volatile combustion products, which are then released as fine particulate matter into the air.[14]

Effects on Complete Blood Count and Associated Potential Disease Burden

Acute and chronic active TC smoking increases the white blood cell (WBC) count, as does passive TC smoking through SHSe.[22,23] Specifically, nonsmokers who are exposed to passive TC smoking and active TC smokers showed a significant increase in WBC, lymphocyte, and granulocyte count.[24]

An increase in WBC count and analysis of total blood count is an objective way to gain an overview of an individual's systemic and cardiovascular health status. Elevated or deflated cell counts could indicate overall systemic problems ranging from infection and inflammatory disease to bone marrow and immune diseases.[25] Elevated levels of circulating WBCs are involved in low-grade inflammation, as seen associated with atherosclerosis. Chronic active TC smoking elevates proteins' acute inflammatory load such as interleukins 4, 5, and 6 and interferon gamma.[24]

Meanwhile, chronic passive TC smoking (SHSe) has shown elevated levels of C-reactive protein, in addition to elevated levels of IL-4/5/6 and interferon gamma, which can be indicative of cancers, cardiovascular disease, fibrosis, and obstructive sleep apnea.[23] The same study found that active and passive EC vaping showed no significant change in complete blood count indices and no increase in WBC count.[24]

Effects on Lung Function and Associated Potential Disease Burden

Lung function parameters are measured as indicators of the respiratory health of individuals following chronic and acute exposure to TC smoke and EC vapor. Lung function is measured by spirometry, which calculates volume and speed that air can be inhaled and exhaled; breath carbon monoxide (CO) monitor, which

assesses exhaled CO; and breath nitric oxide (NO) analyzer, which measures the fraction of exhaled nitric oxide (FeNO). FeNO indices are used as noninvasive markers of bronchial inflammation.

Studies show that acute active and chronic passive EC vaping generated smaller changes in lung function compared to acute active and passive TC smoking for both current smokers and never-smokers.[26] Although it seems that the ECs have minimal deleterious effects, another study shows that EC use results in greater negative clinical changes. It has been reported that acute use of EC for 5 minutes results in an immediate decrease of FeNO, which consequently results in an increase of total respiratory impedance and peripheral flow resistance.[18] Because other studies have shown that changes in flow resistance precedes peak expiratory flow (PEF) and forced expiratory volume (FEV), spirometry alone is not an effective way to measure lung function.[27] Although negative clinical changes have been reported, changes may be too small to be of major clinical importance or to indicate dyspnea or breathing difficulties. It is important to note that Vardavas et al.'s study was limited to a comparison between sham ECs (control) and real ECs. There was no comparison to TC use.[18] This study is strictly used to demonstrate that EC use has potential for negative clinical changes.

Acute active and passive TC smoking repeatedly undermined lung function. TC smoking contributes to the development of chronic lung disease. Studies found an increased production rate of growth factors and type 1 procollagen in the small airways,[28] leucocyte bounding to endothelial cells,[29] increased lung inflammation,[30] and increased platelet activation[31]—all of which are linked chronic lung disease and eventual carcinoma.

Effects on Myocardial Function and Associated Potential Disease Burden

A study by Farsalinos et al. evaluated acute effects of EC use versus TC use on left ventricular myocardial function.[32] Assessment was done through complete echocardiographic exams and measurement of Doppler flow parameters. All participants—who were ex-smokers—showed similar characteristics of baseline echocardiogram and hemodynamic parameters. Participants were exposed to relative amounts of nicotine through either EC or TC use.

Those who smoked TCs presented data indicative of acute impairment of left ventricular function, such as a decrease in Em velocity and Em/Am ratio and an increase in isovolumic relaxation time and myocardial performance index.

Those who vaped ECs showed no signs of alterations from baseline levels, indicating that there were no acute adverse effects on cardiac function.

CONCLUSION

ECs are nicotine-delivery devices. As a result, EC users will always risk the potential disease burdens associated with nicotine use and related side effects such as increased blood pressure, heart rate, microvascular injury, and dependence. That said, ECs present decreased potential disease burden compared to TCs. It is generally understood that the toxicants from burning tobacco and TC components are responsible for most adverse health effects, whereas nicotine is responsible for the addictive quality in TCs.

Studies show that EC use has the potential to effectively allow TC smokers to quit or decrease TC use, thereby eliminating combustion of carcinogenic TC components and subsequent active and passive exposure to carcinogens exposed directly to smokers, secondhand smokers, and the environment.

Major concerns remain that persist, as well as considerations that should be taken into account. At present, the manufacturing and distribution of the EC device and cartridge manufacturing and production is unregulated and highly variable, which has resulted in ECs of differing design, materials, utilization, combustion voltage, and liquid cartridge concentration. This is confusing for the common consumer and also is a barrier to effectively studying the potential adverse and beneficial effects of ECs. Further concerns involve the novelty of EC use. Whereas ECs offer exciting potential in decreasing the disease burden imparted by use of TCs, the short-term existence of ECs in the public market should be taken into account. Presently, there are no long-term studies investigating the reduction of disease development in those who have switched from TC use to EC use, or in those who have been using ECs for an extensive period of time. Without this data, ECs can only claim potential for decreasing disease burden, as speculated by the lower carcinogenic profile found in ECs versus TCs. Chemical analyses show decreased carcinogenic content in ECs, but there is yet to be a study demonstrating that the decreased carcinogenic content is directly correlated to reduced disease development, such as cancer, in former TC smokers.

Last, we must take into account the role of health care providers as advocates or antagonists of EC use as therapy for smoking cessation—especially with regard to adolescents, the age group showing the most significant increase in EC use.[33] Whether providers support or oppose the use of ECs as a transitional nicotine delivery device, it is the responsibility of providers to be knowledgeable and up-to-date about emerging health care issues.[34] Important EC-related topics are the following: 1) consumer surveys and subjective views on vaping; 2) chemical analysis of e-cigarette liquid cartridges, vapor, and third-hand deposition of vapor; 3) nicotine content, delivery, and pharmacokinetics; and 4) clinical and physiological studies investigating the effects of acute EC use.[35] Furthermore, due to the controversy and unknowns surrounding ECs, perhaps the use of ECs should be strictly regulated and limited until studies show evidence of disease reduction. It is in the best interest of providers and users to incorporate screening, counseling, and education prior to EC use.[36]

As the debate on TC versus EC continues, there are a few key things to keep in mind: 1) TC combustion is a continuous process, meaning that carcinogens are actively and passively released during the entire

smoking session. Meanwhile, ECs only release vapors during exhalation. 2) As ECs become increasingly sophisticated, they will be able to more effectively deliver accurate doses of nicotine, eliminating current issues regarding noncompliance or ease of use. 3) The EC components discussed in this review strictly apply to EC liquid cartridge components that are heated and vaporized. Heating the metal and silicate components of the actual device itself (to extreme temperatures) may present a whole new set of potential disease burdens associated with ECs. 4) Finally, the potential disease burden of long-term EC is unknown because ECs are a novel commodity, but analysis of parameters related to health after acute EC vaping could be indicative of long-term toxicity.

Future Research

Future research on ECs should cover: 1) long-term active and passive EC vapor inhalation and comparisons of various nicotine dosing; 2) modified, indoor air-quality study using other flavors of EC liquid cartridges—or flavored versus nonflavored liquid cartridges to determine additional pollutant in flavored liquids; 3) various voltages of EC to see whether increasing the heat of the EC will change the decomposition of components and lead to increased toxicity; and 4) repeated studies once EC production is more regulated and standardized. Current studies use different brands or types of EC with different doses of liquid cartridges, resulting in differing nicotine dosages.

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Addiction

REVIEW

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Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit

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ABSTRACT

Aims We reviewed available research on the use, content and safety of electronic cigarettes (EC), and on their effects on users, to assess their potential for harm or benefit and to extract evidence that can guide future policy. **Methods** Studies were identified by systematic database searches and screening references to February 2014. **Results** EC aerosol can contain some of the toxicants present in tobacco smoke, but at levels which are much lower. Long-term health effects of EC use are unknown but compared with cigarettes, EC are likely to be much less, if at all, harmful to users or bystanders. EC are increasingly popular among smokers, but to date there is no evidence of regular use by never-smokers or by non-smoking children. EC enable some users to reduce or quit smoking. **Conclusions** Allowing EC to compete with cigarettes in the market-place might decrease smoking-related morbidity and mortality. Regulating EC as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence. Health professionals may consider advising smokers unable or unwilling to quit through other routes to switch to EC as a safer alternative to smoking and a possible pathway to complete cessation of nicotine use.

Keywords Electronic cigarettes, harm reduction, prevalence, product safety, regulation, smoking cessation.

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INTRODUCTION

Electronic cigarettes (EC) are devices designed to deliver nicotine without tobacco smoke by heating a solution of nicotine, flavouring, additives and propylene glycol and/or vegetable glycerine. Invented by Lik Hon in Hong Kong in 2003 [1], they became available in Europe and the United States in 2006 [2]. EC are undergoing a rapid evolution driven by competition. There are dozens of manufacturers and hundreds of EC models. Tobacco manufacturers joined this market in 2012, when Lorillard bought Blu e-cigs (http://investors.lorillard.com/investor-relations/news/2012/default.aspx).

During the past few years EC have been gaining popularity, primarily among smokers who want to reduce the risks of smoking [3,4]. The growing sales of EC, driven initially by word of mouth and user enthusiasm, are now seen by financial analysts to threaten sales of cigarettes [5,6]. The reaction by the public health community to this unfolding phenomenon has ranged from enthusiastic support to vigorous opposition. Regulatory bodies around the world are deciding whether to allow EC to compete with cigarettes freely, submit them to a more restrictive regulation than cigarettes, e.g. as medicinal devices, or ban them. Their verdicts will probably feature among the key public health decisions of our time.

Commentators in favour of EC restrictions believe that the product has a potential to increase cigarette use by re-normalizing smoking, i.e. reducing motivation of smokers to quit completely, providing a gateway to smoking for non-smokers or facilitating an increase in smoking prevalence indirectly. They argue that EC should be banned or submitted to much stricter controls than smoked tobacco. They emphasize evidence that nicotine can be addictive and warn that health risks from long-term EC use may yet emerge (e.g. [7–10]).

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EC advocates believe that, on the contrary, the product has a potential to reduce and, if it continues to develop, eventually end cigarette use by allowing smokers to switch to a safer product. They argue that achieving this potential requires little government expenditure and involvement and that it is in the public health interest to allow EC to compete with cigarettes in the market-place. They emphasize evidence that use of nicotine without tobacco toxicants poses minimal risks, except in the case of well-defined subpopulations such as pregnant smokers (e.g. [11–15]).

Both sides of the debate agree that any policy and regulatory decisions affecting EC should be guided by evidence. This review summarizes the literature on patterns of EC use, content, safety and effects on users and considers the implications of the evidence.

Search strategy and selection criteria

We searched Medline, PsycINFO, EBM reviews (including Cochrane Methodology Register, Health Technology Assessment and NHS economic evaluation database), Google Scholar, EMBASE and CINAHL (to February 2014). We combined the following search terms 'e-cig*' OR 'elect* cigar*' OR 'electronic nicotine'. We also searched the reference lists of articles identified by this search strategy and selected those that addressed the key themes of the review. After removing duplicates, this search identified 286 records that were screened independently by two reviewers (P.H. and H.M.). Most papers were opinion-pieces. Ninety-nine full-text papers were reviewed. Papers were deemed relevant ($n = 81$) to this review if they presented original data and provided evidence that could guide regulatory decisions.

Note that we use the words 'EC' for electronic cigarettes and 'cigarettes' for conventional cigarettes. EC use is increasingly labelled as 'vaping' and EC users as 'vapers', but we are using EC use/EC user throughout.

SURVEYS OF EC USERS

Prevalence of EC use and characteristics of users

EC use was negligible in 2008–09, but increased steadily over the following years: in the United States in the general population it increased from 0.6% in 2009 to 2.7% in 2010 [16] and to 6.2% in 2011 [17]. In the United Kingdom, use in smokers increased from 2.7% in 2010 to 6.7% in 2012 [2] and to 11% in 2013 [18]. About one-third (30% to 38%) of ever users used EC within the past 30 days [2,16,17,19–23]. Some 12–14% of smokers who tried EC progressed to daily use [23,24].

EC users tend to be younger, more educated and have higher income than non-users [17,25,26]. There is no clear association between e-cigarette use and gender [20,26–28]. Most of these surveys are from Europe and the United States, and the results may not apply to other countries.

EC experimentation and regular use by never-smokers

Studies conducted to date have found that the prevalence of EC experimentation (ever use) in never-smokers ranged from 0.1 to 3.8% (median 0.5%), and use in the past 30 days ranged from 0 to 2.2% (median 0.3%) [2,16,17,20,22,23,25,27–29]. A recent report on EC use among US children was interpreted as showing worryingly high levels of use [30], but extrapolated data show that among middle school students in 2012, 0.5% of never smokers tried EC. The figure for high school students was 0.7%. Among children, current use was confined to those who have already tried smoking [18]. 'Current use' in non-smokers (any use over the past 30 days, not daily use) was reported in only 0.04% [31]. A study assessing daily use in non-smokers found none [23]. For comparison, 39.5% of twelfth-graders (17–18-year-olds) tried cigarettes in the United States in 2011 [32], and about half of children who try conventional cigarettes progress to regular use.

Surveys of regular EC users

A number of studies recruited EC users over the internet. These results need to be interpreted with caution, because internet surveys attract primarily EC enthusiasts [3].

The most popular e-liquids had a nicotine content of 18 mg/ml [3,33–37], and the most popular flavours were tobacco, mint and fruit [3,4,36,38].

Users reported consistently that EC helped them either to quit smoking (42–99%) [3,4,34–37,39] or to reduce it (60–86%) [3,24,36,39]. EC were perceived as less addictive than cigarettes [35,37], and time from waking up to use was longer for EC than for cigarettes [36,37]. Only 18% reported that they craved EC as much as tobacco [36].

Summary

EC use is on the increase. Experimentation by children is a small fraction of experimentation with cigarettes, and daily use in never-smokers has not been documented so far. It appears that some 12–14% of smokers who try EC become daily users, suggesting that EC in their current form are less satisfactory than cigarettes to most users. In surveys, regular EC users report that these devices helped them to limit or stop smoking and they perceive EC as less addictive than cigarettes.

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EC CONTENT

The interpretation of studies of the chemical composition of the e-liquids and aerosols is complicated by the fact that there exist many brands and models with different e-liquids, batteries, heating elements, nicotine concentrations and flavourings, although most of them use e-liquids from a small number of manufacturers in China, the United States and Europe [40]. It is also important to differentiate between the chemical compositions of e-liquid and aerosols that users inhale.

Propylene glycol (PG) and glycerol

The results of extensive studies on animals, reviewed elsewhere [40,41], suggest that PG should be safe for inhalation in humans, although in children, chronic exposure to PG in indoor air may exacerbate or induce rhinitis, asthma, eczema and allergic symptoms [42]. Acute and chronic respiratory effects, including reduced lung function, were reported in people chronically exposed to theatre fogs containing PG [43]. PG has a desiccation effect, which is why EC users sometimes report dry throat and mouth [3,4,36,37].

Glycerol (purified vegetable glycerine) is non-toxic, but can produce toxic acrolein when heated to higher temperatures. Acrolein was detected in the aerosol of some EC brands, but at levels much lower than in cigarette smoke [44]. Acrolein intake by smokers given glycerol-based EC was reduced by 60% in those who continued to smoke (EC use was accompanied by a reduction in smoking) and by 80% in those who stopped smoking [45].

Impurities and toxicants in e-liquids

Nicotine in e-liquids, like nicotine in nicotine replacement treatment (NRT), is extracted from tobacco and thus includes impurities such as cotinine, anabasine, anatabine, myosmine and beta-nicotyrine [46,47]. An early study found nitrosamines and tobacco-specific impurities 'at very low levels' and diethylene glycol in one of the cartridges [48]. Later studies of other products found no evidence of diethylene glycol [46]. No tobacco-specific nitrosamines or polycyclic aromatic hydrocarbons were found in 20 EC products [49], while an analysis of samples from 11 manufacturers [50] found nitrosamine concentrations approximately 1000 times lower than those in smokeless tobacco products [51]. Analysis of EC aerosol (as opposed to e-liquid) identified low levels of some toxicants [44]. In some cases these were comparable to levels found in NRT, which are considered safe, and overall at levels 9–450 times lower than in cigarette smoke [44].

Metal particles were found in the liquid and aerosol from an EC model [52], but the report did not assess the clinical significance of the levels detected. These levels are 10–50 times below the levels allowed in inhalation medicines [53].

EC liquid can be cytotoxic in *in-vitro* studies (e.g. [54]) but users inhale aerosol, not liquid. Aerosol from one of 21 e-liquids was cytotoxic, due to the flavouring containing substances from roasted coffee beans, but this was 800 times less cytotoxic than tobacco smoke [55].

