

Review

NIH Electronic Cigarette Workshop: Developing a Research Agenda

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Abstract

Background: Electronic cigarettes (e-cigarettes) represent an emerging public health issue. These devices deliver nicotine along with other constituents, including flavorants, via an inhalable aerosol. Their uptake is rapidly increasing in both adults and youths, primarily among current smokers. Public debate is increasing on how these devices should be regulated and used, yet only limited peer-reviewed research exists. To develop an informed policy for e-cigarettes, their effects on human behavior, physiology, and health need to be understood.

Purpose: This paper describes proceedings from a National Institutes of Health–sponsored workshop, which was held in November 2013, to identify research needs related to the effects of

e-cigarettes. Discussion topics included e-cigarette risks and abuse potential; the potential role for e-cigarettes in harm reduction and smoking cessation; unintended consequences of e-cigarette use, such as becoming a gateway to conventional cigarettes; and dual use of both e-cigarettes and conventional cigarettes.

Results and Conclusions: The research needs identified by the workshop participants included the following: standards to measure the contents and emissions of e-cigarettes; biomarkers of exposure; physiological effects of e-cigarettes on tissues and organ systems, including pulmonary and cardiovascular; information on e-cigarette users, how the devices are used, and identification of the best tools to assess these measures; factors that drive use and influence patterns of use; and appropriate methods for evaluating a potential role for e-cigarettes in smoking or nicotine cessation. To understand fully the challenges and the opportunities that e-cigarettes represent, expertise will be needed in basic, behavioral, translational, and clinical sciences.

Introduction

Electronic cigarettes (e-cigarettes), a type of electronic nicotine delivery system, represent a dramatic new nicotine delivery technology. These devices can deliver nicotine along with other constituents via an aerosol, which is then inhaled, mimicking the feel of a conventional cigarette. This may serve to satisfy many of the behavioral and sensory cues of smoking in addition to providing nicotine. Introduced in the United States in 2007, e-cigarettes sales have been doubling annually and by 2013 were projected to become a nearly \$2 billion industry.^{1,2} This rapid uptake suggests e-cigarettes are a disruptive innovation to the conventional cigarette market. They may represent a less risky alternative to conventional cigarettes because users are not exposed to carbon monoxide (CO) or other toxicants at the same levels produced by the combustion of tobacco as in conventional cigarettes. However, the consequences of long-term exposure to the constituents of e-cigarettes remain unknown.

Data on the effects of e-cigarettes on human physiology and health are limited in part due to their recent emergence as well as their rapidly evolving construction and lack of standardization.³⁻⁵ Currently in the United States, the devices are largely unregulated at the federal level. Although some jurisdictions in the United States have laws prohibiting use in some public places and prohibiting sales to minors, the US Food and Drug Administration (FDA) currently does not have the authority to regulate e-cigarettes as tobacco products. A rule was proposed in April 2014 to extend the FDA's "tobacco product" authorities (which currently only apply to conventional cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco) to additional categories of tobacco products that meet the statutory definition of "tobacco product," including e-cigarettes (www.regulations.gov/#1documentDetail;D=FDA-2014-N-0189-0001).

Given the increasing popularity of e-cigarettes and their potential impact on the use of conventional cigarettes, the health science community must understand the effects of e-cigarettes on human health, how they affect nicotine addiction, and their potential role in smoking cessation and replacing combustible tobacco.

The National Institutes of Health (NIH) in 2013 sponsored an e-cigarette workshop to inform and promote research in this area. The goal was to facilitate interaction among investigators experienced in working with conventional and e-cigarettes and to discuss the need for a broad research perspective that should include tobacco use, nicotine addiction, biomarkers, harm reduction, epidemiology, and smoking cessation. Although not intended to be all-inclusive, this workshop represented an effort to identify many of the important research gaps.

The workshop focused on device design and characteristics, delivery of nicotine and other constituents, physiological consequences of exposure, patterns of e-cigarette use and issues associated with designing clinical studies to evaluate e-cigarette use in harm reduction and smoking cessation. These topics were further divided into subsections, presented below. In addition, regulatory perspectives were provided by representatives from the FDA Center for Tobacco Products (CTP) and the FDA Center for Drug Evaluation and Research (CDER).

E-Cigarette Design and E-Liquid Constituents

A typical e-cigarette consists of a battery, a reservoir containing e-liquid (usually a mixture of propylene glycol, glycerol, nicotine, flavorants, and other additives), a microprocessor, an air flow sensor or activating button, and a heating element. The heating element is usually a wire or rod made from various metals (e.g., nickel, chromium, copper coated with silver). In many devices, when a user takes a "puff," an air flow sensor activates the flow of electricity to the heating element, which heats and aerosolizes some of the e-liquid. This aerosol is analogous to the mainstream smoke from a conventional cigarette.⁶ Numerous e-cigarette designs are currently on the market with new ones rapidly becoming available. The original e-cigarette design, often called "cigalikes," resemble conventional cigarettes. Newer, larger devices often referred to as "tank systems" or "personal vaporizers," deliver nicotine more effectively and are increasingly popular.^{2,3} Tank systems have larger e-liquid reservoirs, larger batteries, and often bear no resemblance to a conventional cigarette. Because voltage affects delivery of nicotine (and other e-liquid constituents) to the aerosol, many devices now incorporate a tunable voltage battery.^{2,7,8} Users can adjust, or "tune," the voltage to optimize the amount of nicotine in each puff. Other customizable features that may result in higher concentrations of nicotine or other constituents in the aerosol include dual coil atomizers and multiple chamber atomizers.⁶

The chemical composition of the e-liquids varies considerably from brand to brand.⁹ In most products, nicotine is dissolved in mixtures containing propylene glycol and/or glycerol. Although some manufacturers indicate use of current Good Manufacturing Practices to generate their e-liquids, no standards are mandated. E-cigarettes may contain undisclosed additives and new formulations are continually introduced into the market. US regulation bans conventional cigarettes with characterizing flavors (not including menthol), such as pineapple, chocolate, and cherry.¹⁰ It is important to note that younger smokers exhibited a preference for flavored cigarettes.¹¹

E-cigarettes are often sold in flavored varieties including fruit and candy flavors and, in a similar manner, the flavors may preferentially increase the product's appeal to younger smokers. Other additives may include ethyl alcohol, stabilizers, and non-nicotine pharmacologically active compounds.

Aerosol Generation and Constituents

A key aspect of e-cigarette function is its ability to deliver nicotine from the e-liquid to an inhalable aerosol, popularly called vapor.¹² Smoking machine technology, developed for quantifying combustible tobacco smoke toxicant yield, can potentially be used with e-cigarettes to generate aerosols for analysis. Nicotine yield in the aerosol is influenced by multiple factors, including the way air flows through the device, puff volume, and puff duration (i.e., the "puff topography").^{6,7,13} The correlation between experimental product emissions and what is generated by the user is high when machine puffing exactly mimics human behavior.¹⁴ However, accurate data on puff topography are required. For example, current e-cigarettes generally deliver less nicotine per puff than conventional cigarettes.^{4,15} Because an e-cigarette can contain up to 40 times more nicotine than a conventional cigarette, the user can compensate for the decreased nicotine per puff by employing a different frequency, depth, and intensity of puffing to obtain more nicotine. Understanding the topography will allow accurate characterization of the devices.

