LEGACY
FOR LONGER HEALTHIER LIVES

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July 2, 2015

Dr. Stephen Ostroff, M.D.
Acting Commissioner
ATTN: Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2014-N-1936

Dear Dr. Ostroff:

Legacy applauds the Food and Drug Administration's (FDA) proactive hosting of three public workshops as part of its process of gathering a wide range of scientific information on electronic nicotine delivery systems (ENDS), including e-cigarettes and other similar, non-combustible products. Given the public health urgency of regulating these (and other still-unregulated) tobacco products, it was important to host these workshops even though the long-awaited deeming regulation has still not been issued. Finalizing the deeming regulation must, of course, be the first order of business. As soon as that is accomplished, it is essential that FDA immediately move forward, using the information garnered from these public workshops and other sources, to start the overdue process of regulating ENDS. The overarching goal of such regulation must be to protect the public health by maximizing ENDS benefits and minimizing ENDS potential harms in order to reduce the death and disease burden from tobacco use.

In our view, this is best accomplished by following a strategy to minimize harm from *all* tobacco products. This harm minimization strategy holds that while the best way to eliminate tobacco-based harms is to eliminate tobacco use entirely, and to do so as early in life as possible, the death and disease that flow from tobacco use can be significantly reduced if tobacco users who are unable or unwilling to quit switch as early as possible to the exclusive use of the least harmful non-combustible or medicinal nicotine delivery products. Thus, we continue to support regulations that protect youth from accessing these products, while still making them available to those unable or unwilling to quit combustible tobacco products.[1-3]

Therefore, we encourage FDA to move quickly to put the following measures into place:

- Regulations to ensure safety, quality and accurate labeling of ENDS devices and ingredients for human consumption via inhalation.
- Mandate child resistant packaging to minimize unintentional exposures in children with clear warnings and instructions about safe handling of nicotine containing liquids.
- Institute a minimum national age for purchase of all tobacco products, including age verification measures for internet, phone and mail order purchases.
- Expand youth marketing restrictions currently imposed on cigarettes and smokeless products to all tobacco products.
- Eliminate flavors (including menthol) in all tobacco products with a possible limited exception of lower harm non-combustible products whose manufacturer(s) can demonstrate to the FDA that the flavored product does not appeal to and is not marketed to youth (verified with careful post-market surveillance of actual usage patterns).

Over the longer term, FDA should put in place a comprehensive nicotine regulation approach across the Center for Tobacco Products (CTP) and the Center for Drug Evaluation and Research (CDER) to most effectively and expeditiously reduce the death and disease burden caused by combusting tobacco products, primarily cigarettes.[2-4] This should include a plan to inform consumers about the relative health risks of a broad range of combustible and non-combustible classes of tobacco products and about how to use that knowledge to minimize potential individual harms. For example, informing consumers that individual harm will only be significantly reduced to the extent that any initial dual use of combustibles and less harmful products leads, as soon as possible, either to complete cessation of all tobacco products or exclusive use of the lower harm product.

For both short-term and long-term issues, FDA should employ a two pronged approach to regulating all tobacco and nicotine delivery products, including ENDS: First, FDA should adopt product standards that will reduce the appeal, toxicity, and addictiveness of combustible tobacco products, which include cigarettes, cigars, roll-your-own tobacco, pipe, and hookah. As part of this, it is essential to eliminate menthol as a characterizing flavor which is shown by strong evidence to appeal to youth and make it harder for smokers to quit.[5-7] Second, FDA should simultaneously develop a regulatory scheme that will: (a) promote cessation of *all* product use as the ideal way to eliminate all harm as early in life as possible; (b) promote movement away from combustible tobacco use towards complete switching to less harmful products (i.e., a reduce-to-quit indication); (c) include long term use if necessary to prevent relapse back to combustible tobacco use; and (d) prevent uptake of any and all tobacco or nicotine products by youth and other non-users. Thus, while the first priority is for regulation to prevent the uptake of any and all tobacco or nicotine containing products entirely, Legacy supports harm minimization, the displacement of combustible tobacco use as soon as possible for those unable to quit the most harmful combustible products in favor of exclusive use of less harmful, non-combustible products.[3]

We recognize that the science is rapidly developing and, with regard to some issues, there remain unresolved questions. It is important to keep in mind, however, that instead of waiting for decades to conduct “definitive” studies, other scientific methods can be used to guide prudent regulation that saves lives and reduces the disease burden of tobacco. For example, use of modern statistical methods for causal inference in epidemiological and post-marketing studies, and mathematical simulation modeling, will be essential to guide and support regulatory policy with the goal of protecting the public health by maximizing benefits and minimizing potential harms in order to rapidly reduce the death and disease burden from tobacco use behavior.