PG and glycerol inhalation is likely to pose a low risk, although their long-term effects as well as the effects of long-term inhalation of EC flavourings and additives need to be studied.

Passive exposure

Most second-hand smoke from cigarettes is generated as sidestream smoke from the tip. EC do not generate sidestream aerosol. It is only what is exhaled by the users that enters the ambient air. EC aerosol does not include most of the chemicals found in tobacco smoke or the 'sidestream' smoke, but users exhale nicotine and some other particles, primarily consisting of flavours, aroma transporters, glycerol and PG [56–59].

No long-term study has been conducted so far, but pollutant levels are much lower than from cigarettes and are likely to pose a much lower risk (if any) compared to cigarettes [41,56].

Labelling of nicotine content of e-liquid

Nicotine is the addictive chemical in tobacco smoke, but its involvement in smoking-related harm (outside pregnancy) is very small, if any, compared to cigarette smoking [60,61].

In several reports, nicotine was detected in products labelled as zero nicotine. In one study, a manufacturer included similar nicotine levels in differently labelled cartridges, including zero nicotine [47]. In all other cases, nicotine detected in zero-nicotine cartridges was only at trace levels and unlikely to have any psychoactive effects [47–49].

For the major e-liquid brands tested thus far, the labelling of nicotine content is accurate [46] and the nicotine content across cartridges and across batches has good consistency [62,63], although labelling for some brands can be vague, inaccurate or absent. However, beyond the general rule that EC users cannot obtain high nicotine levels if there is too little nicotine in the e-liquid, there is little relationship between nicotine in cartridges and nicotine in aerosol [63]. This is because the mechanical features of EC, such as the size of the battery, the nature of the heating element and the ventilation holes, etc. play a major role. In addition, individual inhalation characteristics have further substantial influence on nicotine levels delivered to the user (see below).

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Summary

E-liquids and aerosols tested so far contain some toxicants in concentrations much lower than in tobacco smoke and negligible concentrations of carcinogens. Passive exposure to EC aerosol can expose non-users to nicotine, but at concentrations unlikely to have any pharmacological significance. Humectants in EC appear to be safe for inhalation, but the effects on EC users with asthma and other respiratory diseases are not known. Nicotine intake from EC is determined by a host of factors in addition to nicotine content of the e-liquid.

EC SAFETY

Adverse events

None of the experimental [37,59,64–73] or prospective follow-up studies [74,75] reported serious adverse events (SAEs). Adverse events (AEs) were mild to moderate and included symptoms such as mouth and throat irritation and dry cough, similar to those reported in surveys of EC users [3,4,35–37]. There were no significant differences in AEs between EC and control groups in two randomized trials [76,77]. There were no SAEs in one trial [77], and in the other SAEs were considered to be unrelated to the products under study [76].

Among reports from 481 EC users on online forums that had sections dedicated specifically to the reporting of adverse health effects of EC use, the most common AEs were effects on the mouth and throat (around 50% of events) [78]. An increase in blood pressure, a potentially more concerning effect, was reported by 2% of correspondents.

The US Food and Drug Administration Center for Tobacco Products (CTP) collects data regarding AEs from a variety of sources. Between 2008 and the first quarter of 2012, the CTP received 47 reports of AEs related to EC, eight of which were deemed serious. With the exception of two, no causality was attributed to the EC. The two were infant death caused by choking on an EC cartridge and facial burns caused by EC exploding [79]. We are aware of two further media reports of exploding EC [80,81].

Regarding AEs reported in the medical literature, an EC user developed lipoid pneumonia, which resolved when EC use ceased [82]. An elderly heavy smoker experienced three episodes of acute asymptomatic atrial fibrillation, each preceded by EC use. She stopped EC use and had no further episodes [83].

Regarding the cardiovascular effects of EC, nicotine in EC increases heart rate after overnight abstinence [72,73]. Short-term EC use does not adversely affect haematological or blood chemistry parameters, or cardiovascular function in smokers or ex-smokers [84–87].

Regarding effects on respiratory function, 5 minutes of EC use generated an increase in airways resistance, associated with a 16% decrease in fractional exhaled nitric oxide (FeNO), a marker of bronchial inflammation, with no change in the control group. These effects were not considered clinically significant [59].

In another study, smoking a cigarette led to a significant reduction in forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), while EC use generated no acute change in lung function. There were no significant changes in FeNO in either group [69].

Risks of nicotine poisoning

A claim is often repeated that an ingestion of 30–60 mg of nicotine is fatal [88], but this assertion is based on dubious self-experiments in the 1890s [89]. Tobacco and NRT have been available to hundreds of millions of people, but fatal poisoning by nicotine is extremely rare. We are aware of one newspaper report of a fatal poisoning of a 2-year-old child who drank e-liquid [90] and of one case study on an 18-month-old child who drank e-liquid, was admitted to hospital with vomiting, ataxia and lethargy, and was discharged after 24 hours of observation [91]. With the increase in EC use, there has been an increase in calls to poison centres following accidental exposures, but these remain lower than calls following such exposure from tobacco and none resulted in any serious harm [92]. Several suicide attempts were recorded where adults drank up to 1500 mg of nicotine in e-liquid, which resulted in vomiting but recovery within a few hours [93].

Summary

Although surveys of users, prospective clinical studies and randomized controlled trials to date have not found any SAEs, several such events have been reported as case studies and in the media. Given the high media interest in EC, the number of such reports is remarkably low. Data to date show that EC pose a minimal risk of nicotine poisoning from the device as intended to be used, but e-liquid can be dangerous or lethal if ingested, particularly by small children.

EFFECTS ON SMOKERS

Nicotine levels in EC users

Early studies using brief fixed puffing schedules and smokers naive to EC use found low or no nicotine delivery [64,68,71]. With greater familiarity with the device and less restricted use, plasma nicotine delivery was comparable to that from oral NRT products (4–5 ng/ml) [3,70,73]. Some experienced EC users achieve nicotine

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levels which are close to those obtained from smoking, but only after extended EC use (up to 14 ng/ml after 60 minutes of *ad libitum* use [33,65,72,94] compared with 10–20 ng/ml after smoking a cigarette) [95,96]. Importantly, users experienced in using the same model differed in how much nicotine they extracted from it [65]. As with cigarettes, user behaviour is an important factor in nicotine delivery.

Effects of EC use on withdrawal symptoms and on smoking behaviour

Using EC after overnight abstinence from smoking significantly reduces urges to smoke within 5–30 minutes [64,66–68,71,73]. Non-nicotine EC can also have this effect [64,66,67].

Three small studies evaluated the effects of EC in smokers not intending to reduce or quit smoking. They reported a ≥50% reduction in smoking at the end of 1 week in 32% of participants, including 14% who stopped smoking altogether [70]; sustained ≥50% reduction in 28% of participants and additional 13% abstinence rate at 2 years [75,97]; and ≥50% reduction in 50% of participants and additional 14% abstinence rate at 1 year in smokers with schizophrenia [74].

Data from representative surveys [19], surveys of EC users [3,4,24,34–37,39] and from clinical trials [45,74–77,97,98] show consistently that smokers who use EC and smoke at the same time (so called dual users) reduce their cigarette consumption.

Effects of EC on smoking cessation

Several case studies reported the benefits of EC in helping people who have failed to quit with other methods [99–101].

Several studies evaluated relationships between EC use and smoking reduction and cessation. Among the general population, EC users and non-users had the same quit rate, but EC use was associated with a significant reduction in cigarette consumption [19]. Among callers to a quitline, those who ever used EC compared with other callers had more previous failed quit attempts, were more likely to live with smokers and were less likely to quit at the current quit attempt [102]. The finding is due probably to bias by intention—more dependent smokers who choose to use EC and are also less likely to quit smoking. Similar findings have been observed with NRT [103]. One other study was interpreted as showing that EC use inhibits cessation, but another interpretation is that it showed that EC use is related to smoking history [104]. Adolescents who tried cigarettes at least once but are not smoking now were less likely to ever try EC than adolescents who smoke. In two cohorts, smokers who have tried EC had a similar likelihood of quitting as other smokers [19,21], but in a large population sample, smokers attempting to stop smoking with the help of EC were more likely to succeed than those using NRT bought from a store (without any professional supervision) or trying to quit unaided [105].

Among 'dual users', 46% quit smoking altogether after 1 year [106].

A randomized trial of 300 smokers not intending to quit compared the effects of two nicotine-containing and a nicotine-free EC provided for 12 weeks. The study used an EC with poor nicotine delivery that often malfunctioned and was subsequently discontinued [77]. At 1 year, smoking abstinence rates were 13, 9 and 4% in the three groups, respectively. There were no differences in smoking reduction in those who continued to smoke. The two nicotine EC groups merged had a higher quit rate than the non-nicotine group (11 versus 4%, $P = 0.04$).

A randomized trial in 657 treatment-seeking smokers compared EC with nicotine patches (21 mg) and with non-nicotine EC. The study used EC with low nicotine delivery [76]. Participants received a referral to a telephone quitline but no face-to-face contact. In this minimal support context, biochemically validated continuous abstinence rates at 6 months were 7.3, 5.8 and 4.1% in the three groups, respectively [not significant (NS)]. While the results were suggestive of a benefit for EC users, the study did not have adequate power to detect what would be a realistic margin of difference from the two active comparators. EC generated significantly higher self-reported smoking reduction and higher user endorsements than patches.

In the United Kingdom, where the use of EC to assist smoking cessation has now overtaken use of NRT, and detailed figures are available on month-to-month changes in smoking behaviour, the rise in EC use has been accompanied by an increase in successful quit attempts [107] and a continuing decrease in smoking prevalence [108].

Summary

EC reduce urges to smoke and there is preliminary evidence that EC use facilitates both quitting and reduction in cigarette consumption in smokers interested in quitting smoking. In England, which has the most detailed data on EC and cigarette use, the growth in EC use has been accompanied by an increase in smoking cessation rates, a continued reduction in prevalence and no increase in smoking uptake [107,108]. Whether EC are contributing to these favourable tobacco control trends is as yet unclear.

CONCLUSIONS

Important regulatory verdicts are being currently made and science-based decisions are needed to maximize

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benefits and minimize risks to public health. The key issue to consider is whether EC use is likely to increase or decrease smoking-related morbidity and mortality. There are several hypothetical routes to a negative outcome and one route to a positive outcome. The reviewed evidence can contribute to their assessment. EC would generate negative outcomes if:

- Chemicals in EC cause excess morbidity and mortality. *Evidence*: health effects of long-term EC use are currently not known and a degree of risk may yet emerge. However, based on the data available regarding the toxicant content of EC liquid and aerosol, long-term use of EC, compared to smoking, is likely to be much less, if at all, harmful to users or bystanders. This is because unlike cigarettes, EC do not deliver combustion-generated toxicants that are linked to cancer, chronic lung disease and cardiovascular disease (CVD).
- Smokers who would otherwise quit combine EC and cigarettes instead of quitting and maintain a similar smoking rate. *Evidence*: EC use is associated with smoking reduction and there is little evidence that it deters smokers interested in stopping smoking tobacco cigarettes from doing so.
- Young people who would not try cigarettes otherwise start using EC and then move on to become smokers. *Evidence*: although there have been claims that EC is acting as a 'gateway' to smoking in young people, the evidence does not support this assertion. Regular use of EC by non-smokers is rare and no migration from EC to smoking has been documented (let alone whether this occurred in individuals not predisposed to smoking in the first place). The advent of EC has been accompanied by a decrease rather than increase in smoking uptake by children [109]. Ongoing surveillance is needed to address this important point.
- EC use will increase smoking prevalence indirectly, e.g. by making smoking acceptable again in the eyes of people who cannot tell the difference between EC and cigarettes, via machinations of the tobacco industry, or by weakening tobacco control activism. *Evidence*: there are no signs that the advance of EC is increasing the popularity of smoking or sales of cigarettes.

There is one hypothetical route to the positive outcome, i.e.:

- That EC reduce harm at the individual and population level by reducing cigarette use. In the most optimistic scenario, EC would continue to improve in providing smokers with what they want from their cigarettes, until the use of conventional cigarettes virtually disappears. *Evidence*: EC reduces cigarette use by facilitating smoking reduction and cessation on individual level, but the prevalence of EC use has been low until recently and the effect of EC use on cigarette consumption on the population level has not been established so far.

Implications for policy makers

The European Parliament has recently rejected a proposal to licence EC as medicines. There is a concern that medicinal regulation would disadvantage EC compared to cigarettes, make them more expensive, stifle their development and may drive them fully into the arms of the tobacco industry as the only player able to afford the large entry barriers [12,110]. In Europe, EC are subject to consumer protection legislation, and most countries are likely to ban sales to people under 18, as has recently been introduced in the United Kingdom. Advertising restrictions are also forthcoming [111,112]. Some regulators, however, believe these actions are not sufficient because of the hypothetical routes to negative outcomes discussed above. Regulatory decisions will provide the greatest public health benefit when they are proportional, based on evidence and incorporate a rational appraisal of likely risks and benefits.

Implications for researchers

Our review points to two key research priorities. One is ongoing surveillance of the temporal relationship between country-specific markers of EC use and smoking behaviour. Close monitoring, for which some instruments already exist [113–115], is needed to track changes in EC use and smoking prevalence. Sales data will also be informative; if increased EC sales are accompanied by an increase in cigarette sales, EC could be re-normalizing smoking and further regulatory steps would be required, while if they are associated with a decrease in cigarette sales, this would indicate a public health benefit of liberal regulation. The second priority concerns EC safety. Epidemiological studies are required that compare health outcomes in cohorts of regular EC users (who either use only EC or both EC and cigarettes) with matched cohorts of smokers and non-smokers. These need to be supplemented by laboratory and clinical studies of EC contents and effects on smoking behaviour.

Implications for health professionals

While there is not yet conclusive evidence about the effectiveness of e-cigarettes to generate smoking cessation or reduction, health-care professionals (HCP) should support smokers unable or unwilling to stop tobacco use who wish to switch to EC to reduce harm from smoking. HCP should emphasize the importance of stopping using cigarettes and nicotine altogether.

Declaration of interests

P.H., N.B. and T.E. have no links with any e-cigarette manufacturer. J.F.E. was reimbursed by a manufacturer of e-liquids for travelling to London and to China. H.M. was

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ash briefing
action on smoking and health

Electronic cigarettes
(also known as vapourisers)

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Summary

- Electronic cigarettes are not cigarettes. They do not contain tobacco and using them is not smoking.
- ASH, in line with the NICE guidance on Tobacco Harm Reduction, always recommends that quitting all forms of nicotine use is the best option for smokers.
- However, for those who remain addicted to nicotine NICE guidance recommends the use of medicinally licensed nicotine containing products as an alternative to smoking or to cut down or for temporary abstinence to help reduce the harms of smoking.
- NICE guidance cannot recommend the use of unlicensed nicotine containing products but many smokers are finding unlicensed electronic cigarettes helpful. Research by ASH shows that their use has grown threefold in the last two years from 700,000 to 2.1 million users.[1]
- Electronic cigarettes are proving more attractive to smokers than NRT[1,2] while providing them with a safer alternative to cigarettes.[3] There is evidence that they can be effective in helping smokers' quit[2,4] and little evidence that they are being used by never smokers.
- The number of children and young people regularly using electronic cigarettes remains very low and their use is almost entirely amongst those who are current or ex-smokers.[1] This is a similar pattern to that found in jurisdictions such as the USA.[5]
- ASH supports enhanced regulation to ensure the safety and reliability of electronic cigarettes and to prevent their promotion to non-smokers and children.
- However, in the absence of evidence of significant harm to bystanders, ASH does not support the inclusion of electronic cigarettes in smokefree laws which would completely prohibit their use in enclosed public places.

Curently electronic cigarettes are regulated as general consumer products. Once the EU Tobacco Products Directive (TPD) comes into effect in Member States in May 2016, electronic cigarettes containing up to 20mg/ml of nicotine will come under the TPD (levels of 18mg/ml have been reported on user websites as suitable for typical smokers).[6] Above that level, or if manufacturers and importers decide to opt into medicines regulation, such products will require authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA) as over the counter medicines in the same way as nicotine replacement therapy (NRT).[7]

Nicotine Substitution

Smoking is the largest preventable cause of premature mortality in the UK.[8] The goal of tobacco control is to diminish the harm caused by tobacco products. While the ideal remains that people should stop using tobacco completely and permanently, consensus currently supports a properly regulated harm reduction approach for those unable to do so.[9,10,11] This is a framework by which the harmful effects of smoking are reduced without requiring the elimination of a behaviour that is not necessarily condoned. Such strategies have proved successful in the past, for example within the contexts of needle exchange programmes for illicit drug use and the promotion of safer sex to prevent HIV infection.[12,13]

In 1976 Professor Michael Russell wrote: "People smoke for nicotine but they die from the tar."[14] Indeed, the harm from smoking is caused primarily through the toxins produced by the burning of tobacco. By contrast, non-tobacco, non-smoked nicotine products, although addictive, are considerably less harmful.

Electronic cigarettes consequently represent a safer alternative to cigarettes for smokers who are unable or unwilling to stop using nicotine.