Analyses of the aerosols from several brands of e-cigarettes revealed differences in their efficacy and consistency of nicotine aerosolization.^{4,9} This is likely to result from differences in device design, including heating elements, cartridge size, and battery strength. An empirically derived mathematical model is under development that may aid in understanding how these differences affect the amount of nicotine in the aerosol.⁷ Studies are also needed to explore how the puffing behavior is influenced by nicotine levels in an aerosol, sensory effects of nicotine and aerosol constituents (e.g., so-called "throat-impact"), taste and flavor of inhaled aerosol, and efficacy and speed of nicotine delivery to the bloodstream and brain to alleviate cravings. These characteristics modulate how smokers use conventional cigarettes, and e-cigarette users are likely to be similarly affected.^{16,17}

In addition to characterizing the aerosol nicotine concentration, the identities and concentrations of other aerosolized constituents and toxicants need to be determined. Recent studies found that though the aerosols contained some toxic and carcinogenic substances, including formaldehyde, acetaldehyde, acrolein, and traces of nitrosamines, the levels were 9–450 times lower than in conventional cigarette smoke and were often comparable with the amounts generated by a nicotine inhaler.^{9,12} The levels of these substances, however, can depend on the voltage used to generate the aerosol.⁸ Heavy metals have also been identified in e-cigarette aerosols.^{9,18,19} Studies are needed to assess whether the levels of toxicants in e-cigarette aerosol pose a health risk and to determine their toxicity thresholds.

Nicotine bioavailability and other biomarkers of exposure need to be measured. The aerosol deposition and absorption sites in the oral cavity and respiratory tract depend to a large extent on particle size. However, tobacco smoke exhibits far greater deposition than would be predicted by particle size due to the so-called "cloud motion" interaction among the particles.²⁰ Although e-cigarette aerosol particles are generally similar in size to that of tobacco smoke, it is unclear if they interact in a similar manner.^{21,22} Data are needed on the sites of e-cigarette aerosol deposition, the route of absorption, and the relationship between the concentration of nicotine in the aerosol and the rate of uptake to the blood stream.

Secondhand and Thirdhand Exposure to Aerosol Constituents

Although e-cigarettes do not generate sidestream aerosol emissions, secondhand mainstream aerosol exhaled by the e-cigarette user may involuntarily expose nonusers to the nicotine, ultrafine particles, volatile organic compounds, and other constituents released with exhaled aerosol.^{18,23–25} Substances remaining on the surfaces in areas where people have used e-cigarettes may contribute to thirdhand exposure. For example, studies show nicotine from tobacco smoke can react with oxidizing chemicals in the air to form secondary pollutants, such as carcinogenic nitrosamines.²⁶ This reaction may also occur with nicotine from e-cigarette aerosol. Research is needed to evaluate the level of exposure and health consequences of secondhand and thirdhand exposure to the constituents in e-cigarette aerosol, especially among vulnerable populations, including children and pregnant women.

Unintended Uses of E-Cigarettes

There is a potential for e-cigarettes to be misused, either by altering how they interact with nicotine liquids or by using the devices to deliver drugs other than nicotine. One reported method of altering the nicotine delivery characteristics is via "dripping," that is, placing drops of the e-liquid directly onto the heater.²⁷ Dripping can produce increased levels of nicotine and volatile aldehydes in the resulting aerosol because the heating element can reach a higher-than-intended temperature when not submerged fully in liquid.^{6,7,28} E-cigarettes may also be used with drugs other than nicotine, such as marijuana extracts.^{29–31}

Abuse Liability: Nicotine

The risk that the use of a drug containing product will lead to addiction is often referred to as its "addiction sustaining liability," "abuse potential," or "abuse liability."^{32,33} The abuse liability of a given drug can be greatly influenced by the design of the product's dosing characteristics including speed of delivery and absorption, and other factors that contribute to the ease, pleasure, and attractiveness of use of the product.^{32,34,35}

Nicotine delivery by e-cigarettes has gained the attention of some tobacco smokers as a means to decrease their exposure to the toxicants from combustible tobacco. However, there is a potential health risk for individuals who are not current tobacco users and may become dependent on nicotine via e-cigarettes. These individuals may be former smokers who relapse or nonsmokers who use nicotine for the first time. Rapid arterial absorption of nicotine via the lungs following inhalation of tobacco smoke leads to a reinforcement of the effects of nicotine and is an important contributor to addiction risk or abuse liability.^{36,37} In contrast, for example, products can be designed to minimize addiction risk, as with nicotine by gum or lozenge in which the delivery is buccal, and provides relatively slow and low venous exposure compared with inhaled nicotine.

Studies of early e-cigarettes indicated nicotine was absorbed at low levels, suggesting a lower risk of abuse liability than with conventional cigarettes.^{3,38–40} Newer versions of e-cigarettes, however, can readily deliver higher levels of nicotine. Furthermore, e-cigarette users can modify their behavior to optimize nicotine delivery, with some able to achieve conventional cigarette-like plasma nicotine concentrations.^{27,41,42} Evolution in design could lead to devices that carry an equal or higher risk of abuse liability and addiction than conventional cigarettes, which may be positively related to the likelihood of uptake, continued use, and the potential to substitute for combusted tobacco.

Thus, the abuse liability of e-cigarettes needs to be assessed, both with current models and with new devices as they develop to deliver greater amounts of nicotine. As previously noted, the behavioral and sensory aspects of e-cigarettes may also play an important role in their abuse liability and these may be useful to consider when assessing the devices. A variety of methods are used to assess abuse liability of drugs, and can include measurements such as liking, craving, withdrawal, and other psychological responses.^{32,40,43} Furthermore, investigations should take into account the variety of populations that may use these products. Policies and practices regarding e-cigarettes will require balancing their potential to assist adult users of conventional cigarettes to quit, with their potential to facilitate nicotine addiction among youth and adult nonsmokers, and relapse among former smokers.

Effects of Chemosensory Agents and Flavorants

Flavorants and other constituents that contribute to the chemosensory effects of a product can affect its appeal and abuse liability.³⁴ Agents that may have these effects, such as pyrazines, inorganic acids, and essential oils, are added to the liquids of at least some e-cigarettes.^{18,44} The Merit brand conventional cigarette had pyrazines artificially added to enhance its flavor.^{45,46} Consumer testing sponsored by the manufacturer of Merit, Philip Morris, found the majority of participants reported that the new Merit was equal or superior in taste to brands that delivered 60% more tar.^{46,47} Merit subsequently gained a large portion of the conventional cigarette market.⁴⁶ Similar compounds, found in the “flavor” fluids of e-cigarettes, may alter the sensory and chemosensory effects of the e-cigarette aerosol in a way that increases user satisfaction.^{48,49} These characteristics not only have the potential to make e-cigarettes more satisfying and promote switching from conventional cigarettes, but may also increase their abuse potential. Moreover, some of these agents were identified as potential reproductive toxicants.⁵⁰

Evaluating Acute and Long-Term Biophysical Effects

The measures for tobacco-induced harm (particularly smoking) were designed to detect changes occurring over many years, long after initiation. The recent introduction of e-cigarettes requires measures that must also assess the acute health impact. Use of e-cigarettes can increase lung flow resistance, modulate oxidative stress, and increase heart rate and blood pressure, with some of these effects directly related to the delivery of nicotine.^{40,42,51,52} However, few reports focusing on the acute effects of e-cigarettes are available, and both basic and clinical studies are needed. The majority of the e-liquid in e-cigarettes is comprised of propylene glycol and glycerol. These compounds have the designation, “Generally Regarded as Safe” as a food additive (www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm). Additionally, propylene glycol is used in some asthma inhalers. However, there is limited data available on the inhalation of either compound at the concentrations present in e-cigarettes. For glycerol-containing solutions, one concern is that when heated they can produce acrolein, a compound shown to be harmful to lung function.^{53–55} Propylene glycol can cause airway irritation, eye inflammation, and nasal congestion,^{56,57} and some of these effects have been reported by users of e-cigarettes.^{51,58} The health effects of inhaling these constituents repeatedly throughout each day for years need to be evaluated. Relevant assessments include pulmonary, cardiovascular, and carcinogenic measures. Evaluations of associated health risks are needed to assess the potential role of e-cigarettes in harm reduction. Specifically, data are needed to evaluate both their short-term use as a smoking or nicotine cessation therapy and their

longer term use as an alternative to and potentially less risky source of nicotine than combustible tobacco products.

Biomarkers of Exposure

Studies on the acute use of e-cigarettes will require urine or plasma biomarkers that can provide an objective indicator of dose. This approach is extremely useful in assessing toxicant and carcinogen exposure in people who use tobacco products.⁵⁹ Measures have yet to be identified that specifically report on e-cigarette use and would not show altered levels from dual use with conventional cigarettes. Previously described biomarkers not unique to e-cigarette use include total nicotine equivalents (sum of nicotine, cotinine, 3'-hydroxycotinine, and their glucuronides), which can be measured in urine.⁶⁰ These urinary compounds represent approximately 73%–96% of the nicotine dose and provide a superb indicator of nicotine uptake. The nicotine metabolite ratio (ratio of 3'-hydroxycotinine to cotinine) in plasma is an excellent phenotypic indicator of hepatic CYP2A6 activity in smokers and can be used as a measure of individual risk for addiction.⁶¹

The tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosornicotine (NNN), may provide important indicators of relative combustible tobacco and e-cigarette use, as their levels in e-cigarettes were recently shown to often be substantially lower than in combustible tobacco.^{9,62} The ratio of cotinine to total NNK metabolites (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides) in urine could be a useful biomarker of dual use of combustible tobacco products and e-cigarettes as it is expected to be significantly lower in combustible tobacco product users than in e-cigarette users.^{63,64} Total NNN, including its glucuronide, can be measured in urine. Although NNN is expected to be low in e-cigarette users, it can be generated in the body by nitrosation of nornicotine, which is co-extracted with the nicotine from tobacco or can be generated in vivo through nicotine metabolism.

Quantification of e-cigarette contaminant exposure is also important. 3-Hydroxypropylmercapturic acid (3-HPMA) and 2-HPMA (metabolites of acrolein and propylene oxide, respectively) can be measured. Acrolein is produced by the heating of glycerol, and propylene oxide is a potential decomposition product of propylene glycol. Additional toxic effects of e-cigarettes potentially could be assessed by measuring DNA adducts of formaldehyde and acrolein in leukocytes.⁵⁹ This suite of biomarkers has the potential to provide objective data on levels of nicotine as well as selected important carcinogens and toxicants that may be associated with e-cigarette use.

Determining Patterns of Use

Data on how e-cigarettes are being used and how they affect the prevalence of conventional cigarettes are critical for understanding the impact of these devices on public health. To fully explain the interest in these devices, it is important to know the patterns of use, the beliefs about the devices, the reasons for their use, and how these are affected by the changing marketplace. A pressing challenge is how to gather and integrate information over time to best understand the specific patterns of risk and exposures. Cross-sectional studies of e-cigarette use from 2010 to 2012 among US adults showed they were primarily being used by current smokers, with “ever use” ranging from 6.8% to 11.4% in 2010^{65,66} and increasing to 32.2% in 2012.⁶⁷ This rapid uptake by current smokers could indicate their desire to find a less risky alternative to conventional cigarettes. The

perception that e-cigarettes are less harmful/toxic than conventional cigarettes is one of the most commonly cited reasons for use; other reasons include believing e-cigarettes will help reduce tobacco craving and withdrawal symptoms, wanting to reduce conventional cigarettes smoked or to quit smoking conventional cigarettes altogether, and wanting to prevent relapse to conventional cigarettes.⁶⁶⁻⁷² Use by former smokers increased from 2.5% in 2010 to 7.4% in 2011, though what fraction were recent quitters of conventional cigarettes is unknown. Use by never-smokers ranged between 1.0% and 2.0% over the years 2010–2012, with no apparent directional trend.⁶⁵⁻⁶⁷ Additional assessments are needed to determine if this low rate will continue.

Surveillance systems and studies are needed to further understand the patterns and trajectories of use. The Population Assessment of Tobacco and Health (PATH) Study is a longitudinal study of up to 59,000 individuals, includes youths and adults and will likely provide invaluable information on e-cigarette use (www.pathstudyinfo.nih.gov). However, the PATH Study's annual data collection may make rapid assessment of e-cigarette use difficult. Monitoring the Future surveys 50,000 8th, 10th, and 12th graders and also includes questions about e-cigarettes (www.monitoringthefuture.org). This annual survey should supply key information about how the devices are being used by US youth. Nonetheless, reporting more often than annually is needed to spot trends in this rapidly changing area and to efficiently identify the populations using e-cigarettes, how they are being used, why they are being used, and under what conditions. For example, the Legacy Longitudinal Survey is bi-annual and surveys young adults 18–29 years of age. This survey recently found that among the 23% of young adult current conventional cigarette users, 30% reported dual use with other tobacco or nicotine containing products, with e-cigarettes accounting for 9% of total dual use.⁷³

Dual Use

Many e-cigarette users are not exclusive users of the devices, but are “dual users,” that is, users of both e-cigarettes and conventional cigarettes.⁷⁴ This suggests that rather than quitting their combustible use, the smokers instead added e-cigarettes. Although dual use can lead to substantial reductions in conventional cigarette consumption, this behavior may not confer significant reduction in harm, particularly for long-term conventional cigarette users. However, long-term dual use of nicotine replacement therapy (NRT) and conventional cigarettes does not produce significant adverse events and increases, not decreases, the motivation to stop smoking.^{75,76} Mean cotinine levels of e-cigarette dual users appear to be similar to that of conventional cigarette-only users, indicating nicotine intake remains relatively constant.^{77,78} Thus far, limited longitudinal data provide a conflicting picture of whether dual use is linked to consistent changes in motivation to stop conventional cigarette use.^{77,79-81}

Assessments of dual use will need to be very clear about how it is characterized. Definitions that may exclude or include the very different situations of using 1 e-cigarette a week and 20 conventional cigarettes per day versus using 5 conventional cigarettes a week and e-cigarettes daily could result in very different measurements of dual use. These differing definitions will affect measurement of the prevalence and incidence of dual use, the percent of e-cigarette users who dual use, and the direction of trends in dual use.