The National Institute for Health and Care Excellence (NICE) has developed guidance on a harm reduction approach to smoking.[15] NICE's recommendations aim to inform on how best to reduce illness and deaths attributable to smoking through a harm reduction approach. As part of this guidance, NICE supports the use of licensed nicotine containing products (NCPs) to help smokers cut down, for temporary abstinence and as a substitute for smoking, possibly indefinitely. NICE guidance cannot recommend the use of unlicensed nicotine containing products. However, the guidance is clear that using an electronic cigarette is safer than smoking.[13]

What are electronic cigarettes?

Electronic cigarettes, also known as vapourisers or electronic nicotine delivery systems (ENDS),[16] are often, although not always, designed to look and feel like cigarettes. They have been marketed as less harmful alternatives to cigarettes and for use in places where smoking is not permitted since they do not produce smoke.

There are three main types of electronic cigarettes or vapourisers:

- Disposable products (non-rechargeable)
- An electronic cigarette kit that is rechargeable with replaceable pre-filled cartridges
- An electronic cigarette that is rechargeable and has a tank or reservoir which has to be filled with liquid nicotine

The first two types of electronic cigarette are often known as 'cigalike' products as they resemble cigarettes and often have a light at the end that glows when the user draws on the device to resemble a lit cigarette. The liquid in the devices usually contains nicotine suspended in propylene glycol and glycerine. The level of nicotine in the cartridges may vary and most also contain flavourings.[17] When a user sucks on the device, a sensor detects air flow and heats the liquid in the cartridge so that it evaporates. The vapour delivers the nicotine to the user. There is no side-stream smoke but some nicotine vapour is released into the air as the smoker exhales.

Are electronic cigarettes safe to use?

Compared with smoking using an electronic cigarette is safer. However, in the absence of a thorough clinical evaluation and long term population level surveillance, absolute safety of such products cannot be guaranteed. By comparison, the harm from tobacco smoking – the leading cause of preventable death in the UK – is well established.

Most, but not all electronic cigarettes contain nicotine. As noted above, the harm from smoking comes mainly from inhaling tobacco smoke rather than the nicotine. However, nicotine is an addictive drug which stimulates the nervous system, increasing the heart rate and blood pressure.[18]

Toxins have been found in a number of studies of electronic cigarettes[19,20,21,22] although these are at levels much lower than those found in cigarettes and not at levels which would generally cause concern.[23,24,25]

One small study showed that after switching from tobacco to electronic cigarettes nicotine exposure was unchanged while exposure to selected toxicants was substantially reduced.[26]

Most of the safety concerns regarding electronic cigarettes relate to the absence of appropriate product regulation and inconsistencies in quality control. The current lack of regulatory oversight means that there is significant variability in device effectiveness, nicotine delivery and cartridge nicotine content both between and sometimes within product brands.[15]

Research has identified possible concerns about specific products. A recent study by the US Food and Drug Administration (FDA) has raised some safety concerns over the presence of toxins, released in low concentrations, from the vaporisation process of certain cartridges.[27]

There is little evidence of harmful effects in the short to medium term from repeated exposure to propylene glycol, the chemical in which nicotine is suspended.[28,29] One study concludes that electronic cigarettes have a low toxicity profile, are well tolerated, and are associated with only mild adverse effects.[30] More research is needed on long-term impact, particularly on the lungs.

Is there a risk to non-users from electronic cigarette vapour?

Although electronic cigarettes do not produce smoke, users exhale a smoke-like vapour which consists largely of propylene glycol and glycerine. The level of nicotine present in electronic cigarette vapour is about one tenth of that generated by a cigarette.[31] Any health risks of secondhand exposure to propylene glycol vapour are likely to be limited to irritation of the throat. One study exposed animals to propylene glycol for 12 to 18 months at doses 50 to 700 times the level the animal could absorb through inhalation. Compared to animals living in normal room atmosphere, no localised or generalised irritation was found and kidney, liver, spleen and bone marrow were all found to be normal.[25] A recent review of the impact of electronic cigarettes noted that passive exposure to the aerosol can expose non-users to nicotine but at concentrations that are unlikely to have any pharmacological significance.[32]

The fact that many electronic cigarettes look similar to conventional cigarettes has been said to risk confusion as to their use in enclosed public places, such as on public transport.[33,34] However, given that the most distinctive feature of cigarette smoking is the smell of the smoke, which travels rapidly, and that this is absent from electronic cigarette use, it is not clear how any such confusion would be sustained.

Furthermore, the absence of risk from “secondhand” inhalation of vapour from electronic cigarettes has been described as an “often unconsidered advantage” of electronic cigarettes.[35] As an alternative to smoking, electronic cigarettes are preferable in situations where secondhand smoke poses serious health risks to others, such as in vehicles or in the home.

Are electronic cigarettes effective in helping smokers quit?

The degree of effectiveness depends on what effect is being measured. ASH research shows that the most commonly reported reason for using electronic cigarettes (among all who report using or having tried them) was “to help me stop smoking tobacco entirely”.[36] Current smokers also report that they use the devices to “help me reduce the amount I smoke but not stop completely”. Effectiveness also varies between products and between users according to their experience in use.[37]

Currently in the UK, any nicotine-containing product which claims or implies that it can treat nicotine addiction is considered to be a medicinal product and is therefore subject to regulation by the MHRA. Consequently, electronic cigarette manufacturers have avoided making such explicit claims. Furthermore, the WHO has stated that “the electronic cigarette is not a proven nicotine replacement therapy”.[38]

Nevertheless, survey data suggests that, whatever the reason e-cigarette use may have been initiated, about 4 in 10 users in England currently use them in an attempt to quit smoking.[31] Recently published population level data shows they have taken over from over the counter NRT as the most popular support people use when quitting smoking[2] and are 60% more effective than NRT bought over the counter in helping smokers quit.[4] The effectiveness in that study was broadly similar to using a prescription medicine (including NRT) with limited professional support and less than using a prescription medicine with specialist behavioural support. A randomised controlled trial conducted in New Zealand found that electronic cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with broadly similar achievement of abstinence as with nicotine patches.[39] There is also some evidence to suggest that electronic cigarette use leads to abstinence among some smokers who had not intended to quit.[40]

Empirical data on the effectiveness of electronic cigarettes as nicotine delivery devices are still being collected.[41] Some reports from the published literature suggest that electronic cigarettes are inefficient nicotine delivery devices and result in only modest and unreliable increases in plasma nicotine levels.[42] Such findings appear to apply particularly to new users whereas studies using participants experienced in electronic cigarette use have been found to derive more reliable nicotine intake levels.[27] Whether experienced users are able to use these devices in a way in which their nicotine intake is maximised, or the variability is due to such users preferring certain devices which might significantly differ from those used by inexperienced users, is yet to be determined.[43,44]

Nevertheless, growing evidence suggests that electronic cigarettes are becoming more reliable in their nicotine delivery and that they have a beneficial impact in reducing subjective cravings and, in turn, number of cigarettes smoked.[27] Moreover, some studies have demonstrated an ability for certain brands of electronic cigarettes to reduce nicotine cravings despite delivering low plasma nicotine levels.[45] A recent review on the use, safety and effects of electronic cigarettes concluded that the devices do enable some smokers to reduce or quit smoking and that they offer a route to complete cessation of nicotine use.[33]

Another feature of electronic cigarettes that apparently lends to their effectiveness is an ability to provide an approximation to the superficial aspects of the experience of smoking. This has been demonstrated by users exhibiting reduced cravings, withdrawal symptoms and number of cigarettes smoked per day even when given a placebo electronic cigarette.[27]

The potential value, and perceived effectiveness, of electronic cigarettes in aiding smoking cessation has been assessed in user surveys. Caution must be exercised with these data as the samples have been recruited from electronic cigarette users' websites. However, one such survey conducted internationally reported that 72% of users believed that electronic cigarettes were beneficial in reducing cravings and withdrawal symptoms while 92% declared that the devices had reduced the number of conventional cigarettes they smoked. Indeed, in the same survey, 96% of former smokers claimed that electronic cigarettes had helped them quit, and 79% reported a fear that if they stopped using them they would start smoking again.[46]

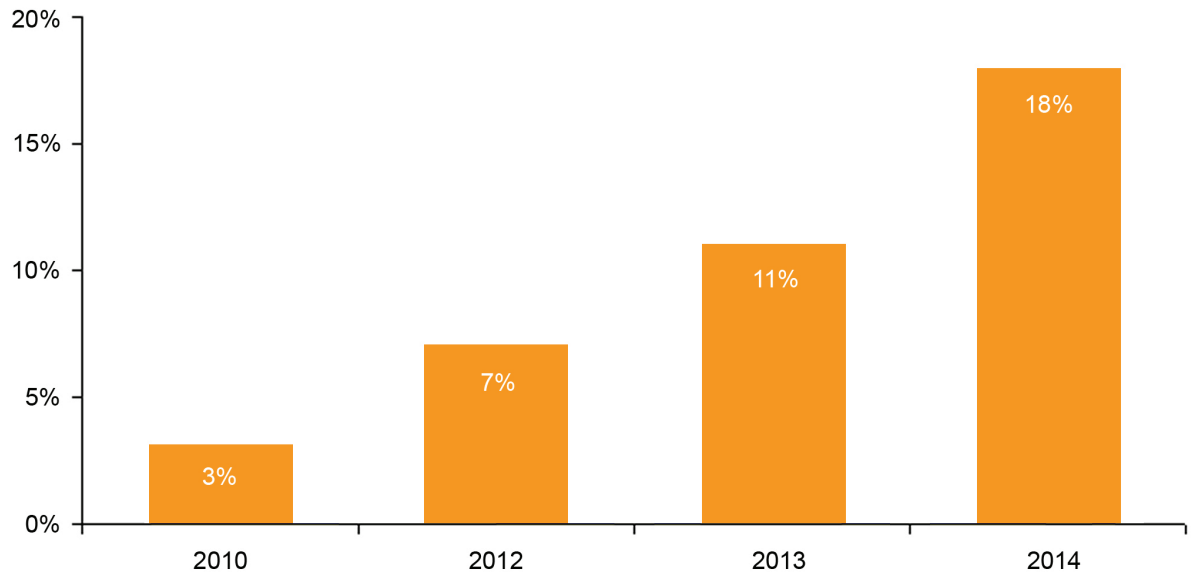
Who uses electronic cigarettes in the UK?

Public awareness of electronic cigarettes has grown substantially in recent years with online media playing an integral role in the growing popularity of the product.

Between the years 2009 and 2011 searches via the search engine Google using the terms 'electronic cigarette' increased fifty fold,[47] a fact the industry has attempted to capitalise on by funding various online adverts, web-pages and social networking site groups.[48] In addition to the influence of online media, there is also evidence to suggest that tighter tobacco control measures are also positively driving electronic cigarette behaviour.[49]

According to surveys commissioned by ASH, 3% of smokers in Great Britain reported using electronic cigarettes regularly in 2010, a figure that has increased to 18% in 2014 (see figure 1). Similarly, the number of smokers reporting having tried electronic cigarettes has increased significantly, from 9% in 2010 to 22% in 2012, 35% in 2013 and 52% in 2014.

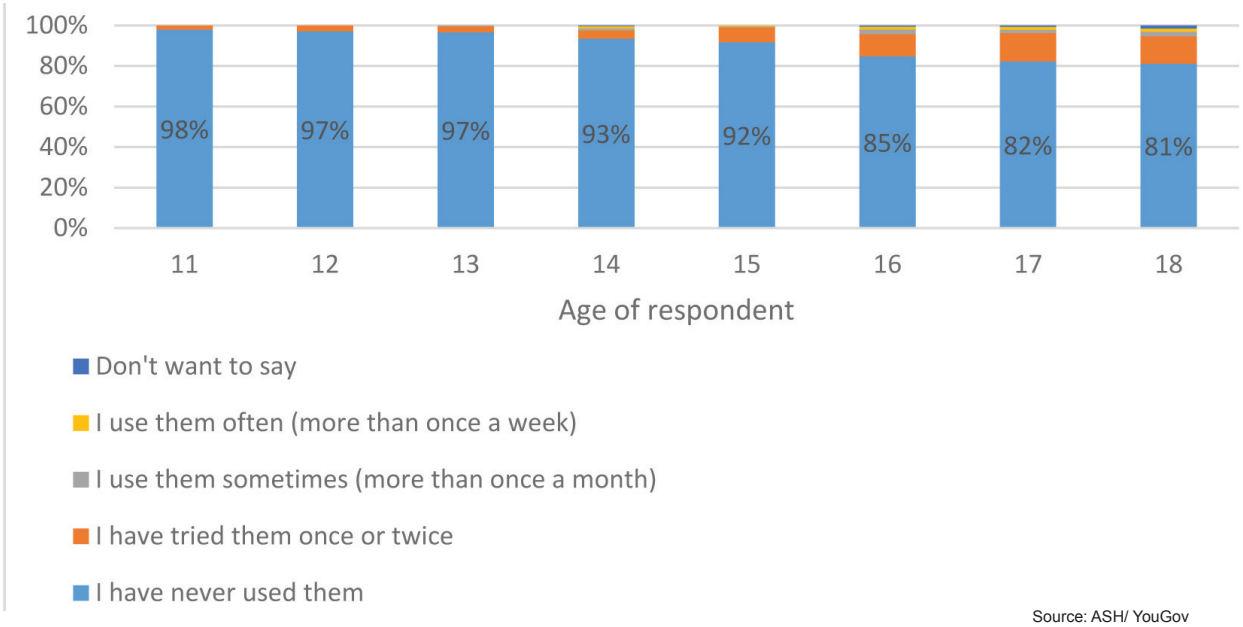
Figure 1: Usage of e-cigarettes amongst adult smokers in Britain



Source: ASH/ YouGov

One of the risks highlighted by professionals is that electronic cigarettes could act as a 'gateway' to smoking tobacco among children. Current evidence suggests this phenomenon is not occurring. Among children, current electronic cigarette use is confined almost entirely to those who have already tried smoking.[50,51] Figure 2 further shows that even having tried electronic cigarettes is rare among children, particularly those under the age of 15.

Figure 2: Usage of electronic cigarettes among children in Britain, 2014



Source: ASH/ YouGov

ASH estimates that there are 2.1 million current users of electronic cigarettes in the UK.[52] This number consists almost entirely of current and ex-smokers; of these approximately one third are ex-smokers while two thirds continue to use tobacco alongside electronic cigarettes. There is little evidence to suggest that anything more than a negligible number of never-smokers regularly use the product.[45]

For further information see:
ASH Factsheet: Use of electronic cigarettes in Great Britain
The National Centre for Smoking Cessation and Training (NCSCT) has produced an e-cigarette briefing summarising the evidence to date, especially in relation to the role of the stop smoking services and how stop smoking practitioners should respond to enquiries about e-cigarettes from smokers.

Regulation

Concerns have been raised about the rapid growth of the electronic cigarette market and the increasing involvement of tobacco companies in the industry. The World Health Organization treaty on tobacco (WHO Framework Convention on Tobacco Control) obliges signatories to protect health policy with respect to tobacco control from the 'commercial and vested interests' of the tobacco industry. Tobacco company involvement in tobacco harm reduction is a cause for concern.

Regulation has been seen as an important part of limiting the risk of tobacco industry involvement and to ensure the market evolves in a way that supports public health objectives.

In February 2014 the EU Tobacco Products Directive (TPD) was passed by the European Parliament and became law on 29 April. Member States now have until 20 May 2016 to transpose the new rules into national law.

Electronic cigarettes containing up to 20mg/ml come under the TPD.[53] Above that level electronic cigarettes will require marketing authorisation as medicines if they are to remain on the market.[5]

The detailed requirements of regulation under the TPD are as follows:

- A limit on nicotine strength of 20mg/ml (vaper websites say 18 ml/mg is the strength usually found suitable by average smokers[54])
- A size limit for e-liquids of 10ml for dedicated refill containers and 2ml for electronic cigarette cartridges and tanks.
- Safety mechanisms (such as childproof fastening and opening) for e-liquid containers, cartridges and tanks.
- Warnings on the two largest surfaces of the packs and any outside packaging covering 30% of the external area. These must state either '*This product contains nicotine which is a highly addictive substance*' or the above plus '*It is not recommended for use by non-smokers*'.
- Consumer information must also include instructions on use, information on addictiveness and toxicity, a list of all ingredients and information on nicotine content along with a prohibition on promotional materials on packs.
- Manufacturers and importers bear full responsibility for the quality and safety of their product and must notify detailed information about their products to competent authorities in each Member State.
- Prohibition on cross-border advertising promotion and sponsorship in line with that for tobacco products.
- Member States will be able to introduce extra safeguards for example on age-limits and flavourings in electronic cigarettes.

Until regulations implementing the EU Directive take effect electronic cigarettes not licenced as medicines will continue to be subject to general consumer protection law and it is the responsibility of trading standards officers to enforce the law.

In addition, the Children & Families Act 2014 gave the Government powers to ban the sale of electronic cigarettes to persons under the age of 18. A consultation on draft regulations is expected soon.

On 12 September 2014, Kind Consumer, a healthcare research and development company, announced that it had been granted marketing authorisation from the MHRA for a novel nicotine inhaler designed to help smokers cut down or quit smoking. The product called Voke is being developed with the company's partner, Nicoventures, a wholly-owned subsidiary of BAT.[55]

The MHRA has said that it "*continues to encourage companies to voluntarily submit medicines licence applications for electronic cigarettes and other NCPs as medicines*".[56] Public Health England supports the regulation by the MHRA of nicotine-containing products – including e-cigarettes – as medicines, to give people access to safe products that are also effective.[57] In the UK medicines regulation has some advantages for electronic cigarette manufacturers and importers over regulation under the TPD.

The following table shows the main elements of regulation under the TPD versus medicines regulation:

Characteristics of regulation under Tobacco Products Directive and MHRA	
Tobacco Products Directive regulation of electronic cigarettes	**MHRA licenced Nicotine Containing Products (NCPs) including e-cigs**
Products not available on prescription	Products available on prescription
20% VAT	5% VAT
Cross border advertising banned by 2016; up to Member States to decide on domestic advertising (billboards, Point of Sale, buses etc.)	Advertising allowed – under OTC rules so no celebrity endorsement, free samples and must be targeted at adult smokers etc.
Products widely available	Products available on general sale (GSL)
Can't make health claims	Can make health claims
Upper limits for nicotine content will be set and likely to be in force by 2017.	MHRA regulation is flexible; there are no upper limits.
30% health warning on packs about nicotine on front and back of packs	No health warnings on packs. Pack contains detailed Patient Information Leaflet.
Member States retain powers e.g. on flavours, domestic advertising.	Flavours require a marketing authorisation
Children and Families Bill allows for age of sale of 18 for nicotine products.	Age of sale 12 but can be varied by product so could be higher for e-cigarettes.

Following a referral from the Department of Health, NICE published guidance on tobacco harm reduction on 5th June 2013 as mentioned above.[7] This guidance recommended the use of licensed NCPs, which are nicotine replacement therapy products licensed by the MHRA (and do not at the current time include electronic cigarettes) for harm reduction purposes. Such purposes include using licensed NCPs as a substitute for tobacco, possibly indefinitely, to cut down prior to quitting, to smoke less, or to temporarily abstain from smoking.

Regulation of Advertising of electronic cigarettes

Some advertising for electronic cigarettes has been criticised as possibly attractive to young people and never-smokers.[58] There is a risk that inappropriate advertising could glamorise smoking and undermine public health goals. The involvement of the tobacco industry in the electronic cigarette market also raises questions about the opportunity of this industry to reach young people with pro-smoking messages.

Following a public consultation, CAP, the Committee on Advertising Practice, published new rules on the advertising of electronic cigarettes to cover the interim period between now and when the TPD comes into effect.

Key measures include:

- Ads must not be likely to appeal to people under 18
- People shown using e-cigarettes must neither be, nor seem to be under 25
- Ads must not be directed at people under 18 through the selection of media or the context in which they appear
- Ads must not encourage non-smokers or non-nicotine users to use electronic cigarettes
- Ads must make clear that the product is an e-cigarette and not a tobacco product.

CAP will monitor the effect of the rules and conduct a review after 12 months.

ASH's response to the public consultation can be viewed here.

Regulation of where electronic cigarettes can be used

Currently, electronic cigarettes are not regulated under smokefree laws in the UK, although this is under consideration in Wales.[59] In general, users are free to use them in most public places such as bars, restaurants and on public transport, although the managers of some premises have prohibited their use.

One stated advantage of smokefree legislation is that it de-normalises smoking, effectively distancing the behaviour from what is an accepted social norm. The ban on smoking in public places has reinforced in many people's minds that such behaviour has gone from a normal, widely accepted activity to one that is abnormal and unaccepted. There are concerns that electronic cigarettes will undermine this process, threatening the now established practice of smokefree public places, such as at work or on public transport. However to date there is little evidence to suggest this is the case.

ASH has worked with the Chartered Institute of Environmental Health and the Trading Standards Institute to produce guidance for organisations considering whether or not to ban the use of electronic cigarettes on their premises.[60] This provides a structure for thinking through the issues but leaves it to organisations to develop their own approach informed by the evidence.

Global Guidance

In August 2014 the World Health Organization published a report on ENDS (electronic nicotine delivery systems, more commonly known as electronic cigarettes) for discussion by the WHO Framework Convention on Tobacco Control Conference of the Parties meeting in October. Parties to the WHO FCTC were asked to note the report and '*provide further guidance*'.[61] The Framework Convention Alliance (FCA), which represents civil society organisations, developed a consensus position in advance of the COP on the principles which should underpin any regulatory system. See box below.[62]

The COP agreed with the FCA that global guidelines are not yet feasible but did invite "Parties to consider prohibiting or regulating ENDS including as tobacco products, medicinal products, consumer products, or other categories, as appropriate, taking into account a high level of protection for human health". Furthermore, the WHO was asked to prepare a report for the next COP with an update on the evidence of the health impacts, the potential role in quitting tobacco usage, methods to measure contents and emissions of these products, and impact on tobacco control efforts and policy options.

Principles to guide policy on tobacco harm reduction and electronic cigarettes:

- The global burden of death and disease from tobacco is primarily caused by smoking.
- While quitting tobacco use is paramount, quitting nicotine use altogether is the best option.
- For those unable to quit, switching to alternative sources of nicotine that are less harmful than tobacco can reduce, often very substantially, the harm smoking causes to the individual.
- The benefits of such an approach would be maximized if uptake were limited to existing smokers who are unable to quit.
- The risks of such an approach would be minimized by limiting uptake by never-smokers, in particular amongst young people, and by taking measures to protect non-users and discourage long-term dual use.
- There could be negative unintended consequences from over-regulation just as there could be from under-regulation.
- The involvement of tobacco companies in the production and marketing of electronic cigarettes is a matter of particular concern as there is an irreconcilable conflict of interest between those profiting from the sale of tobacco and public health.

Conclusion

ASH recognises that whilst efforts to help people stop smoking should remain a priority, many smokers either do not wish to stop quit or find it very hard to do so because of their addiction to nicotine. For this group, nicotine containing products which have been properly regulated to ensure product safety, quality and efficacy should be available as an alternative to tobacco.

Most of the diseases associated with smoking are caused by inhaling smoke which contains thousands of toxic chemicals. By contrast, nicotine is relatively safe. Electronic cigarettes, which deliver nicotine without the harmful toxins found in tobacco smoke, are a safer alternative to smoking. In addition, electronic cigarettes reduce secondhand smoke exposure in places where smoking is allowed since they do not produce smoke. Nonetheless, nicotine is an addictive substance, electronic cigarettes currently available are highly variable in terms of delivery of nicotine and product quality, and smokers are uncertain about the effectiveness of the product. There are concerns, as yet unsupported by evidence, that these products may provide a gateway into smoking for children and young people. The regulation of these products, in particular with respect to their advertising, promotion and sponsorship needs to be undertaken with these factors in mind.

In the UK smokefree legislation exists to protect the public from the demonstrable harms of secondhand smoke. ASH does not consider it appropriate for electronic cigarettes to be subject to this legislation, but that it should be for organisations to determine on a voluntary basis how these products should be used on their premises.[55]

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Adults:

March 2010: 2,297 adult smokers
March 2012: 12,436 adults
February 2013: 12,171 adults
March 2014: 12,269 adults

Children:

March 2013: 2,178 children aged 11-18
March 2014: 2,068 children aged 11-18

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Addiction

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Electronic Cigarettes

Electronic cigarettes: getting the science right and communicating it accurately

Electronic cigarettes are being used by millions of people worldwide, mostly in an attempt to reduce smoking or stop altogether. Policy makers, smokers, clinicians and the public in general need accurate information on their safety and potential for reducing smoking rates. Unfortunately in some notable cases the science is being misused, with findings being distorted, misinterpreted or misrepresented. Interestingly, up until now this appears to be mainly (though not exclusively) by those who are opposed to electronic cigarettes. Addiction's goal in this debate is to present evidence as dispassionately as possible whatever it shows, and to correct misinformation where it appears. It is worth highlighting the ways in which science is being misused so that readers can be better placed to evaluate the messages.

Failure to quantify: e.g., statement that e-cigarette vapour contains toxins so creating the impression that they are dangerous as cigarettes, without indicating that the concentrations are typically orders of magnitude less than tobacco smoke.

Failure to account for confounding and reverse causality: e.g., arguing that use of e-cigarettes reduces chances of stopping because in cross-sectional surveys the prevalence of e-cigarette use is higher in smokers than in recent ex-smokers.

Selective reporting: e.g., focusing on studies that appear to show harmful effects while ignoring those that do not.

Misrepresentation of outcome measures: e.g., claiming that e-cigarette use is prevalent among youth by using data on the proportion who have ever tried and creating the misleading impression that they are all current e-cigarette users.

Double standards in what is accepted as evidence: e.g., uncritically accepting conclusions from observational studies with major limitations when these claim that electronic cigarettes are causing harm, but discounting similar or better controlled studies when these appear to show the opposite.

Discrediting the source: e.g., arguing that researchers who have received financial support from e-cigarette manufacturers (and even companies that do not manufacture e-cigarettes) are necessarily biased and their results untrustworthy, and presenting themselves as having no conflicts of interest when their professional and moral stance represents a substantial vested interest.

These tactics are not restricted to the e-cigarette debate. We must be vigilant in recognising them to ensure that policies are based on the most accurate interpretation of evidence possible. Addiction will seek to adhere to the highest standards of critical review of papers submitted to us whichever direction the findings on e-cigarettes appear to point.

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Articles

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AHA Policy Statement

FACT AND FICTION IN POLICY

Electronic Cigarettes

A Policy Statement From the American Heart Association

Aruni Bhatnagar, PhD, FAHA, Chair; Laurie P. Whitsel, PhD; Kurt M. Ribisl, PhD; Chris Bullen, MBChB, PhD; Frank Chaloupka, PhD; Mariann R. Piano, PhD; Rose Marie Robertson, MD, FAHA; Timothy McAuley, PhD; David Goff, MD, PhD, FAHA; Neal Benowitz, MD; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research

SHOULD BE SUPPORTED BY RESEARCH

For decades, advocacy for tobacco control has been a priority of the American Heart Association (AHA). In partnership with major public health organizations, the association has made major strides in tobacco use prevention and cessation by prioritizing evidence-based strategies such as increasing excise taxes; passing comprehensive smoke-free air laws; facilitating US Food and Drug Administration (FDA) authority to regulate tobacco, including comprehensive tobacco cessation treatment within healthcare plans; and supporting adequate funding of comprehensive tobacco control programs in different states. These tobacco control efforts have cut in half the youth smoking rate from 1997 to 2007 and have saved >8 million lives in the past 50 years.[1] However, the work is far from done and has stalled, especially for people living below the poverty line, those with mental illnesses,[2] and those with low educational attainment.[3] Unless current trends reverse, ≈5.6 million children alive today in the United States will die prematurely of smoking-related diseases.[1] Even now, cigarette smoking kills nearly half a million Americans each year, and an additional 16 million individuals suffer from smoking-related illness, which costs the United States $289 billion dollars annually in direct medical care and other economic costs.[1]

This statement reviews the latest science concerning one of the newest classes of products to enter the tobacco product landscape—electronic cigarettes (e-cigarettes), also called electronic nicotine delivery systems (ENDS)—and provides an overview on design, operations, constituents, toxicology, safety, user profiles, public health, youth access, impact as a cessation aid, and secondhand exposure. On the basis of the current evidence, we provide policy recommendations in key areas of tobacco control such as clean indoor air laws, taxation, regulation, preventing youth access, marketing and advertising to youth, counseling for cessation, surveillance, and defining e-cigarettes in state laws. The statement concludes by outlining a future research agenda to further our understanding of this emerging area of tobacco control and the impact of e-cigarettes on public health.

FACT

E-Cigarettes or ENDS

The first concept of an electric cigarette was patented in 1965 by Herbert A Gilbert.[4] Subsequently, an aerosolized, high-frequency e-cigarette was patented in China by Mr. Hon Lik and Ruyan Technology; it entered the marketplace in 2003[5] and was patented internationally in 2007.[6] Ruyan has since registered patents in >40 countries, including the United States,[7] and has already brought patent infringement lawsuits against several e-cigarette manufacturers.[8] E-cigarette design and manufacturing processes continue to evolve, and most products on the market today use a simpler, battery-powered heating element instead of the high-frequency, ultrasonic technology patented by Ruyan.[7]

As of early 2014, there were 466 brands and 7764 unique flavors of e-cigarette products.[9] These products are now widely available online[10] and in retail outlets in many countries across the world.[11,12] In contrast to combustible products, e-cigarette availability in retail outlets in the United States is currently more likely in neighborhoods with higher median household income and a lower percentage of black and

FACT

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Hispanic residents.[12] E-cigarette availability in retail outlets is also higher in states with weak or nonexistent laws for clean indoor air and low cigarette taxes.[12]

Although the sale of e-cigarettes is prohibited in some countries (Australia, Brazil, Canada, Mexico, Panama, Singapore, and Switzerland), it is allowed in most others, including the United States.[13] The number of e-cigarettes sold has increased exponentially year by year. Wells Fargo has predicted that sales margins for e-cigarettes could grow to $10 billion by 2017, surpassing conventional cigarette sales margins.[14] The big 3 major tobacco companies have been purchasing independent e-cigarette companies and may share 75% of the profit pool in 10 years.[14]

E-cigarettes are battery-powered devices that have cartridges or refillable tanks containing a liquid mixture composed primarily of propylene glycol and/or glycerol and nicotine, as well as flavorings and other chemicals.[5] During use, inhalation activates a pressure-sensitive circuit that heats the atomizer and turns the liquid into an aerosol that is inhaled by the user through the mouthpiece and exhaled as a fine mist.[5] Some e-cigarettes have buttons that allow the user to manually activate the heating element. The exhaled aerosol does not contain smoke, tar, or carbon monoxide. Studies of specific types of e-cigarettes have shown that compared with conventional cigarettes, the byproducts from their aerosols produce very low levels of air toxins.[15–17] Proponents of e-cigarettes maintain that these products emulate smoking behavior without exposing the user to the toxic smoke constituents of conventional cigarettes that are deleterious to health, so there would be a public health benefit if individual smokers completely switched or substantially reduced their cigarette smoking habit.[18–20] However, the use of e-cigarettes could be a problem at the population level. For instance, e-cigarettes could fuel and promote nicotine addiction, especially in children, and their acceptance has the potential to renormalize smoking behavior. E-cigarette use could also potentially serve as a gateway to other drugs and harmful substances.[21]

FACT SUPPORTED BY RESEARCH

NO RESEARCH TO PROVE

E-Cigarettes: Design and Operation

Since their initial manufacturing in 2003, there has been a rapid growth and evolution in the types, design, and overall engineering characteristics of e-cigarettes.[22,23] This has resulted in a large degree of product variability in size, potential nicotine concentrations, and e-liquid formulations. There have also been changes in electrical circuitry (eg, heating element or atomizer) and battery life that allow for more e-liquid delivery, adjustments in flavor, and longer device use.

Different types of e-cigarettes are being developed continuously. Table 1 lists some of the different e-cigarette types and name brands on the market today. Newer second- and third-generation devices allow for multiple types of user customization. This has resulted in cross-product and within-product differences in aerosol production, nicotine delivery, and product use risk.[22] These developments significantly complicate the ability to assess the impact of e-cigarettes on individual and population health.[22,23]

Regardless of type, there are 3 basic e-cigarette components: a battery, an e-liquid–containing cartridge, and an atomizer (ie, a vaporization chamber with heating element).[21] Other components include an airflow sensor (sensing inhalation), a microchip for controlling the heating element, and a light-emitting diode light at the tip that simulates a burning cigarette tip.[21] All devices have air holes, which control the pressure drop and facilitate the flow of air required for puffing.[22] E-cigarettes are available with automatic or manual button–activated batteries. The battery in an automatic device is activated by inhalation or the drag, whereas manual devices require the depression of a button for battery activation.[22] The smokelike aerosol produced by these devices is not because of the combustion of organic material; rather, it is an aerosol of the e-liquid. As noted, the "atomizers" contain the heating elements that convert the fluid into an aerosol. Such atomizers are an essential component of all vaporizers, and they consist of a small heating element that evaporates the fluid and a wicking device that draws in the fluid. Since the inception of e-cigarettes, the atomizers have undergone dramatic engineering changes. Developments include the evolution of the atomizer into "cartomizers" (cartridge plus atomizer), which is a combination of an e-liquid distribution system and a wick/fiber and heating element.[23]

Second- and third-generation e-cigarettes models, which are larger than the first "cigarette-like" e-cigarettes (cigalikes), are referred to as "clearomizers," "tankomizers," or "carotanks" because they can hold several milliliters of fluid in refillable reservoirs. Some second- and third-generation e-cigarette batteries are available in different voltages (3.0 to 7.0 V) and with greater battery life (greater milliampere-hour) than earlier models. Within the atomizer, a resistance wire is encircled around the wicking device that draws the fluid in. When activated by the sensing device, the resistance wire rapidly heats up, turning the fluid into an aerosol, which is then inhaled by the user. The resistance and voltage applied to the heating element, as well as the material from which the heating element is made, are important determinants of the temperature achieved, which determines in part the amount and quality of the aerosol produced by the atomizer.