The long-term impact of dual use is unknown. Does dual use lead to greater reductions in conventional cigarette use over time, facilitate or delay quit attempts, or alter dependence (e.g., increased dependence because of greater nicotine exposure or decreased

dependence due to less rapid delivery of nicotine via e-cigarettes)? The scientific literature is also sparse on the effects of dual use on the smoking topography of usual brand cigarettes and resultant nicotine and toxicant exposures.

Youth and E-Cigarettes

The prevalence of e-cigarette use among US adolescents doubled between 2011 and 2012.⁸² The percentage of high school students who reported ever use increased from 4.7% in 2011 to 10.0% in 2012 and use within the past 30 days increased from 1.5% to 2.8% over the same time. Use nearly doubled among middle school students, from 1.4% in 2011 to 2.7% in 2012. A cross-sectional survey of four high schools in Connecticut and New York indicated similar trends, with past 30-day e-cigarette use increasing from 0.9% in 2010 to 2.3% in 2011.⁸³ Greater than 75% of high school e-cigarette users were dual users with conventional cigarettes.^{82,83} However, the increased prevalence of e-cigarette use in US youth is occurring at a time when overall smoking by teens showed a decrease, from 10.6% in 2012 to 9.6% in 2013.⁸⁵

A primary question is whether e-cigarettes promote nicotine addiction or conventional cigarette use in youth above what would otherwise be the case if the devices did not exist, whether they would further reduce conventional cigarette use, or result in dual use. In high school, youth current smokers have the highest rate of knowledge, willingness to use, or use of e-cigarettes.^{84,86-88} Although some youths who are nonsmokers also report e-cigarette ever use, estimates suggest this represents about 10% of middle and high school users.⁸² There are multiple reasons for teens and young adults to become interested in using e-cigarettes, varying across age groups.^{84,89-92} Focus groups of college, high school, and middle school students uniformly reported use due to curiosity and the attractiveness of flavors.⁹⁰ Among college and high school students, use of e-cigarettes by friends and family and the desire to quit smoking were motivating factors for use. Availability was also an important factor among high school students as were signs of independence among middle school students. Factors deterring initiation of e-cigarette use included smoking perceived as not cool, the expense, and their similarity to cigarettes.^{84,90} When those who tried e-cigarettes were asked the reason for e-cigarette discontinuation, youth smokers noted that they were not the same as cigarettes and youth nonsmokers indicated that the novelty wore off.^{84,90} An understanding of the trajectory of youth e-cigarette use, reasons for use, and consequences of use are needed.⁹³ Additionally, the role of flavors in the initiation and maintenance of e-cigarette use in youth, and strategies to reduce and prevent youth initiation need to be evaluated.

E-Cigarettes and Pregnant Women

Pregnant women who smoke conventional cigarettes are a population especially vulnerable to the use of e-cigarettes because of the popular view that the devices represent a less risky alternative to nicotine delivery. This is despite several studies indicating that NRT is not efficacious for smoking cessation during pregnancy.⁹⁴⁻⁹⁷ Although some high-income countries recommend NRT for pregnant smokers when behavioral therapies have failed, other countries do not recommend NRT presumably due to lack of maternal and fetal safety and smoking cessation efficacy data.⁹⁸ However, NRT treatment did lead to increased birth weight and gestational age compared with placebo, probably due to a reduction in CO and other toxicants in tobacco smoke.^{96,97} Similar to NRT, e-cigarettes do not produce CO and e-cigarette aerosols may

have reduced toxicant exposure relative to conventional cigarettes. The potential for e-cigarettes to not only deliver nicotine but also mimic the sensory aspect of smoking may be an important factor in reducing cigarette cravings in women by these devices.^{99,100}

As pregnant women are considered a vulnerable population, and nicotine, CO, carcinogens, and other chemicals in tobacco are reproductive toxicants,⁹⁶ the risk/benefit profile of e-cigarettes needs to be determined in this population of smokers. Of primary interest is to characterize the prevalence rates, overall nicotine exposure, cessation outcomes, and maternal and infant health outcomes of women who use e-cigarettes during pregnancy. Short-term clinical studies examining changes in acute and overall nicotine exposure and maternal and fetal hemodynamic parameters with e-cigarettes compared with conventional cigarettes and NRT are needed prior to longer term efficacy trials. Despite the potential for e-cigarettes to be useful for cessation in this population, the safety of the constituents in e-cigarettes has yet to be fully investigated and use during pregnancy may pose additional risks to the mother and the fetus.^{9,101}

Clinical Studies

Prospective clinical studies are needed to understand whether e-cigarettes have value in harm reduction by leading to a complete switch from conventional cigarettes to e-cigarettes, by reducing conventional cigarette use or by aiding in nicotine cessation. Data from the limited number of clinical trials using e-cigarettes for smoking cessation suggest no differences in abstinence rates between e-cigarettes that do or do not contain nicotine or between NRT and e-cigarettes.^{77,79} However, caveats with these studies include the limited size of the samples, the use of first-generation e-cigarette products that may not have delivered nicotine effectively, and the possible use of inadequate instructions. A retrospective analysis of data from the U.K. Smoking Toolkit Study indicated that individuals using e-cigarettes to quit smoking were about 1.6-fold more successful than users of NRT with no professional support or no aid.¹⁰² It is unknown what proportion of the e-cigarettes users who quit smoking still used the devices. Regardless, if e-cigarettes are equally effective for smoking cessation as NRT but more popular, on a population level there may be a greater overall decrease in smoking with the devices.

Several challenges and product-specific considerations are associated with e-cigarette clinical trials. For example, comparing e-cigarette trials with studies evaluating other cessation treatments may be difficult because of the differences in the marketing practices, as well as differences in the motivations of the participants for entering a trial (e.g., reducing harm by smoking fewer cigarettes, converting to long-term use of e-cigarettes, or using e-cigarettes as a means of quitting the use of all nicotine products). Additional important factors include the specific characteristics of the device used (including voltage of power supply, resistance of heater, concentration of nicotine, and nicotine delivery to the user), the sample population, the participant's perceptions of the product, and their rationale for entering the study.

Comparative effectiveness designs of nicotine cessation trials may be particularly informative for evaluating e-cigarettes. Understanding the value of the devices relative to current cessation therapeutics is needed to make informed risk/benefit analyses; trials comparing only placebo versus active treatment are less useful.

In conducting clinical trials with e-cigarettes, specific parameters need to be considered, such as the optimal duration of use and dose, which can be particularly challenging as differences in puff topography among users could lead to substantial variations in nicotine exposure. Clinical trials may require providing instructions to

subjects on how to use the product, in order to standardize exposures. Additionally, the availability of e-liquids with varying nicotine concentrations suggests that trials to assess gradual nicotine reduction may be particularly suitable for these devices.¹⁰³

Outcomes that may be especially important in determining the relative effectiveness of e-cigarettes as a smoking cessation aid would include the health effects of long-term use, patterns of dual use, nicotine and toxicant exposure biomarkers, and abstinence from combustible products. Exposure biomarkers that differentiate between e-cigarette and conventional cigarette use would be important for studies investigating a switch from combustible tobacco to e-cigarettes.