Some second- and third-generation e-cigarettes have programmed pumps, diaphragms, or micropumps on microelectromechanical systems. These allow for a specific programmed amount or a combination of e-liquid delivery to the aerosol generator.[22] Some e-cigarettes contain programmable logic units, integrated circuits, and other electronic components that are used to display average use cycle and safety warnings.[22] Ongoing product development and evolution are likely to continue, and therefore, new regulatory policies will be important to ensure appropriate quality control.

Profile of Users

The number and duration of surveys are increasing and variably include current, former, and nonsmoker categories.[24,25] These surveys are difficult to consolidate because they have been undertaken in different populations and jurisdictions, using different sampling methods and definitions, over a number of years while e-cigarette types, visibility, and use have increased dramatically. Generally, non-Hispanic whites, current smokers, young adults, and those with a higher education and higher income perceive e-cigarettes as less harmful than combustible tobacco products and are more likely to use

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Table 1. Types of E-Cigarettes

Generation	Examples
First generation	
First generation e-cigarettes were designed to look and feel like tobacco cigarettes. Although there is some variation in size, most resemble cigarettes and therefore have also been referred to as "cigalikes." These battery-operated devices were initially composed of 3 pieces: a battery, atomizer, and cartridge. Now, the atomizer and cartridge have been replaced by a combined "cartomizer," which screws into and connects with a battery, some of which are rechargeable. The disposable e-cigarettes are designed for 1-time use and are discarded after use. These cigalike devices are all available in various nicotine concentrations and with different flavorings.	Halo White Cloud Green Smoke Apollo Blu South Beach V2 Cigs Atlantic
Second generation	
These e-cigarette devices are larger and typically do not resemble a cigarette. These medium-battery (rechargeable)–style e-cigarettes are also referred to as "tank-styled" e-cigarettes. Sizes, shapes, and colors can resemble pens, small screwdrivers, or the tip of a hookah pipe. These larger e-cigarette devices have the basic e-cigarette components: the battery, the atomizer, and the cartridge. However, there are some key differences between these devices and the first-generation e-cigarette devices: second-generation e-cigarette devices have larger-capacity batteries (greater milliampere-hours) and therefore stay charged longer, have larger atomizers and electronic circuits that deliver greater energy (which enhances nicotine delivery to the user), and have large, separate cartridges ("tanks") that the user can fill up using different purchased e-liquids and flavorings. Some also have a manual switch that allows modulation of both puff length and frequency.	eGo Riva Tornado KGo
Third generation	
These devices are similar to the second generation but are larger and allow for more personal and custom modifications; therefore, they are sometimes referred to as "personalized vapors" or aerosols. Similar to the second-generation devices, these devices come with a range of different cartridge and atomizer options (eg, cartomizer, clearomizer, tankomizer) and batteries (greater milliampere-hours coupled with a certain voltage [3.0–6.0 V]). Some e-cigarettes devices allow the user to adjust the resistance on the atomizer/cartomizer. A low-resistance cartomizer produces higher heating element temperatures, thus generating more heat and affecting the amount and quantity of the aerosol. Users of these devices can pair different atomizers (that allow different resistances) with high-capacity batteries to maximize both aerosol production and battery life.	Companies with personal vapors: Apollo Henly Vapor Zone Volcano
E-cigars could either be classified as a second- or third-generation e-cigarette device. Available in disposable and rechargeable forms. Designed to simulate a cigar in terms of size. Some e-cigars have an LED tip that is partially hidden behind some type of screen to mimic a real cigar's ash.	E-cigar: Cuvana Marcello-rechargeable Vapor Zeus Royale premium

E-cigars indicates electronic cigars; e-cigarettes, electronic cigarettes; LED, light-emitting diode.

Circulation

them.[24,26–29] European and North American surveys conducted in 2012 and 2013 report that most e-cigarette users are current or former smokers[30]; 40% to 70% of all adults have heard about them, with awareness highest in smokers and growing.[26,31–33] Such surveys also report that ≈3% to 7% of the adult population has ever used e-cigarettes[26,34] Among smokers in the United States and Great Britain, ≈11% report ever having used e-cigarettes, whereas the use of e-cigarettes is significantly lower (0.5%–1.0%) in nonsmokers.[25,26,35] A study conducted in the Czech Republic in 2012 revealed that almost 20% of smokers who try e-cigarettes go on to become regular users.[36]

It is uncertain how many e-cigarette users are smokers who really want to stop cigarette smoking or ex-smokers but persistent e-cigarette users, or who want to be dual users. At present, there are few longitudinal studies to assess how many smokers are able to completely quit cigarette use, whether they continue e-cigarette use after quitting or whether they continue dual use, that is, using them concurrently with combustible products.[36] Epidemiological studies and population surveys also indicate that although many e-cigarette users plan to use the devices to quit or reduce their smoking, they are usually using them in a dual-use capacity, especially in places where smoking is restricted.[35–40] A survey conducted in 2012 showed that >80% of current e-cigarette users do not use them on a daily basis, and almost half of all smokers indicated they may use e-cigarettes in the future.[35] Finally, among college students, another e-cigarette user group, e-cigarette use may not be motivated by the desire to quit smoking, nor may it lead to quitting.[41] In conclusion, the overall use patterns are unclear and constantly changing, which makes it difficult to draw firm conclusions about the prevalence, preference, and purpose of e-cigarette use.

Youth

Concerned public health advocates see e-cigarettes as a route to nicotine addiction and possibly as a potential gateway to tobacco use in youth or nonsmokers and to reinitiation of tobacco product use by former users.[42] Data from the 2011 to 2012 National Youth Tobacco Survey[43] showed that among students in grades 6 through 12, current e-cigarette use (≥1 day in the past 30 days) increased from 1.1% in 2011 to 2.1% in 2012 and any use of e-cigarettes (ever use) increased from 3.3% to 6.8% in the same corresponding years. Overall, by 2012, 1.78 million high school and middle school students nationwide had tried e-cigarettes. For those students who had ever used e-cigarettes, 9.3% reported never smoking conventional cigarettes, whereas 76.3% of current e-cigarette users responded that they also smoke conventional cigarettes. Among never-smokers, 0.7% were currently users (past 30 days), which indicates that few never-smokers who try e-cigarettes continue their use.[44] A survey of 40 000 middle school and high school students from ≈200 schools has shown that e-cigarette use is higher in current smokers and ever-smokers

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and among those intending to quit.[43] This surveillance does not address whether adolescents are using e-cigarettes as a gateway to smoking cigarettes, but adolescents do consider e-cigarettes as high-tech, accessible, and convenient, especially in places where smoking cigarettes is not allowed.[45] Increasingly, there is robust marketing and advertising using celebrities and appealing flavors (eg, chocolate, strawberry, and vanilla) to make e-cigarettes especially more attractive and appealing to children and adolescents.[45] Much of the marketing for e-cigarettes has been through the Internet and social media outlets such as YouTube,[46] but increasingly, e-cigarettes are advertised on television, radio, and in the print media, where broadcast cigarette ads have been banned since 1971.[47] Data from a US population survey indicated that for those reporting they have heard about e-cigarettes, the majority (48%) reported television as their primary source, followed by "in-person conversation" and the Internet.[35] Another study found that youth exposure to television advertisements for e-cigarettes increased 256% between 2011 and 2013, with 24 million youth reached.[48] Online searches for e-cigarettes have surpassed those for nicotine replacement therapies (NRTs) and snus, products that have been on the market much longer.[49]

E-Cigarettes and Public Health

The major public health issues regarding e-cigarettes include whether or not they may contribute to reducing overall tobacco-related harm through complete cessation or possibly through reduction of the number of cigarettes smoked, denormalization of smoking, reduction in prevalence of use of combustible products (especially cigarettes), reduction of second-hand smoke exposure, and diminishing the influence of the tobacco industry. Although some believe that acceptance of e-cigarettes has the potential to reverse the social norm for prohibiting smoking in public places achieved over decades of advocacy work, others see these products as a way to denormalize smoking because they are a potential mechanism for quitting.[20] It is not known whether the emerging e-cigarette technology will shift people from combustible products to the exclusive use of e-cigarettes or whether dual use will persist.[50]

E-Cigarettes as a Cessation Aid

Current evidence evaluating the efficacy of these products as a cessation aid is sparse, confined to 2 randomized controlled trials and 1 large cross-sectional study, anecdotal reports, and Internet-based surveys. A large cross-sectional study showed that smokers who wanted to quit without professional help were significantly more likely to report abstinence using e-cigarettes than with traditional cessation aids or going "cold turkey."[51] The adjusted odds ratio for self-reported cigarette abstinence in e-cigarette users was 1.63 (95% confidence interval 1.17–2.27) higher than with NRT use and 1.61 (95% confidence interval 1.19–2.18) higher than for those using no aid. In a survey in the United Kingdom, 67.8% of e-cigarette users "completely replaced tobacco cigarettes with electronic cigarettes"; however, these reports are confounded by a self-selection bias in that the respondents are often e-cigarette enthusiasts.[39] In contrast, other surveys suggest that compared with never-users, e-cigarette users are less likely to be tobacco abstinent[52] and that e-cigarette users were no more likely than cigarette smokers to have quit permanently despite having reduced their cigarette consumption.[24]

FACT

The largest randomized controlled trial conducted to date, which used e-cigarettes available on the market in 2010 that are now obsolete, had cartridges labeled as containing 16 mg of nicotine and showed that the study e-cigarettes were modestly effective with or without nicotine at helping smokers quit, on par with the abstinence achieved with nicotine patches.[53] At 6 months, the verified quit rates were 7.3% with nicotine e-cigarettes, 5.8% with nicotine patch, and 4.1% with placebo e-cigarette treatment. This study also found that dual use persisted at 6 months at moderately high levels (approximately one third of participants); dual use also occurred with patch users but at much lower levels (7%).

Health Effects and Safety

The overall health effects of e-cigarettes should be considered both in the context of the intrinsic toxicity of e-cigarettes and with regard to their relative toxicity compared with the well-known injurious effects of smoking conventional cigarettes. Even if there are some intrinsic adverse health effects of e-cigarettes, there would be a public health benefit if e-cigarettes proved to be much less hazardous than combustible cigarettes and if smokers could switch entirely from conventional cigarettes to e-cigarettes. However, in general, the health effects of e-cigarettes have not been well studied, and the potential harm incurred by long-term use of these devices remains completely unknown. Nevertheless, some studies have examined the health effects of e-cigarettes by considering the constituents of their aerosol and their known toxicities and through toxicological evaluation of e-cigarette liquids and aerosols. Current data from human exposures, including experimental studies, and surveys of adverse effects and accidental exposure are discussed below. Available data on the safety and health effects of e-cigarettes have been reviewed elsewhere.[54–56]

FACT

The constituent and toxicant levels within the e-liquid and aerosol vary depending on the type of e-liquid (or e-juice) formulation and the specific design of the device.[57] Typically, e-liquid formulations contain nicotine, flavors, water, glycerin, and propylene glycol.[57] Exposure to levels and types of metals or other materials within the aerosol depends on the material and other engineering features of the heating coils.[57] Potential metallic and nanoparticles derived from the heating coils can include tin, iron, nickel, and chromium.[22,58] Other materials in e-cigarettes could include ceramics, plastics, rubber, filament fibers, and foams. Some of these materials can be aerosolized and inhaled. Importantly, low levels of harmful or potentially harmful metals such as lead, nickel, and chromium are listed as having been detected.[22,59] The e-liquids typically contain many flavorings, including tobacco flavoring. In tobacco-flavored products, other tobacco "contaminants" may be present. Trace levels of tobacco-specific *N*-nitrosamines, polycyclic aromatic hydrocarbons, and volatile organic compounds in the e-liquid and vapor have been reported; however, the amounts are deemed too low to cause human risk.[57,60] Other flavorings include fruit and spices (eg, strawberry, black cherry, and Ceylon cinnamon) or flavorings such as "bubble gum" or "chocolate truffle."

NO EVIDENCE TO SUPPORT

FACT

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Propylene glycol is a major ingredient in e-cigarettes. It is approved by the FDA as a solubilizing agent for different types of medications and is considered generally nontoxic.[59] However, in 1 product, small amounts of diethylene glycol, a potential byproduct of nonpharmaceutical grade propylene glycol, have been detected.[61] Other contaminants found in particular products have included the weight-loss chemical rimonabant (Zimulti) and the erectile dysfunction medication tadalafil (the active ingredient in Cialis). As a result, the FDA has issued warnings to several e-cigarette companies for selling e-cartridges with these contaminants.[61]

Nicotine

Nicotine is delivered by most but not all e-cigarette products. Most e-liquids contain 24 mg/mL, 18 mg/mL, 12 mg/mL, or 6 mg/mL nicotine and are qualified by the manufacturers as high, medium, or low nicotine strength.[62] Some e-liquids are available in 36 mg/mL concentrations.[62] Nicotine solutions of 100 mg/mL for use in making e-cigarette refill liquids are available over the Internet. As a point of context, 1 regular cigarette contains ≈10 to 15 mg of nicotine and delivers a systemic dose of ≈1 mg of nicotine. Testing has revealed that the nicotine content noted in some e-cigarette products and refill solutions has been incorrect and either overestimates or underestimates the amount of nicotine,[61] which indicates a need for regulatory oversight.[61] The overall total amount of nicotine in the e-liquid depends on the size of the refill vial; for example, a 10-mL bottle of 24 mg/mL contains a total of 240 mg of nicotine.

Blood levels of nicotine are generally lower from e-cigarette use than from conventional cigarettes, but users of some e-cigarette tank systems with more powerful batteries that heat liquids to higher temperatures may achieve blood nicotine levels comparable to those of cigarette smokers.[63,64] The extent to which nicotine inhaled from an e-cigarette is absorbed through the lungs or via the throat and upper airway has not been determined. The size distribution of particles generated by e-cigarettes, discussed later in this report, suggests that at least some pulmonary absorption is likely. In 1 study,[58] it was found that absorption of nicotine from e-cigarettes was lower than from tobacco cigarettes even with the new-generation cartomizers, which suggests that most absorption from the devices occurs in the buccal mucosa or upper airways. Compared with smoking 1 tobacco cigarette, the electronic devices and liquid used in this study delivered one third to one fourth the amount of nicotine after 5 minutes of use. New-generation e-cigarette devices were more efficient in nicotine delivery but still delivered nicotine much more slowly than tobacco cigarettes.

FACT

The main health concern for nicotine in cigarette smokers is maintenance of addiction. Most of the adverse health effects of smoking are caused by tobacco combustion products,[65] but there are some health concerns that are related to nicotine per se. Many of these concerns are related to the ability of nicotine to release catecholamines, including hemodynamic effects (increase in heart rate, a transient increase in blood pressure, vasoconstriction of coronary and other vascular beds), adverse effects on lipids, and induction of insulin resistance.[65] Nicotine has also been reported to produce endothelial dysfunction and to cause fetal teratogenicity, operating by different mechanisms.[66] Nicotine in vitro and in animals can inhibit apoptosis and enhance angiogenesis, effects that raise concerns about a role of nicotine in promoting the development and spread of cancer and in the acceleration of atherosclerotic disease.[67]

Because most people use nicotine in the form of tobacco products, there are relatively few data on the health effects of prolonged exposure to pure nicotine. There are some studies of prolonged NRT in smokers who have quit smoking.[68,69] In these studies, no adverse effects have been found when nicotine medication was administered for months to several years. Other studies indicate that patients with known cardiovascular disease tolerate NRT well for periods up to 12 weeks.[65]

FACT

Because most of the toxicity from cigarette smoking derives from combustion products, the health effects of smokeless tobacco could be examined to assess potential long-term adverse effects of nicotine without exposure to combustion products. Smokeless tobacco users take in as much nicotine as cigarette smokers, although not by the pulmonary route.[70] The most extensive and rigorous epidemiological studies on smokeless tobacco use come from Scandinavia, where a large percentage of men use snus, a smokeless tobacco product that contains nicotine but relatively low levels of carcinogens and other toxins. These studies report only a very small cardiovascular disease risk in snus users compared with tobacco smokers.[71] However, discontinuation of snus use after MI has been found to be associated with nearly halved mortality risk, which is similar in magnitude to the benefit associated with smoking cessation.[72] Thus, although the adverse health effects of e-cigarettes are not known, they are likely to be much less than those of cigarette smoking, but could be significant in individuals with heart disease.