FDA Regulations and Requirements for E-Cigarettes in Clinical Studies

In 2008 and prior to the enactment of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), FDA determined that certain e-cigarettes were unapproved drug/device combination products. This determination was challenged in court. The US Court of Appeals for the D.C. Circuit ruled that e-cigarettes and other products "made or derived from tobacco" can be regulated as tobacco products and are not drugs and/or devices unless they are marketed for therapeutic purposes (*Sottera, Inc. v. Food & Drug Administration*, 627 F.3d 891 [D.C. Cir. 2010]).

Table 1. Key Research Gaps: Definitions and Methods

Definitions
<ul style="list-style-type: none"> • What should the devices be called: electronic nicotine delivery systems (ENDS, though some contain no nicotine), electronic cigarettes, e-cigarettes, aerosolized delivery system? • What is the definition of ENDS and electronic cigarettes? • How should the various types of e-cigarettes be classified? • What terms should be used when surveying consumer use, such as e-hookah or hookah pen?
Methods, populations, moderating factors
<ul style="list-style-type: none"> • What standardized methods should be used to assess the function and effects of e-cigarettes? <ul style="list-style-type: none"> –Machine-determined exposures (mimic human behaviors) –Aerosol generation and constituent evaluation –Pharmacokinetic and acute effects studies (control for volume, duration, naive vs. experienced users, etc.) –Quantification of e-cigarette use—number of cartridges, tank refills, disposable products –Quantification of dependence –Clinical trial methods and outcome measures –Animal models • What tools could be developed to understand effects? <ul style="list-style-type: none"> –Labeled nicotine tracer in e-cigarette liquid to assess delivery –Placebo e-cigarettes with additive (e.g., capsaicin) to mimic nicotine harshness • What are the intra- and inter-variation in user response to e-cigarettes? • What factors within populations moderate the effects of e-cigarettes? <ul style="list-style-type: none"> –Age –Sex –Race –Pregnancy –Vulnerable populations (low income, co-morbid mental illness or other disease, high-risk groups such as youth) –History of e-cigarette use, e.g., naive and experienced users

Currently, FDA CTP does not have regulatory authority over e-cigarettes. However, in April 2014, FDA proposed a rule, which would deem additional tobacco products to be subject to regulation under the Tobacco Control Act. If this rule is finalized, any e-cigarette that meets the legal definition of a “new tobacco product” will require a marketing authorization order from CTP. CTP may exempt a “new tobacco product” that is intended for investigational use from the Tobacco Control Act’s new tobacco product provisions. CTP may also issue regulations establishing the conditions under which persons can use a tobacco product for investigational use. Investigators with questions about exemptions from new tobacco product regulations may request a meeting with CTP’s Office of Science. CTP intends to develop a guidance document to clarify the process and describe CTP’s current thinking about investigational tobacco products.

FDA CDER does have jurisdiction over drug products, including e-cigarettes, with therapeutic claims. In general, a study evaluating the use of e-cigarettes for a therapeutic purpose requires an investigational new drug (IND) application if it is a “clinical investigation.” A “clinical investigation” is any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects (21 CFR 312.3(b)). In clinical investigations where an e-cigarette is being evaluated for a therapeutic purpose, the e-cigarette would be considered a drug/device combination product for which FDA CDER has primary regulatory jurisdiction. An IND is required for such research to assure the safety and rights of subjects in all phases of the clinical investigation and, in phases 2 and 3, to help assure that the quality of the research is adequate to permit an evaluation of the drug’s effectiveness and safety (21 CFR 312.22). The applicable procedures and requirements for clinical investigations conducted under an IND are set forth in title 21 of the Code of Federal Regulations, part 312 (21 CFR 312) (the IND regulations).

Whether an IND is required for a study that involves the use of an e-cigarette by human subjects depends largely on the study’s objectives. As noted previously, if the study is intended to evaluate the use of e-cigarettes for a therapeutic purpose, it is regulated by CDER as a study of a drug/device combination product and would most likely require an IND. Investigators with questions regarding whether their study protocol would require an IND can make an inquiry to FDA CDER.

Research Gaps and Key Challenges

Despite the ready availability of e-cigarettes at local stores and on the Internet, only limited published research is available and significant research gaps remain. The paucity of data is not surprising as these devices have been commercially available for less than a decade, became popular only in the last few years, and are rapidly evolving. Tables 1–3 present the key research questions raised by the workshop attendees. As described in Table 1, there is a lack of agreement on what defines the class of devices and appropriate terminology. Table 1 also presents basic research needs, which includes defining measurement standards on the performance and emissions of e-cigarettes and determining how to measure their effects using animal models. Table 2 lists research questions related to product design and constituents, health risks, addiction, and sensory appeal. These questions address gaps in knowledge surrounding technological aspects of the devices and their biochemical and physiological effects. Table 3 presents research questions related to use behaviors and the potential role of e-cigarettes in harm reduction and smoking cessation. The questions identify the need for appropriate standards to measure

their effects in clinical studies and how to evaluate the potential opportunity that e-cigarettes represent for cessation of combustible tobacco and nicotine.

Research gaps that may be best addressed by NIH were considered. For example, clinical studies with e-cigarettes are hampered by the lack of device standards and the rapid pace of device

Table 2. Key Research Gaps: Design, Biomarkers, and Appeal

Design and constituents
<ul style="list-style-type: none"> • What are the characteristics of the different brands and types of e-cigarettes (constituents, dose, stability under different storage conditions, voltage and temperature, particle size and density, lung deposition, changes during use, and so on)? • What are the most important design features that impact health, appeal (sensory aspects), and addiction potential? • What are the most important constituents (e.g., nicotine, minor tobacco alkaloids, monoamine oxidase inhibitors, pyrazines, propylene glycol, glycerol, and so on) including flavorants and impurities in the liquids and aerosols that impact health, appeal (sensory aspects), and addiction potential? • How do the aerosol constituents vary by device and user variables (topography, temperature and so on)? What toxicants are created in the generation of the aerosol? What is the potential for pharmaceutical interactions? • What are the pharmacokinetics of nicotine across products? How does the nicotine pharmacokinetics differ between e-cigarettes and conventional cigarettes? • How should toxicity be measured and what are acceptable levels of toxicity? • What design and composition features of e-cigarettes contribute to minimizing health risks (e.g., minimal/no toxicants, stable and low temperature, minimal or high addiction potential, sealed liquids to block tampering vs. user-accessible constituents)?
Indicators of health risk, addiction, and sensory appeal
<ul style="list-style-type: none"> • How do people use the devices (e.g., puff duration, change in topography over time, flow rate, patterns, and frequency of use) and how does use vary by product design? • What are the relevant pulmonary, cardiovascular, cancer, and fetal toxicity biomarkers to assess the acute and chronic effects of e-cigarettes, evaluating both the e-cigarette overall and the individual constituents? What biomarkers can predict health effects? • What are the health effects of dual or poly-tobacco use compared with e-cigarettes alone or to conventional cigarette products? How do e-cigarettes compare with medicinal nicotine products? What quantitative measures can accurately assess extent of dual use? • What are the health effects of secondhand and thirdhand exposure to e-cigarette aerosol? • How should the abuse liability of e-cigarettes be measured and how do e-cigarettes compare with other tobacco and nicotine only containing products? • How do sensory effects contribute to the abuse liability of e-cigarettes? How are these measured and what are the mechanisms of these effects (peripheral vs. central nervous system)? What role do they play in learned behavior and relapse? • What role does nicotine in varying doses versus sensory aspects play in the e-cigarette’s addiction potential (e.g., subjective effects, withdrawal suppression, concurrent tobacco use, relapse)? • What characteristics of e-cigarettes make users of conventional cigarettes consider switching? • Are there different characteristics of use or of the user population among different generations of e-cigarettes? • What experimental models or self-reports could be used to predict addictiveness or toxicity?