FACT SUPPORT BY RESEARCH

Acute nicotine toxicity is a concern if e-cigarette liquids are ingested, which may occur accidentally by children or intentionally by adults as a suicidal overdose, or with dermal exposure. Nicotine is well absorbed through the skin when in an alkaline solution, and e-cigarette liquids are alkaline. Nicotine intoxication commonly causes dizziness, nausea, vomiting, pallor, tachycardia, and sweating. Abdominal pain, salivation, lacrimation, and diarrhea have also been noted. Confusion, agitation, lethargy, convulsions, and possibly death are seen in cases of severe poisonings that cause hypotension and respiratory muscle weakness.[73] In such cases, respiratory arrest is the most likely the cause of death.[73] Symptoms usually begin within 15 minutes of acute liquid nicotine exposure and resolve within 1 to 2 hours.[73] Cutaneous exposure may lead to delayed onset and prolonged symptoms. A number of cases of accidental exposure in children and adults have been reported by poison control centers.[74,75] The concentrations of nicotine in e-cigarette liquids are high enough to be fatal to a child if even a few milliliters is ingested.[76,77] There are isolated reports of severe toxicity, including death, in children who ingested e-cigarette liquids. Nationally, calls to poison control centers attributable to accidental exposure to e-cigarettes have increased dramatically (161%–333%), mostly involving children who were exposed to the replacement cartridges and liquids containing nicotine.[78,79]

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Minor Tobacco Alkaloids and Tobacco-Specific Nitrosamines

Some but not all e-cigarette liquids contain minor tobacco alkaloids (such as nornicotine, anabasine, or anatabine) and tobacco-specific nitrosamines, such as *N*′-nitrosonornicotine and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK).[76] These may be present in the liquids because nicotine is extracted from tobacco, and these compounds are present in tobacco. Several minor tobacco alkaloids have nicotine-like actions, although they are less potent than nicotine. Extensive evidence has shown that tobacco-specific nitrosamines are highly carcinogenic[80]; however, the levels of both minor alkaloids and nitrosamines present in most e-cigarette products are low and are unlikely to pose a significant human health risk.[81] Minor alkaloids and tobacco-specific nitrosamine are undetectable in nicotine medications.[82]

FACT

Carbonyls and Other Volatile Chemicals

Thermal degradation of propylene glycol can generate propylene oxide, which is classified by the International Agency for Research on Cancer as a class 2B carcinogen. The heating of glycerol can form acrolein, which is an irritant and oxidizing agent thought to contribute to adverse pulmonary and cardiovascular effects of cigarette smoking.[83–85] Analyses of emissions from cigarettes have found primarily formaldehyde, acetaldehyde, and acrolein, along with low levels of toluene, xylene, benzene, and butadiene.[86] Although these compounds are potentially toxic, the levels in e-cigarette emissions are many-fold lower than those found in cigarette smoke and in some cases similar to those found in the mist of medicinal nicotine inhalers. The risk of exposure to low levels of these compounds is unknown. With intense heating, such as from the use of tank models with large batteries, higher amounts of formaldehyde are generated, in some cases similar to levels found in cigarettes smoke.[60,87] Formaldehyde is a carcinogen and an irritant, but the risks of prolonged inhalation of formaldehyde at the levels found in e-cigarette aerosols are unknown.

FACT

Propylene glycol and glycerol are added in e-cigarette liquids to generate an aerosol that resembles cigarette smoke. Animal studies of propylene glycol inhalation for up to several months have revealed little or no toxicity.[88,89] Propylene glycol is used to generate theater fog and is used in aviation industries. It can cause eye and respiratory irritation, and there have been concerns about respiratory irritation in the theater.[90] Thus, there are concerns about potential harm from the inhalation of propylene glycol from e-cigarettes, particularly for people with asthma or chronic obstructive lung disease, although there is little research on the effects in susceptible populations.

Metals

Detectable levels of metals such as tin, silver, iron, nickel, cadmium, and copper have been detected in some but not all e-cigarettes in which they could be generated from the heating element.[58] Some e-cigarette solutions contain tin "whiskers," microscopic crystals that emanate from tin in the solder joints.[58] The nature and amount of metals generated depend on the design of the e-cigarette product, and some generate few or no metals. The levels of metals in e-cigarette emission are generally low, but little is known about the toxicity of prolonged inhalation of low levels of metals.

FACT

Particles

E-cigarettes generate an aerosol that consists of fine and ultrafine particles in a gas phase. These particles are likely generated from supersaturated 1,2-propanediol vapor. Nanoparticles present in some e-cigarette aerosols have been reported also to contain trace levels of tin, chromium, and nickel.[58] It has been reported that particle number concentration of the mainstream aerosol generated by e-cigarettes, averaged across several liquids and types of e-cigarettes, was similar to that of conventional tobacco cigarettes.[91,92] The number of particles in e-cigarette aerosol has been found to be influenced by the liquid nicotine content and puffing time, and higher levels of particles were generated by e-cigarettes that contained higher nicotine concentrations.[91] The particle size distribution from the few e-cigarette devices that have been tested has been reported to be similar to that of conventional cigarettes.[92] Particles such as those generated by e-cigarettes can reach deep into the lungs and potentially cross into the systemic circulation. Carbonaceous particles present in cigarette smoke and ambient air have been demonstrated to have adverse cardiovascular and respiratory effects in both human and animal models.[93,94] It is not known whether the type of particles generated by e-cigarettes have the same toxicity as particles present in ambient air or those generated by conventional cigarettes, but this is an important question for determining the long-term safety of e-cigarettes.

FACT

Toxicology Studies

Results of several toxicology studies with e-cigarette liquids and aerosols have been published. These studies show that e-cigarette liquids and aerosols affect the viability of established cultured cell lines, such as human or mouse fibroblasts, human embryonic stem cells, mouse neural stem cells, and cardiomyoblasts.[95–97] For example, using 3 different cell types (ie, human embryonic stem cells, mouse-derived neural stem cells, and human pulmonary fibroblasts), Bahl et al[95] examined the cytotoxicity of several flavored e-cigarette refill extracts from 4 different manufacturers. They reported that extract flavorings such as Ceylon cinnamon were toxic to all 3 cell types tested. In addition, 1 butterscotch sample was highly toxic, whereas 2 other butterscotch samples from the same company had low toxicity, which shows the within-product and between- product variability.[95] Overall, the human embryonic and neonatal mouse–derived stem cells were more sensitive than adult lung fibroblasts to the cytotoxic effects of the extracts. Cytotoxicity was not caused by nicotine but was correlated with the number and concentrations of flavoring chemicals. In general, cytotoxicity appeared to be related to the concentrations and numbers of flavorings used and unrelated to nicotine. Of particular concern with respect to cytotoxicity of flavorings are the effects of cinnamaldehyde, a flavoring that is approved for use in food but can be dangerous when inhaled.[98] Aerosols of some but not all e-cigarettes have also been reported to be mildly cytoxic.[98]

Although the nature, concentration, and time course of exposure to e-cigarette constituents are likely to be quite different from those present in tobacco cigarette smoke, in

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general, the few studies conducted so far suggest that e-cigarette emissions are much less toxic than cigarette smoke in cytotoxicity tests. The significance of these findings to the in vivo toxicity of e-cigarette liquid constituents is not clear, and additional research is needed to establish the potential toxicity of flavors and other e-cigarette constituents.

Human Health Effects

To date, relatively little research has been conducted on the human health effects of e-cigarettes. Spontaneous reports and clinical trial data have reported common minor side effects of throat and mouth irritation, dry cough, nausea, and vomiting. No serious adverse effects have been reported in clinical trials with >6 months of use compared with nicotine patches, with no difference between groups.[53,99] Because propylene glycol as a constituent of theater fog is known to cause respiratory irritation, pulmonary toxicity has been a reasonable concern. One study of 10 healthy smokers using 1 brand of e-cigarette (Nobacco, 11 mg of nicotine, >60% propylene glycol) as desired for 5 minutes found no significant effect on conventional spirometry measures but did find a small but significant increase in dynamic airway resistance (18%) and a significant decrease in exhaled nitric oxide (16%).[100] Smokers in this study had abstained from cigarette smoking for only 4 hours before using e-cigarettes, and there was no comparison with the effects of a conventional cigarette. Another study examined pulmonary function in 15 cigarette smokers and 15 never-smokers who used the same brand of e-cigarette (60% propylene glycol, 11 mg of nicotine).[101] Cigarette smoking caused a significant decrease in forced expiratory volume in the first second of expiration/forced vital capacity (FEV_1/FVC), which was not seen with e-cigarette use. This study also reported that cigarette smoking increased white blood cell count, which reflects an inflammatory response, whereas there was no significant change with the use of e-cigarettes.[101] A small retrospective study of pulmonary function and symptoms in smokers with asthma who switched to e-cigarettes found no adverse effects of e-cigarettes, but rather, the e-cigarette users had improved pulmonary function and reduced severity of asthma symptoms.[102] Eighteen heavy smokers with mild to moderate asthma who were taking a stable dose of inhaled corticosteroids and long-acting β-agonists had pulmonary function tests before and 6 and 12 months after beginning e-cigarette use. These individuals mostly started with e-cigarettes that were cigarette-like, but most switched later to tank-type devices. Ten individuals quit smoking entirely, whereas 8 continued dual use. Dual users decreased their number of cigarettes smoked per day from an average of 22.4 at baseline to 3.9 per day at 12 months. These subjects showed a small but significant improvement in FEV_1 and forced midexpiratory flow (25%–75%) and reduced airway responsiveness to inhaled methacholine, as well as an improved score on an asthma control questionnaire. The authors comment that the improvement in asthma symptoms may be related to stopping smoking or smoking fewer cigarettes, which could have led to less severe inflammation or a reduction in corticosteroid insensitivity. Although it was small, retrospective, and not controlled, this study does provide evidence that e-cigarette use is not harmful to people with mild to moderate asthma, but more extensive studies are required to establish the safety of e-cigarette use in this population.

Few studies have reported the cardiovascular effects of e-cigarettes. The results of these studies suggest that e-cigarettes can increase heart rate and blood pressure, as expected with systemic absorption in nicotine. The use of e-cigarettes for 7 minutes did not cause diastolic dysfunction, which was seen with conventional cigarette smoking.[55] Another study found that e-cigarette use had no effect on flow velocity reserve of the left anterior descending coronary artery assessed by echocardiography, whereas cigarette smoking caused a decline in flow reserve (16%) and an increase in coronary vascular resistance (19%).[55] A case of atrial fibrillation in an elderly person after e-cigarette use has been reported, an effect that could have been caused by the autonomic nervous system effects of nicotine.[103] One case of lipoid pneumonia has been reported in an e-cigarette user, but the causation is questionable because there is no clear biological plausibility.[102]

In summary, the data on health effects to date, studied primarily in healthy people with short-term exposure, reveal little or no evidence of severe adverse events. Respiratory irritation and the bronchial constriction from a propylene glycol aerosol raise concerns about harm to people with asthma and chronic obstructive pulmonary disease, but 1 small study reports no harm but rather benefit when users quit smoking or smoke fewer cigarettes per day. There are no reports of e-cigarette safety in patients with known cardiovascular disease.

Secondhand E-Cigarette Aerosol Exposure

Passive cigarette smoke exposure is hazardous. It is associated with an increased risk of respiratory disease, including asthma; a variety of infectious diseases; lung cancer; acute coronary events; and stroke.[104] Acute exposure to secondhand smoke produces endothelial dysfunction and platelet activation. Most or all of the acute adverse effects of secondhand smoke are thought to result from exposure to the combustion products of tobacco, including many oxidants and other reactive chemicals.

Most of the secondhand smoke generated from conventional cigarettes results from sidestream smoke, which accounts for 75% of the burning cigarette mass. E-cigarettes do not generate sidestream aerosol. The secondhand emissions from e-cigarettes consist entirely of what is exhaled after inhalation by the user. We focus on data from studies in which aerosol generated by e-cigarette users was evaluated.

Schripp et al[105] studied secondhand emissions by asking a volunteer to use e-cigarettes in a closed chamber. Analysis of the air revealed the presence of formaldehyde, acrolein, isoprene, acetaldehyde, and acetic acid, but at levels 5 to 40 times lower than those generated by a combusted cigarette. Schober et al[106] conducted 6 sessions, each of which consisted of 3 subjects using e-cigarettes as desired for 2 hours in a 45-m^3 ventilated room. The e-cigarettes were refillable tank devices with a liquid that contained both propylene glycol and glycerin and either 22 mg of nicotine per milliliter or zero nicotine. E-cigarette use significantly increased $PM_{2.5}$ (particulate matter <2.5 μm in size), propylene glycol, glycerin, and nicotine, but not formaldehyde, benzene, acrolein, or acetone. There was a 30% to 90% increase in the sum of 16 measured polycyclic aromatic hydrocarbons

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STATED ABOVE MAY NOT BE HARMFUL
FACT

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Not necessarily harmful. Also can get from grilled food

From CDC Tox-guide
Aluminum is ubiquitous in the environment. For the general population, exposure to aluminum most likely occurs through the consumption of food (mainly processed foods), water, and aluminum containing medicinals, such as antacids, buffered analgesics, antidiarrheal agents, or antiulcerative medication. Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally.

and a 2.4-fold increase in ambient aluminum concentration. No comparisons were made to secondhand cigarette smoke. Czogala et al[17] compared ambient levels of nicotine in a ventilated room in which people had either smoked conventional cigarettes or used e-cigarettes. Five subjects generated the aerosol over 1 hour using either pen or tank-type e-cigarettes. With e-cigarette use, the ambient level of nicotine was ≈10% of that seen with smoking conventional cigarettes (3.3 versus 31.6 μg/m^3). The ambient $PM_{2.5}$ concentration after e-cigarette use was ≈18% of that seen with cigarette smoking. In another study by Flouris et al,[101] 15 nonsmokers were exposed in a 60-m^3 ventilated chamber to 1 hour of secondhand cigarette smoke (at a concentration simulating that of a smoky bar) or to e-cigarette aerosol generated by a smoking machine. The study found that serum cotinine was similar in nonsmokers after secondhand tobacco smoke and e-cigarette aerosol exposure (2.6 versus 2.4 ng/mL). Exposure to e-cigarette aerosol had no effect on pulmonary function or white blood cell count. Thus, secondhand exposure to e-cigarette aerosol exposes a nonsmoker to nicotine, particulates, and several potentially toxic organic chemicals, but at much lower levels than from conventional cigarette smoke. The biological effects of such an exposure are expected to be much less than that of secondhand smoke, but nonsmokers are exposed to some nicotine, and the regular use of e-cigarettes has the potential to substantially contaminate the environment with nicotine.

FACT

Policy Guidance

Summary Position

The AHA recognizes the increase in e-cigarette use and the need to develop a clear policy position on their use and their impact on the tobacco control movement. E-cigarettes either do not contain or have lower levels of several tobacco-derived harmful and potentially harmful constituents compared with cigarettes and smokeless tobacco. In comparison with NRTs, e-cigarette use has increased at an unprecedented rate, which presents an opportunity for harm reduction if smokers use them as substitutes for cigarettes. However, although firm evidence is lacking, there are concerns that e-cigarette use and acceptance of e-cigarettes has the potential to renormalize smoking behavior, sustain dual use, and initiate or maintain nicotine addiction. Their use also could serve as a gateway to reinitiation of smoking by ex-smokers. Unregulated e-cigarette use also has the potential to erode gains in smoking cessation and smoke-free laws. The AHA considers e-cigarettes that contain nicotine to be tobacco products and therefore supports their regulation under existing laws relating to the use and marketing of tobacco products. To prevent the potential negative public health impact of e-cigarettes, we strongly support laws and regulation that prohibit the sale and marketing of e-cigarettes to youth. We support effective regulation that addresses marketing, labeling, quality control of manufacturing, and standards for contaminants. We also support the inclusion of e-cigarettes in smoke-free air laws. Moreover, we consider it important to monitor and prevent these products from serving as gateway products or as an initiation to nicotine addiction in nonsmokers and reinitiation in smokers. We will continue to assess the scientific evidence relating to their long-term health effects and their efficacy as a smoking cessation aid and encourage the development of a robust research agenda to understand the public health impact of e-cigarettes, especially in at-risk populations.

FACT

FACT

NO RESEARCH TO SUPPORT THESE STATEMENTS

Below, we summarize the association's current policy guidance on specific issues related to tobacco control, as well as the rationale underlying the policy recommendation. This policy guidance was developed by an expert advisory group and leading researchers in the field of tobacco control and prevention and e-cigarettes, in tandem with a comprehensive review of the literature. The association's policy guidance will continue to be updated as rapidly evolving evidence emerges.

Inclusion of E-Cigarettes in Smoke-Free Air Laws

The AHA supports the inclusion of e-cigarettes in smoke-free air laws.

Although the levels of toxic constituents in e-cigarette aerosol are much lower than those in cigarette smoke,[15] there is still some level of passive exposure to organic compounds, nicotine, and fine particles.[58,105,107] To date, there is insufficient evidence to support the notion that exposure to exhaled aerosol has a deleterious impact on bystanders.[26] Some studies have found very low concentrations of air pollutants across different types, liquids, puff durations, and nicotine concentrations.[15,105] The levels of particle and nicotine exposure vary with the composition of the liquids, the type of e-cigarette, size of the room, puff duration, interval between puffs, and the number of users.[105] Nevertheless, there is concern that nonsmokers will be involuntarily exposed to nicotine, which could be substantial where there is heavy e-cigarette use in confined spaces. Moreover, unregulated e-cigarette use has the potential to recreate a social norm around tobacco product use in public places,[108–110] unraveling decades of work on comprehensive smoke-free air laws. It is not always easy to identify that a person is using an e-cigarette, because there is not the large plume of smoke or the strong detectable odor that comes from conventional cigarettes. Therefore, the use of e-cigarettes creates enforcement issues for employees in restaurants, bars, airport terminals, planes, and other smoke-free public places. E-cigarette companies are marketing their products to be used in all the places where smoking is banned, including bars, restaurants, hotels, offices, and airplanes, which promotes unregulated use.

FACT

NO RESEARCH TO SUPPORT

PROVES YOU CAN TELL THE DIFFERENCE

Although the AHA supports the inclusion of e-cigarettes in new smoke-free laws, the AHA only supports changing existing smoke-free laws to include e-cigarettes when it can be ensured there will be no amendments attached to the legislation that would weaken existing laws.

Preventing Youth Access

The AHA supports the inclusion of e-cigarettes in state and federal laws and regulations that prohibit the sale of e-cigarettes to minors.

There is concern among public health advocates that e-cigarettes could increase nicotine addiction and serve as a gateway for the use of tobacco products, particularly among youth. As discussed above, adolescents view e-cigarettes as safer than conventional cigarettes, more convenient to use, and more readily accessible.[45] Their attraction to these "high-tech" devices is

NO RESEARCH TO SUPPORT

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BIG TOBACCO NOT VAPE INDUSTRY

fueled further by the marketing practices of the tobacco industry, which is manufacturing flavored e-cigarettes that are likely to be more appealing to a younger population. To reduce the availability of e-cigarettes among youth, 22 states have enacted e-cigarette youth access laws and 6 states have youth access laws for tobacco-derived or nicotine-containing products without explicitly using "e-cigarette" or similar terms in their law.[111] For instance, Arizona, California, New Jersey, and New Hampshire have now banned e-cigarette sales to minors. In its proposed rule on "Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act" the FDA proposed to ban the sales of e-cigarettes to consumers under the age of 18, which is similar to the existing federal ban on the sale of cigarettes and smokeless tobacco products to minors under the Family Smoking Prevention and Tobacco Control Act. Given that e-cigarettes are actively sold via Websites across state lines,[10] it is essential to develop a comprehensive federal law or regulation banning e-cigarette sales to minors because state laws are a temporary patchwork approach[112] and only the federal government can regulate interstate commerce.[113–115]

FACT

Marketing and Advertising to Youth

OREGON VAPERS SUPPORT

The AHA supports the inclusion of e-cigarettes in laws that restrict the marketing and advertising of e-cigarettes to minors.

There is robust marketing and advertising of e-cigarettes on television and in magazines using celebrities as well as flavorings to make these products particularly attractive to children and adolescents.[10] Many of these advertisements have themes that promote rebelliousness and glamorize e-cigarette use, which conveys the message to youth that e-cigarette use is fun, socially acceptable, and desirable. Youth exposure to e-cigarette advertising increased more than 250% from 2011 to 2013, with e-cigarette advertisements reaching >24 million youths during this period.[48] Such marketing practices are likely to recruit a new generation of nicotine addicts. The public health community is unified in developing regulation and passing legislation that restricts the marketing and access of e-cigarettes to minors, similar to existing laws restricting marketing and youth access to combustible products.

Taxing E-Cigarettes

The AHA supports taxing e-cigarettes at a rate high enough to discourage youth use, while retaining or increasing differentials with combustible products by increasing taxes on combustibles. Any revenue generated through taxation ideally should support tobacco cessation and prevention programs.

The diversity of products makes it difficult to develop a uniform tax policy for various devices and refills, and it also creates opportunities for avoidance. An ad valorem tax, one levied as a percentage of price, preferably at the retail level, could include all components of e-cigarettes and related devices. However, a tax that is too high would create a barrier to switching to e-cigarettes among low-income users of combustible tobacco. Growing evidence shows that e-cigarette users are more responsive to price than cigarette use, with 1 study estimating that a 10% increase in e-cigarette prices would reduce sales of reusable e-cigarettes by ≈19% and sales of disposable e-cigarettes by ≈12%.[116] Similarly, data from a survey with adult tobacco users show that their low prices relative to other tobacco products is a key reason for use among many current e-cigarette users (F. Chaloupka, written communication, June 6, 2014).[116] The initial cost of a reusable e-cigarette is higher, although over the long-term, they are cheaper because the reusable devices can be used over and over again. Hence, although a tax on the initial product could be punitive, especially for the low-income users, it is critical that the tax be high enough to deter youth access, because it has been demonstrated repeatedly that youth are especially price sensitive.[118,119] At the same time, increasing taxes on combustible tobacco products would prevent youth uptake, encourage some adult users to quit or cut back, and likely increase interest in switching from combustible products to e-cigarettes.

SUPPORT

WHY WOULD AHA MAKE THIS LAST STATEMENT ENCOURAGING E-CIGARETTE USE IF HARMFUL?

FDA Regulation of E-Cigarettes

The AHA supports effective FDA regulation of e-cigarettes that addresses marketing, youth access, labeling, quality control over manufacturing, free sampling, and standards for contaminants. The regulation should allow for quality-controlled products for adults who want to transition from conventional cigarettes to e-cigarettes or to quit or reduce smoking. Bottles containing nicotine refill liquids can be toxic if swallowed, so cartridges and bottles should have proper warning labeling and child-proof packaging.[120] It is important that the relevant government agency monitor whether these devices are used for delivery of other drugs and medications. Companies should not be able to claim that e-cigarettes are a cessation aid unless they are approved by the FDA for that purpose.

The FDA has currently issued its proposed rule to give the agency oversight over e-cigarettes, addressing youth access, sampling, ingredient listing, manufacturing, and warning labels, but not addressing marketing and advertising or flavorings. Some products currently on the market are unreliable and poorly designed, and there is inadequate and inaccurate labeling of constituents.[121,122] Several companies are moving their manufacturing processes from China to the United States to prepare for the standardization and quality control that will be required under FDA oversight.[123] Adverse event reports regarding e-cigarette use are being monitored in many countries across the globe. In the United States, the Center for Tobacco Products under the FDA is developing a tobacco-specific adverse event reporting system for e-cigarettes. Consumers or healthcare providers can report adverse events for any tobacco products through the Department of Health and Human Services' Safety Reporting Portal.[124] The FDA would regulate e-cigarettes for tobacco cessation under current rules via the Center for Drug Evaluation Research, and as is the case for all other approved cessation aides, this would require rigorous safety and efficacy studies. FDA oversight is critically important to ensure that e-cigarettes and similar products are not harmful to public health.

The entry of the major US cigarette manufacturers (Altria Group, Reynolds American, and Lorillard) into the marketplace raises a number of potential public health concerns. Rather than encouraging cessation, the tobacco industry could promote e-cigarettes as a way to circumvent clean indoor air policies, thereby promoting dual use to sell more conventional cigarettes. The industry could also steer e-cigarette users to combustible products and thereby increase rather than

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decrease nicotine and tobacco addiction.[125] E-cigarette manufacturers are spending millions of dollars and working with major lobbying firms to pass legislation or influence regulation to exempt e-cigarettes or carve out a special classification.[126]

In the European Union, starting in 2016, advertisements for e-cigarettes will be banned in all 28 nations, the packaging must be childproof and have graphic warning labels, and the nicotine content will be limited to 20 mg/mL.[127] The new regulations are part of a larger regulatory package that will impose even stricter rules on combustible tobacco products. The European Parliament backed off of its original proposal, which would have treated e-cigarettes as a medical or drug-delivery device, but allows member states to categorize them as a cessation aid if member states choose to do so.[127]

E-Cigarettes and the Potential to Regulate Nicotine Content of Conventional Cigarettes

The public health benefit of e-cigarettes competing with conventional cigarettes in a free marketplace is uncertain. Some potential harms, such as toxicity of unregulated products and marketing to youth, could be mitigated by effective FDA regulation. Possibly in the context of free market competition and perhaps with improved e-cigarette products, smokers would find e-cigarettes sufficiently attractive to use them to quit smoking. On the other hand, the permissive availability of e-cigarettes could result in an increase in nicotine addiction without a reduction in overall use of conventional cigarettes. A broader public health strategy could be developed that would combine regulation for combustible products, including regulation of characteristics and pricing, with the regulation of e-cigarettes or other electronic nicotine devices that appeal to smokers.[128] In 1994, the idea of reducing the nicotine content of cigarettes to make cigarettes less addictive was proposed, but the strategy was not implemented.[129] In 2009, the FDA gained regulatory authority over tobacco, which includes the authority to reduce nicotine in cigarettes to make them less addictive, as long as the nicotine level is not reduced to zero. Such a nicotine reduction regulatory policy could mandate nicotine reduction in all manufactured tobacco products so that they would not sustain addiction. Research is ongoing on the safety and the effects of smoking behavior with cigarettes with reduced nicotine content.[130,131] If a reduced nicotine content regulatory strategy becomes policy, cigarettes could become less addictive because of limited nicotine availability, and therefore, less attractive to the smoker. If at the same time, e-cigarettes are widely available, it could potentially help the cigarette smoker to transfer their nicotine addiction from tobacco to a cleaner form of nicotine delivery. This transition could be facilitated by differential taxation and could reduce the burden of cigarette-induced disease. Nevertheless, at present, it remains unclear whether society would be accepting of recreational nicotine addiction if associated with minimal health consequences. Modeling the health effects of reducing the nicotine content of cigarettes to nonaddictive levels, Tengs et al[132] concluded that "Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population."

Cessation Counseling

The AHA maintains that e-cigarette use should be part of tobacco screening questions incorporated into clinical visits and worksite/community health screenings that are tied to healthcare delivery. Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients regarding comprehensive tobacco cessation strategies. There is not yet enough evidence for clinicians to counsel their patients who are using combustible tobacco products to use e-cigarettes as a primary cessation aid. The association will continue to monitor the evidence concerning e-cigarettes as cessation devices to determine whether they might be integrated into comprehensive cessation strategies. For patients with existing cardiovascular disease and stroke, or at risk of a cardiovascular disease event, intensive cessation counseling should be offered as soon as possible. (See Table 2 for a summary of recommended clinical guidance.)

The efficacy of e-cigarettes as a primary smoking cessation aid has not been established as being better than other cessation modalities. Current evidence[50,53,134] suggests at best a modest effect on cessation, likely equal to or slightly better than that of nicotine patches without behavioral support. If a patient has failed initial treatment, has been intolerant to

Table 2. Summary of Current Recommendations for Clinical Guidance

E-cigarette use should be included in tobacco screening questions that are part of every health examination.
Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients regarding comprehensive tobacco cessation strategies.
Patients should be separated into 3 treatment categories based on their tobacco/e-cigarette use status[133]: 1. Tobacco product users who are willing to quit should receive intervention to help them quit 2. Tobacco product users unwilling to quit at the time should receive interventions to increase their motivation to quit 3. Those who recently quit using tobacco products should be provided relapse prevention treatment
There is not yet enough evidence for clinicians to counsel their patients who are using tobacco products to use e-cigarettes as a primary cessation aid.
If a patient has failed initial treatment, has been intolerant to or refuses to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt. However, patients should be informed that although e-cigarette aerosol is likely to be much less toxic than cigarette smoking, the products are unregulated, may contain low levels of toxic chemicals, and have not been proven to be effective as cessation devices.
In the absence of long-term safety studies of e-cigarette use, it may be appropriate to advise the patient to consider setting a quit date for their e-cigarette use and not to plan to use it indefinitely (unless needed to prevent relapse to cigarettes).
It is also important to stress that patients should quit smoking cigarettes entirely as soon as possible, because continued cigarette smoking, even at reduced levels, continues to impose tobacco-induced health risks.
For patients with existing CVD or stroke, or at risk of a CVD event, intensive cessation counseling and pharmacotherapy should be offered as soon as possible.

CVD indicates cardiovascular disease; e-cigarette, electronic cigarette.

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or refused to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt. However, subjects should be informed that although e-cigarette aerosol is likely to be much less toxic than cigarette smoking, the products are unregulated, may contain low levels of toxic chemicals, and have not been proven as cessation devices. Because there are as yet no long-term safety studies of e-cigarette use, it may be appropriate to advise the patient to consider setting a quit date for their e-cigarette use and not plan to use it indefinitely (unless needed to prevent relapse to cigarettes). It is also important to stress that patients should quit smoking cigarettes entirely as soon as possible, because continued cigarette smoking, even at reduced levels, continues to impose tobacco-induced health risks.

Employers will have to decide whether employees who use e-cigarettes exclusively will be considered tobacco users. Within the context of incentive design within healthcare plans associated with a worksite wellness programs, employers may charge tobacco users up to 50% more for their health insurance under the new Affordable Care Act regulations. There is no significant evidence that these tobacco surcharges increase quit rates, although 1 study showed that self-reported quit rates did increase more than the national average in Georgia State Health Benefit Plan employees.[135] With currently available methods, it is not possible to distinguish between a cigarette smoker and an e-cigarette user, because only the levels of cotinine are measured. Because cotinine is a metabolite of nicotine, it is likely to be present in the blood or urine of a user of e-cigarettes, combustible cigarettes, other tobacco products, and even nicotine patches. Hence, until newer methods are developed to distinguish between e-cigarettes and conventional cigarette use, employers would have to base their decisions primarily on self-report. Whether or not employers choose to penalize employees who are using e-cigarettes, employers should provide comprehensive cessation benefits to employees that include behavioral counseling and pharmacotherapy with a minimal copay or deductible for all users of tobacco products.

Insurance companies may also assess the 50% penalty in the individual market, although 10 states prohibit or restrict the ability of insurance companies to do that.[136,137] Along with age, geographic location, and family size, tobacco use is 1 of 4 variables that insurers can take into account when selling plans on the individual market. The AHA is concerned that the tobacco surcharge will make it difficult for tobacco users to access the cessation services they need. At minimum, insurers in the individual marketplace, like employers, should provide comprehensive tobacco cessation benefits with minimal copays or deductibles for all e-cigarette and tobacco users.

Surveillance for E-cigarette Use and Health Impact

The AHA recognizes the need to improve and increase surveillance on e-cigarette use throughout the US and global population and establish a research agenda to elucidate the longitudinal public health impact of e-cigarette use.

There is a need to increase or maintain surveillance using high-quality longitudinal studies on the prevalence of e-cigarette use in adults, children, and adolescents; quit attempts; quit rates; e-cigarette rates versus smoking rates; dual use (with combustible tobacco or other tobacco products); and reinitiation of ex-smokers to e-cigarettes and then perhaps back to tobacco. Current surveillance should also include adequate reference to the emerging products entering the marketplace to ensure there is a thorough understanding of the true prevalence of use of these alternatives to combustible products. Surveillance should also capture how these devices are being used for delivery of other legal or illicit drugs. There must be further experimental research and surveillance on the short-, medium-, and long-term physiological effects of deep lung inhalation of not only the nicotine but also propylene glycol and glycerol, flavorings, and other ingredients. Experimental research and surveillance also needs to capture the long-term population health impact, effect on fetal development, and physiological and behavioral effects of these ingredients, as well as the health impact of secondhand and thirdhand exposure.

Defining E-Cigarettes in State Law

The AHA supports including e-cigarettes in the definition of tobacco products (or tobacco-derived products) and smoking, not by creating a separate definition for e-cigarettes, because a separate definition can create a risk of e-cigarettes being exempted from other tobacco control laws, including smoke-free laws. E-cigarettes defined as tobacco products could still be treated differently within taxation legislation and regulation.