Table 3. Key Research Gaps: Behavior, Cessation, and Harm Reduction

Behaviors of use
<ul style="list-style-type: none"> • How are e-cigarettes used by current, former, and never-smokers? Is conventional cigarette use affected (measured using cohort studies, analyses of pattern of use, and retail outlet geocoding)? Are the social patterns of use different between e-cigarette and conventional cigarette users? • How can modeling and population surveillance techniques be used to estimate and understand trends in use (e-cigarette uptake, complete or partial substitution for cigarettes, and as gateway to smoking cigarettes) and factors moderating these trends? • Do e-cigarettes delay or facilitate cessation? What characteristics influence cessation? • How is dual use defined? What are the patterns of and reasons for dual use? Does dual use lead to conventional cigarette or nicotine cessation? Does dual use lead to altered addiction levels or changes in health risk? What factors can decrease the likelihood of sustained dual use? • How will use of e-cigarettes affect smoking prevalence and morbidity and mortality outcomes? • Does e-cigarette availability affect uptake by former users? Can this lead to smoking relapse? • Does e-cigarette availability lead to uptake in never-smokers? Does this substitute or complement uptake of conventional cigarettes? • How should relative risk information be communicated to consumers, health professionals, and adolescents? How do clinicians view e-cigarettes? • What guidance are clinicians providing to patients on e-cigarettes? Are they providing guidance on e-liquid toxicity and unintentional exposures, especially for infants and young children? • What are the attitudes, knowledge, and beliefs about e-cigarettes? How do they affect behavior? How do various advertisement channels and messages affect attitudes, knowledge, belief, and behavior? How do messages about e-cigarettes conveyed by family and peers affect use? • Is it possible to encourage users of conventional cigarettes to transition to e-cigarettes, while continuing to discourage e-cigarette use among youth and former cigarette smokers? • How do changes in product types, cost, and availability affect uptake and continued use?
Cessation and harm reduction
<ul style="list-style-type: none"> • What is the efficacy of e-cigarettes in cessation of conventional cigarettes or nicotine, either alone (placebo or nicotine e-cigarettes) or with approved therapies? How will e-cigarette use affect exposure biomarkers and toxicants? Will nicotine fading be an effective treatment? • What roles do nicotine delivery and behavioral aspects of e-cigarettes have in cessation of combustible tobacco or nicotine? • Are there acceptable outcome measures unique to e-cigarettes short of cessation, such as level of combustible use, toxicant exposure, degree of dependence? • Who are the best candidates for cessation or conventional cigarette reduction intervention with e-cigarettes? What are the unique considerations for special populations, individuals with comorbidities, or institutionalized populations? • What is the optimal instructional set in a clinical study for using e-cigarettes to replace conventional cigarettes or for nicotine cessation? Are there complexities unique to e-cigarettes due to the variability of nicotine puff yield between naïve and experienced users? • How can cessation opportunities with e-cigarettes be maximized? • What is the population reach of e-cigarettes; is it different from approved cessation products?

evolution. Many clinical studies cannot begin without an IND for a chosen e-cigarette. IND approval requires a level of product data and manufacturing documentation that is currently unavailable to many researchers. The research community needs to have access to a standard, well-characterized e-cigarette for clinical studies. Creating this resource and making it generally available for researchers is a large task that would benefit from the coordination and experience of NIH. In addition, NIH has experience in coordinating some of the large annual surveys of tobacco use and adolescent behavior. These may be considered a model for initiating more frequent studies to assess e-cigarette use in order to obtain more timely information about this rapidly moving phenomenon. Addressing e-cigarette knowledge gaps and facilitating e-cigarette research should be a priority for NIH.

Conclusions

There is extensive public discussion on whether e-cigarettes could substantially reduce conventional cigarette smoking, be an effective aid for nicotine cessation, or both. However, there is limited data available that directly addresses these issues. Concerns have also been raised about the potential for e-cigarettes to facilitate nicotine addiction, especially among youths and young adults, and to promote relapse among former smokers. The short-term and long-term effects of e-cigarettes on human physiology and behavior have yet to be fully explored. Independent, peer-reviewed research is the appropriate mechanism to evaluate e-cigarettes to assess both the potential risks and potential opportunities they represent.

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Declaration of Interests

MLG has received research funds from Pfizer. JEH, through his employer, Pinney Associates, provides consulting services to GlaxoSmithKline Consumer Healthcare regarding smoking cessation and to NJOY, a marketer of electronic nicotine delivery systems. JEH has a financial interest in a potential nicotine replacement therapy. JRH has received consulting fees from many for-profit and nonprofit developers and marketers of pharmacological and behavioral treatments for smoking cessation and organizations engaged in tobacco control. CAO is receiving free nicotine and placebo inhaler from Pfizer for an NIH-funded study of nicotine replacement for smoking cessation during pregnancy. CAO has previously received grant support from Pfizer and Nabi Biopharmaceuticals, and has also served on an advisory board for Pfizer. JER has received research funding support in the past from Philip Morris, United States, and has consulting and patent purchase agreements with Philip Morris International for nicotine inhalation technology. KMW was previously an employee in Neuroscience Discovery Research at Pfizer.