Bringing e-cigarettes within a general definition of "tobacco products" in state or local law is also entirely consistent with their treatment under federal law. In *Sottera, Inc. (dba NJOY) v FDA* (627 F2d 891 [DC Cir 2010]), an e-cigarette manufacturer argued that its products could only be regulated by the FDA as tobacco products under the Family Smoking Prevention and Tobacco Control Act of 2009, not under the drug/device provisions of the Food, Drug, and Cosmetic Act.[138] The court agreed with the manufacturer, holding that e-cigarettes fit within the broad definition of *tobacco product* in the Tobacco Control Act ("any product made or derived from tobacco that is intended for human consumption"). The court further held that e-cigarettes could be regulated only under the Food, Drug, and Cosmetic Act if marketed with therapeutic claims. Thus, in *Sottera,* an e-cigarette manufacturer sought to be regulated by the FDA as a manufacturer of a "tobacco product," and the court agreed that such regulation was within the FDA's authority as a matter of federal law.[138,139] These decisions were made although e-cigarettes do not actually contain tobacco, only nicotine derived from tobacco. The AHA agrees with the courts' rulings in defining e-cigarettes as tobacco products in legislation and regulation and has worked with public health partners to develop a consensus definition of tobacco products that includes e-cigarettes (Table 3). This definition includes e-cigarettes even if they do not contain nicotine, that is, any electronic device that delivers nicotine or other substances. The inclusion of all e-cigarettes in the definition facilitates implementation of laws and regulation. For example, when enforcing a clean indoor air policy, it would be impossible to determine whether someone who is "vaping" is using an e-cigarette that does or does not contain nicotine

Future Research Agenda

Because e-cigarettes are relatively new products, little is known about their use, their characteristics, or their long-term health effects on individual users and public health. Extensive

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research is required to address these questions. This will help in developing more robust policies to regulate e-cigarette use, marketing, and distribution. In view of the paucity of evidence, current guidelines must be regarded as provisional and should be revised in light of future research. However, e-cigarette research faces major challenges. E-cigarettes are not a well-defined entity but a collection of rapidly changing devices that deliver nicotine and contain a variety of additives that are also changing constantly. As a result, it is possible that research on specific e-cigarettes would become obsolete as product characteristics, design features, constituents, and additives change and new products appear on the market. Therefore, research will have to keep pace with the rapidly evolving market. Nonetheless, several invariant areas of future research could be identified, which are listed below.

Physicochemical Studies

Extensive work is required to develop a better understanding of the types of e-cigarettes currently in use and the ingredients they contain. To understand the nature of e-cigarette exposure, it is important to determine how heating time and duration of puffing alter exposure and the composition and characteristics of the vapor, as well as how each of these factors is affected by the design features of different devices. It will be important to evaluate how smoking e-cigarettes deposits nicotine and other chemicals in the environment and how these emissions and depositions affect secondhand and thirdhand exposures. Additional research is needed to evaluate the efficacy of vaping devices in delivering chemicals, drugs, and pharmaceuticals other than nicotine and to document manufacturing practices and quality control issues, so that the listed ingredients correspond to the actual composition of the device.

Perception

Profiles and perceptions of e-cigarette users have been documented in the literature; however, most of these data are derived from informal surveys from the Internet and other sources. New research is needed to determine the use and spread of e-cigarettes in different population subgroups and communities and to identify demographic factors that contribute to e-cigarette use in the general population. Additional research is also required to examine use trajectories, harm perception, and user expectations, as well as to determine how flavors affect perception and how future regulations might affect user profile and perception.

Use Pattern

Although extant data provide some indication of how e-cigarettes are currently being used, additional work is required to determine typical e-cigarette usage, with special emphasis on understanding brand/type preference and loyalty, frequency of use, brand switching, flavor preference, and the effects of puff duration. These issues also relate to questions about optimal dosing, such as the optimal dose (or use) for cessation by product type and the dose and use patterns that sustain nicotine addiction or satisfy nicotine craving over time. It would be important to know whether and how these devices are being used to deliver other drugs and medication and whether their use is particularly widespread in vulnerable populations, such as youth, trendsetters, populations with low socioeconomic status, current smokers, ex-smokers, veterans, the mentally ill, those with substance use disorders, and the lesbian/gay/bisexual/transgender community.

Health Effects and Toxicity

Preclinical studies, preferably in animal models, are required to evaluate e-cigarette toxicity. Although animal models have obvious limitations, and their relevance to human exposures is often uncertain, these models could be useful in assessing the pharmacokinetic, pharmacodynamic, and toxicokinetic properties of e-cigarette exposures. Data from these studies will be useful in assessing acute and chronic toxicity, as well as the respiratory, carcinogenic, teratogenic, metabolic, immunological, and cardiovascular effects of e-cigarettes. The pathophysiological outcomes and biomarkers, identified in animal studies, should also be evaluated in controlled human exposure studies to develop validated concordance between animal and human data.

Data from in vitro and animal studies could inform the design of studies to evaluate the acute and chronic health effects of e-cigarettes. Acute effects could be evaluated in cross-sectional or cross-over studies examining the respiratory, metabolic, neurological, and cardiovascular effects, as well as the effects on insulin resistance, appetite, and weight loss. These data would be particularly informative and interesting if the health effects of e-cigarettes are compared directly with conventional cigarettes or other tobacco products. Such comparisons will help in identifying not only e-cigarette–specific health effects but also the effects common to e-cigarettes and other tobacco products. Because cross-sectionals studies cannot establish directionality, progression, or causality, long-term longitudinal cohort studies are needed to assess how e-cigarette use affects the progression of subclinical disease. The results of well-powered, multicenter, prospective cohort studies with significant follow-up will provide important data for further refining policy recommendations.

Environmental Effects

Environmental research is needed to characterize e-cigarette emissions and to determine the chemical nature, size, and abundance of particulate matter generated in e-cigarette emission. In this research, it will be important to address the relative distribution of fine and ultrafine particles and to identify the chemical composition of these particles. Such studies are required to determine how changes in design features, additives, and constituents affect the direct toxicity of e-cigarette emissions. A particularly important issue that has direct bearing on regulation is the extent of secondhand and thirdhand exposure. Although e-cigarette emissions contain fewer chemicals and lower concentrations of toxicants than conventional cigarettes, the health effects of secondhand e-cigarette aerosol exposure are not known. Currently, most communities advocate the inclusion of e-cigarettes in smoking bans. This is justified because public use of e-cigarettes leads to involuntary exposure to a psychoactive drug (nicotine) in bystanders. However, additional work is required to identify constituents of e-cigarette emissions, how these emissions are dispersed in the environment, and how the

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characteristics of the environment affect the dispersal and the health effects of such emissions.

Psychological Effects

Evaluation of the psychological effects of e-cigarettes is of utmost importance in understanding how the use of these devices supports or promotes nicotine addiction and whether they aid nicotine cessation or abstinence. Although the results of some studies suggest that as a cessation aid, e-cigarettes can be at least as effective as other NRTs, further work with larger cohorts is required to establish not only their efficacy as cessation aids but also how these devices affect nicotine addiction and withdrawal, as well as how they compare with other NRTs in user satisfaction and dependence. An important question is whether e-cigarette use merely facilitates abstinence from smoking conventional cigarettes or results in complete independence from nicotine addiction. In studying the use of these devices for cessation, it is important to determine whether counseling or behavioral support would enhance efficacy, and if so, what are the most effective instructions required for the proper use of these devices as a cessation aid? And should physicians and health providers counsel for or against e-cigarette use? Research findings addressing these questions are likely to have a major impact on our understanding of the nature of nicotine addiction and how it is supported by conventional cigarettes versus e-cigarettes. Again, prospective cohort studies with long-term follow-up will be most useful in assessing how e-cigarette use affects nicotine addiction.

Marketing and Communications

Marketing and communications research is needed to determine how e-cigarettes are being marketed and how information about them is being communicated to their target audience. Research is needed to identify how specific marketing techniques are used to target specific groups, which specific groups are being targeted, and what effects labeling, product placement, advertisements, free sample distribution, location in stores, and celebrity endorsement have on e-cigarette sales, preference, and use. Additional research is needed to identify effective communication techniques for conveying health information, potential hazard or benefit, and regulatory information. By establishing a partnership with consumers, it may be possible to identify consumer perceptions and expectations and to identify cultural, social, and economic factors that impact e-cigarette use.

Surveillance

Surveillance of e-cigarette use is just beginning at the national level in the United States and is generally lacking at the state and local level. At the national level, several surveys have been collecting information, including the National Youth Tobacco Survey in 2011 and 2012 (http://www.cdc.gov/tobacco/data_statistics/surveys/NYTS/), the National Health and Nutrition Examination Survey beginning in 2013 (http://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/SMQ_ACASI_H.pdf), and the National Health Interview Survey beginning in 2014 (ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2014/english/qadult.pdf). The Behavioral Risk Factor Surveillance System, a major source of information regarding health behaviors at the state level, did not collect information about use of e-cigarettes as of 2013 (http://www.cdc.gov/brfss/questionnaires/pdf-ques/2013%20BRFSS_English.pdf).

The questions included in these surveys differ somewhat, primarily in the breadth of information collected. E-cigarette questions in the surveys above should use a similar format so the data can be pooled. Efforts to understand the public health impact of e-cigarettes require improved monitoring of awareness of the availability of e-cigarettes, beliefs about their health effects, and attitudes and behaviors regarding their use. Additional information is needed across the life span, especially in vulnerable groups, including children, and at the appropriate level to guide policy development, implementation, and evaluation; for these purposes, local and state-level data will be particularly important.

Postmarket surveillance is essential to understand and evaluate the public health impact of e-cigarettes. Such surveillance could include monitoring sales data, following the development and changes in the role of big tobacco companies and small entrepreneurs. Continuous pharmacovigilance is required to assess the safety and efficacy of these devices, changes in sales and marketing strategies, design features, and constituents. Such activities will be significantly facilitated by future regulation, which could define parameters for evaluating safety and regulatory compliance.

Economic Studies

Future research in economic issues relating to e-cigarettes is needed to evaluate the effect of taxation on e-cigarette sales and to assess the impact of e-cigarettes on healthcare costs and insurance premiums. Evaluation of the effect of taxation would be particularly important because this could have a significant impact on e-cigarette use across different populations. This type of research can be accomplished by both empirical research and observational studies, which will take longer and will require continuous analysis of sales data and purchasing behavior. Modeling work can be performed more quickly to predict what might happen with different approaches to taxation. Research in this area could be extended to include the cost of different devices and the contribution of e-cigarette sales to local and federal economies.

Legal and Regulatory Issues

Research is required to monitor and assess the effect of regulation on use, safety, and quality control and to determine the impact of legislation and regulation on industry and user responses.

Conclusions

E-cigarettes represent a major change in the tobacco control landscape. This policy guidance is developed from the current international evidence base and tobacco control environment in the United States. The AHA will continue to monitor the impact of these new technologies on population health, cardiovascular disease, and stroke and will give special attention to the effect on youth and adolescents. The association's policy position and clinical guidance will evolve over time with the rapidly emerging research and evidence base for this field.

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Appendix: Definitions*

"Tobacco product" means:

(a) Any product containing, made, or derived from tobacco or containing nicotine, whether synthetically produced or derived from other sources that is intended for human consumption (and not marketed for cessation), whether smoked, heated, chewed, absorbed, dissolved, inhaled, snorted, sniffed, or ingested by any other means, including but not limited to cigarettes, cigars, little cigars, chewing tobacco, pipe tobacco, snuff†; and

(b) Any electronic device that delivers nicotine or other substances to the person inhaling from the device, including but not limited to an electronic cigarette (e-cigarette), cigar, pipe, or hookah.

(c) Notwithstanding any provision of subsections (a) and (b) to the contrary, "tobacco product" includes any component, part, or accessory of a tobacco product, whether or not sold separately. "Tobacco product" does not include any product that has been approved by the US Food and Drug Administration for sale as a tobacco cessation product or for other therapeutic purposes where such product is marketed and sold solely for such an approved purpose.

It is important to note that this definition would include e-cigarettes, even if they do not contain nicotine. Thus, subsection (b) refers to "any electronic device that **delivers nicotine or other substances"** to cover devices (and components) regardless of whether they actually have nicotine or are being used to deliver nicotine. It was also recognized that there are alternative phrases that could be used to similarly expand coverage to non-nicotine products. For instance, the definition could refer to devices that "can be used to deliver nicotine."

"Simulate Smoking" Language

It is not desirable to include language describing e-cigarettes as devices that are, or can be, used to "simulate smoking." The vagueness of this phrase may give certain companies the opportunity to argue that their particular products are not covered because users are "vaping" instead of "smoking." Given the wide variety of e-cigarette designs emerging in the exploding marketplace for these products, there is some potential for companies to argue that their particular design looks nothing like a cigarette and that its use cannot be said to "simulate smoking." Because the phrase could have a limiting effect on the products covered and does not appear to be needed to effectively regulate e-cigarettes, it would be best to avoid including it.

Separate Definition of "E-Cigarette"

Generally speaking, use of this "tobacco product" definition or similar language would obviate the need to include a definition of "e-cigarette" that is separate and distinct from the definition of "tobacco product." However, in some states, it may not be possible to include the full description of e-cigarettes in the tobacco product definition. Also, if special circumstances arise in a state that suggests the desirability of both including e-cigarettes as "tobacco products" while also including a definition of e-cigarettes apart from the definition of "tobacco product," a separate definition of e-cigarette could be adapted from subparts (b) and (c) of the consensus "tobacco product" definition:

E-cigarette‡ means:

> *Any electronic device that delivers nicotine or other substances to the person inhaling from the device, including but not limited to an electronic cigarette, cigar, pipe, or hookah, including any component, part, or accessory of such a device, whether or not sold separately. E-cigarette shall not include any product that has been approved by the US States Food and Drug Administration for sale as a tobacco cessation product or for other therapeutic purposes where such product is marketed and sold solely for such an approved purpose.*

Finally, if a definition of "e-cigarettes" separate from the definition of "tobacco product" is desirable, then the definition of "tobacco product" will need to list "e-cigarettes" as one of the products to be considered "tobacco products."

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*These definitions were developed by an expert advisory group convened by the Campaign for Tobacco-Free Kids in April 2014. Participants were Chris Sherwin of the American Heart Association, Thomas Carr of the American Lung Association, Cathy Calloway of the American Cancer Society Cancer Action Network, and Nichole Veatch, Denny Henigan, and Ann Boonn of the Campaign for Tobacco-Free Kids.

†This list of products is subject to adjustment to conform to terms used in specific state or local laws.

‡Terms such as "electronic smoking device" or "electronic nicotine delivery systems" could be used interchangeably with "e-cigarettes."

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Steve A. Schroeder	UCSF	Robert Wood Johnson Foundation†	American Legacy Foundation†	None	None	None	None	None
Kenneth Warner	University of Michigan	Robert Wood Johnson Foundation (finishing grant on the tobacco endgame)*; Robert Wood Johnson Foundation (finishing grant on Tobacco Regulation Economics that relates to FDA's economic analysis of its graphic warning proposal)*	None	None	None	None	None	None
Rachel Widome	University of Minnesota	None	None	None	None	None	Association for Non-Smokers Minnesota*	None

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*Modest.

†Significant.

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American Heart Association®

Electronic Cigarettes: A Policy Statement From the American Heart Association

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on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research

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A statement made by Dr. David Abrams P.H.D, Executive Director Schroeder Institute for Tobacco Research and Policy Studies, a tobacco-policy think tank at the American Legacy Foundation, a DC anti-smoking nonprofit formed in 1999 as part of the landmark tobacco settlement.

I quote "5.6 million children alive today are expected to die as a result of cigarette use, along with 480 000 adults annually. Moving cigarette users to safer e-cigarettes benefits adults and youth. There is little evidence that e-cigarettes are a gateway to cigarettes. A recent study suggested this possibility, but confused correlation with causation. Youth e-cigarette experimentation (2.1% in 2012) is not associated with increased cigarette use. On the contrary, youth smoking declined 10% annually between 2010 and 2013 to record lows (9.6%). In addition, concern that e-cigarettes will addict another generation is not supported by evidence. Combustion delivers freebase nicotine in its most highly addictive form. Non-combusted nicotine delivery has reduced potential for addiction; nicotine is sold over the counter in nicotine replacement products with minimal addiction. The pharmacokinetic profile of e-cigarettes is much closer to nicotine replacement products in terms of addiction risk and harm. Both nicotine replacement products and e-cigarettes are now suggested for lifetime use instead of cigarettes, and a recent randomized trial found e-cigarettes were as effective as nicotine replacement therapy at stopping smoking.

Because cigarettes make up 92% of a $100 billion market, there is plenty of room for e-cigarettes in the market. E-Cigarette manufacturers do not need to addict youth. However, it is important to distinguish between Big Tobacco, which aims to promote cigarette and e-cigarette use, and independent manufacturers, which aim to eliminate cigarettes in favor of e-cigarettes. E-Cigarettes can create competition for entrenched tobacco products and speed the demise of cigarettes. Making it harder for independent e-cigarette manufacturers to compete with cigarettes will delay the obsolescence of cigarettes and perpetuate the status quo. Policies that recognize the differences in harm can help shift use to less harmful, less addictive e-cigarettes so that they are a gateway out of lifelong addiction to cigarettes. This approach is articulated in the 2014 Surgeon General's report: "Death … is overwhelmingly caused by cigarettes and other combustibles … promotion of e-cigarettes and other innovative products is … likely to be beneficial where the appeal, accessibility … and use of cigarettes are … rapidly reduced."

Policy making relies on science, not dogma. The danger is that concerns about hypothetical risks will lead not to the management of such risks but to status quo policies that perpetuate cigarette use. It is not nicotine per se that kills people; it is exposure to toxic compounds generated by burning tobacco. If nicotine can be decoupled from deadly tobacco smoke, adults and youth can be saved. The public health standard need not be weighted to favor youth prevention over adult cessation."

Quite a profound statement from one of the most respected people in tobacco research and anti-smoking policy!
Very Respectfully

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