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References

- Abrams DB. Promise and peril of e-cigarettes can disruptive technology make cigarettes obsolete? *JAMA*. 2014;311(2):135–136.
- Herzog B. US tobacco trends: Disruptive innovation should drive outsized growth. www.ecigarette-politics.com/files/WF-DallasMarch2014.ppt. Accessed May 1, 2014.
- Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014;4:4133.
- Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res*. 2013;15:158–166.
- Henningfield JE, Zaatarı GS. Electronic nicotine delivery systems: emerging science foundation for policy. *Tob Control*. 2010;19(2):89–90.
- Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control*. 2014;23(suppl 2):ii4–i10.
- Balhas Z, Talih S, Salman R, Karaoghlanian N, Shihadeh A. Effects of user puff topography and device characteristics on electronic cigarette nicotine yield. Paper presented at the Society for Research on Nicotine and Tobacco 20th Annual Meeting; Seattle, WA; February, 2014.
- Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*. 2014;16:1319–1326.
- Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23(2):133–139.
- Food and Drug Administration. Tobacco products. www.fda.gov/TobaccoProducts/ProtectingKidsfromTobacco/FlavoredTobacco/default.htm. Published 2013. Accessed October 21, 2014.
- Klein SM, Giovino GA, Barker DC, Tworek C, Cummings KM, O'Connor RJ. Use of flavored cigarettes among older adolescent and adult smokers: United States, 2004–2005. *Nicotine Tob Res*. 2008;10(7):1209–1214.
- Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control*. 2014;23(suppl 2):iii11–iii17.
- Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. *Tob Control*. 2014;23(suppl 2):ii30–ii35.
- Shihadeh AL, Eissenberg TE. Significance of smoking machine toxicant yields to blood-level exposure in water pipe tobacco smokers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(11):2457–2460.
- Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. *Addiction*. 2014;109(3):500–507.
- Benowitz NL, Jacob P 3rd, Yu L, Talcott R, Hall S, Jones RT. Reduced tar, nicotine, and carbon monoxide exposure while smoking ultralow- but not low-yield cigarettes. *JAMA*. 1986;256:241–246.
- Kozlowski LT, O'Connor RJ. Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tob Control*. 2002;11(suppl 1), i40–i50.
- Schober W, Szendrei K, Matzen W, et al. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health*. 2014;217:628–637.
- Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One*. 2013;8:e57987.
- Martonen TB, Musante CJ. Importance of cloud motion on cigarette smoke deposition in lung airways. *Inhal Toxicol*. 2000;12(suppl 4):261–280.
- Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. *Environ Pollut*. 2014;184:523–529.
- Zhang Y, Sumner W, Chen D. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine Tob Res*. 2013;15:501–508.
- Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res*. 2014;16:647–654.
- McAuley TR, Hopke PK, Zhao J, Babiak S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol*. 2012;24:850–857.
- Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air*. 2013;23(1):25–31.
- Sleiman M, Gundel LA, Pankow JF, Jacob P 3rd, Singer BC, Destailats H. Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci USA*. 2010;107:6576–6581.
- McQueen A, Tower S, Sumner W. Interviews with “vapers”: implications for future research with electronic cigarettes. *Nicotine Tob Res*. 2011;13(9):860–867.
- Shihadeh A, Salmon R, Balhus Z, Karaoghlanian N, Melvani R, Eissenberg T. Factors influencing the toxicant content of electronic cigarette vapor: device characteristics and puff topography. Paper presented at the Society for Research on Nicotine and Tobacco 19th Annual Meeting; Boston, MA; March, 2013.
- Bryan M. Pot smoke and mirrors: vaporizer pens hide marijuana use. www.npr.org/blogs/health/2014/04/18/302992602/pot-smoke-and-mirrors-vaporizer-pens-hide-marijuana-use. Published 2014. Accessed May 9, 2014.
- Welch WW. (March 17 2014). Vaporizers, e-cigs of the pot world, are booming. *USA Today*. www.usatoday.com/story/money/business/2014/03/15/marijuana-vaporizing-gains/6042675/. Accessed October 21, 2014.
- Wells J. It's pot, it's smokeless - and it's publicly traded. www.cnbc.com/id/101560701. Published 2014. Accessed April 7, 2014.
- Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):3241–3262.
- Schuster CR, Henningfield J. Conference on abuse liability assessment of CNS drugs. *Drug Alcohol Depend*. 2003;70(3):S1–S4.
- Henningfield JE, Hatsukami DK, Zeller M, Peters E. Conference on abuse liability and appeal of tobacco products: conclusions and recommendations. *Drug Alcohol Depend*. 2011;116:1–7.
- World Health Organization. WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: fourth report of a WHO study group. WHO Technical Report Series, No. 967. www.who.int/tobacco/publications/prod_regulation/trs_967/en/. Published 2012. Accessed October 21, 2014.
- Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362:2295–2303.
- Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend*. 1993;33(1):23–29.
- Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control*. 2010;19:98–103.
- Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)*. 2014;231(2):401–407.
- Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction*. 2012;107(8):1493–1500.
- Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluation of electronic cigarette use (Vaping) topography and estimation

- of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *Int J Environ Res Public Health*. 2013;10(6):2500–2514.
42. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res*. 2013;15(1):267–270.
 43. Food and Drug Administration. Guidance for industry assessment of abuse potential of drugs. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf. Published 2010. Accessed October 21, 2014.
 44. Totally Wicked. Totally wicked e-liquid lab report. http://casaa.org/uploads/Totally_Wicked_Lab_report.pdf. Published 2009. Accessed May 8, 2014.
 45. Crellin RA. *Alkylpyrazine Levels in Philip Morris Brands: Report no RD 1509 Restricted* (Bates no. 105467378). British-American Tobacco Company Limited; 1977. <http://legacy.library.ucsf.edu/tid/chu37a99;jsessionid=1FED38E33E49809AE8D0352FCF260521.tobacco03>. Legacy Tobacco Documents Library, University of California, San Francisco.
 46. John J, Wakeham H. *Breakthrough of the High Taste, Low Tar Cigarette: A Case History of Innovation* (Bates No. 2021566196/6216). Philip Morris; 1980. <http://legacy.library.ucsf.edu/tid/pgb68e00;jsessionid=1660F38987C09BDE21EA6B9F20F70EB2.tobacco03>. Legacy Tobacco Documents Library, University of California, San Francisco.
 47. Lin SS. *Basic Flavor Investigation Low Tar / High Flavor Literature Review Special* (Bates No. 2046741788/1830). Philip Morris; 1990. <http://legacy.library.ucsf.edu/tid/qs80b00;jsessionid=139CC6C6CC2D842706D039DC51C5BB27.tobacco03>. Legacy Tobacco Documents Library, University of California, San Francisco.
 48. Carpenter CM, Wayne GF, Connolly GN. The role of sensory perception in the development and targeting of tobacco products. *Addiction*. 2007;102(1):136–147.
 49. Megerdichian CL, Rees VW, Wayne GF, Connolly GN. Internal tobacco industry research on olfactory and trigeminal nerve response to nicotine and other smoke components. *Nicotine Tob Res*. 2007;9(11):1119–1129.
 50. US Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
 51. Nides MA, Leischow SJ, Bhattar M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav*. 2014;38(2):265–274.
 52. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest*. 2012;141(6):1400–1406.
 53. Stein YS, Antal Jr, MJ, Jones Jr, M. A study of the gas-phase pyrolysis of glycerol. *J Anal Appl Pyrolysis*. 1983;4(4):283–296.
 54. Stevens JF, Maier CS. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. *Mol Nutr Food Res*. 2008;52(1):7–25.
 55. Uchiyama S, Ohta K, Inaba Y, Kunugita N. Determination of carbonyl compounds generated from the E-cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatography. *Anal Sci*. 2013;29(12):1219–1222.
 56. Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. *Am J Ind Med*. 2005;47(5):411–418.
 57. Wieslander G, Norbäck D, Lindgren T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup Environ Med*. 2001;58:649–655.
 58. Hua M, Alf M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res*. 2013;15(4):e59.
 59. Hecht SS, Yuan JM, Hatsukami D. Applying tobacco carcinogen and toxicant biomarkers in product regulation and cancer prevention. *Chem Res Toxicol*. 2010;23:1001–1008.
 60. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*. 2005;57(1):79–115.
 61. Strasser AA, Benowitz NL, Pinto AG, et al. Nicotine metabolite ratio predicts smoking topography and carcinogen biomarker level. *Cancer Epidemiol Biomarkers Prev*. 2011;20:234–238.
 62. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regul Toxicol Pharmacol*. 2005;41:185–227.
 63. Carmella SG, Ming X, Olvera N, Brookmeyer C, Yoder A, Hecht SS. High throughput liquid and gas chromatography-tandem mass spectrometry assays for tobacco-specific nitrosamine and polycyclic aromatic hydrocarbon metabolites associated with lung cancer in smokers. *Chem Res Toxicol*. 2013;26(8):1209–1217.
 64. Goniewicz ML, Eisner MD, Laczcano-Ponce E, et al. Comparison of urine cotinine and the tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and their ratio to discriminate active from passive smoking. *Nicotine Tob Res*. 2011;13(3):202–208.
 65. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among US adults, 2010–2011. *Nicotine Tob Res*. 2013;15(9):1623–1627.
 66. Pearson JL, Richardson A, Niaura RS, Vallone DM, Abrams DB. E-cigarette awareness, use, and harm perceptions in US adults. *Am J Public Health*. 2012;102(9):1758–1766.
 67. Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zoref L. The use and perception of electronic cigarettes and snus among the US population. *PLoS One*. 2013;8:e7933.
 68. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014;109:1531–1540.
 69. Etter JF. Electronic cigarettes: a survey of users. *BMC Public Health*. 2010;10:231.
 70. Kralikova E, Novak J, West O, Kmetova A, Hajek P. Do e-cigarettes have the potential to compete with conventional cigarettes?: a survey of conventional cigarette smokers' experiences with e-cigarettes. *Chest*. 2013;144(5):1609–1614.
 71. Li J, Bullen C, Newcombe R, Walker N, Walton D. The use and acceptability of electronic cigarettes among New Zealand smokers. *New Zeal Med J*. 2013;126(1375). <http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2013/vol-126-no-1375/article-li2>.
 72. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res*. 2013;15(10):1787–1791.
 73. Rath JM, Villanti AC, Abrams DB, Vallone DM. Patterns of tobacco use and dual use in US young adults: the missing link between youth prevention and adult cessation. *J Environ Public Health*. 2012;2012:679134.
 74. Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus. *Prev Med*. 2014;62:14–19.
 75. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res*. 2006;8(6):739–749.
 76. Stead LF, Lancaster T. Interventions to reduce harm from continued tobacco use. *Cochrane Database Syst Rev*. 2007;(3):CD005231.
 77. Caponnetto P, Campagna D, Cibella F, et al. Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2013;8(6):e66317.
 78. Etter JF. Levels of saliva cotinine in electronic cigarette users. *Addiction*. 2014;109(5):825–829.
 79. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382:1629–1637.
 80. Etter JF, Bullen C. A longitudinal study of electronic cigarette users. *Addict Behav*. 2014;39:491–494.
 81. Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control*. 2014;23:375–384.

82. Centers for Disease Control and Prevention. Electronic cigarette use among middle and high school students — United States, 2011–2012 (Vol. 62). www.cdc.gov/mmwr/preview/mmwrhtml/mm6235a6.htm. Published 2013. Accessed October 21, 2014.
83. Camenga DR, Delmerico J, Kong G, et al. Trends in use of electronic nicotine delivery systems by adolescents. *Addict Behav.* 2014;39(1):338–340.
84. Camenga DR, Cavallo D, Kong GAP, Morean M, Palmer A, Krishnan-Sarin S. Factors that prevent electronic cigarette initiation in adolescent and young adult smokers and non-smokers. Poster presented at the Society for Research on Nicotine and Tobacco 20th Annual Meeting; Seattle, WA; February, 2014.
85. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Teen smoking continues to decline in 2013: Monitoring the Future. <http://home.isr.umich.edu/releases/teen-smoking-continues-to-decline-in-2013/>. Published 2013. Accessed May 25, 2014.
86. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among US Adolescents. *JAMA Pediatr.* 2014;168(7):684.
87. Niaura RS, Glynn TJ, Abrams DB. Youth experimentation with e-cigarettes: another interpretation of the data. *JAMA.* 2014;312(6):641–642.
88. Pepper JK, Reiter PL, McRee AL, Cameron LD, Gilkey MB, Brewer NT. Adolescent males' awareness of and willingness to try electronic cigarettes. *J Adolesc Health.* 2013;52(2):144–150.
89. Cavallo D, Kong G, Camenga D, Palmer A, Morean M, Krishnan-Sarin S. A qualitative study on marketing e-cigarettes to adolescents and young adults. Paper presented at the Society for Research on Nicotine and Tobacco 20th Annual Meeting; Seattle, WA; February, 2014.
90. Kong G, Cavallo D, Camenga DR, Palmer A, Morean M, Krishnan-Sarin S. E-cigarette initiation and discontinuation: a qualitative study. Poster presented at the Society for Research on Nicotine and Tobacco 20th Annual Meeting; Seattle, WA; February, 2014.
91. Morean ME, Kong G., Camenga DR, et al. High school and college students' knowledge about and perceptions of flavored electronic cigarettes. Poster presented at the Society for Research on Nicotine and Tobacco 20th Annual Meeting; Seattle, WA; February, 2014.
92. Pokhrel P, Little MA, Fagan P, Muranaka N, Herzog TA. Electronic cigarette use outcome expectancies among college students. *Addict Behav.* 2014;39(6):1062–1065.
93. Durmowicz EL. The impact of electronic cigarettes on the paediatric population. *Tob Control.* 2014;23(suppl 2):ii41–ii46.
94. Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev.* 2012;9:CD010078.
95. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. *N Engl J Med.* 2012;366:808–818.
96. Oncken C, Dornelas E, Greene J, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstet Gynecol.* 2008;112(4):859–867.
97. Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol.* 2000;96(6):967–971.
98. World Health Organization. WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. www.who.int/tobacco/publications/pregnancy/guidelinestobaccosmokeexposure/en/. Published 2013. Accessed October 21, 2014.
99. Perkins KA, Fonte C, Meeker J, White W, Wilson A. The discriminative stimulus and reinforcing effects of nicotine in humans following nicotine pretreatment. *Behav Pharmacol.* 2001;12:35–44.
100. Vogel RI, Hertsgaard LA, Dermody SS, et al. Sex differences in response to reduced nicotine content cigarettes. *Addict Behav.* 2014;39:1197–1204.
101. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro.* 2014;28:198–208.
102. Brown J, West R, Beard E, Michie S, Shahab L, McNeill A. Prevalence and characteristics of e-cigarette users in Great Britain: findings from a general population survey of smokers. *Addict Behav.* 2014;39(6):1120–1125.
103. Lindson-Hawley N, Aveyard P, Hughes JR. Gradual reduction vs abrupt cessation as a smoking cessation strategy in smokers who want to quit. *JAMA.* 2013;310(1):91–92.