Our comments consist of three major sections. First, we discuss how to apply the public health standard in regulating ENDS in the context of other tobacco products. Second, we provide recommendations for reviewing and interpreting the science on ENDS. Third, we provide answers to selected questions FDA posed for each workshop based on our ongoing systematic review of scientific literature on ENDS.

SECTION 1. Regulating ENDS under the Public Health Standard

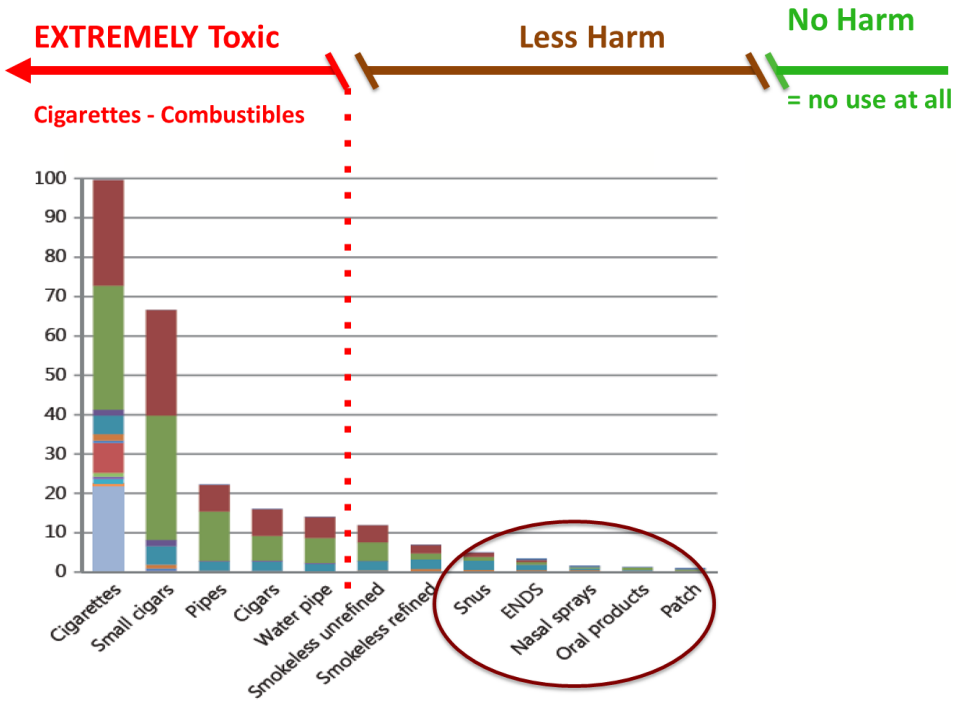
A continuum of harm exists, and regulation of ENDS must reflect that continuum.
As it applies the public health standard to the regulation of ENDS, FDA needs to keep in mind the public health implications across the full range of tobacco products. Importantly, as the Surgeon General's 2014 50th anniversary report states:

> *"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."* (Exec Summary *pp 15-17)*

Based on the 2014 Surgeon General's Report,[8] a key element of improving the public health is to move as many tobacco users as possible away from combustible tobacco products – the most toxic tobacco products (see Figure 1 below). Thus, the actual patterns of use of ENDS must not only be viewed in light of the ultimate goal of no tobacco use, but also in the context of current patterns of uptake and continued use of combustibles.[9] To benefit overall population health, ENDS need not be harmless or risk-free. Rather, they must be significantly less harmful, than cigarettes and other combustible products and be used in a manner that speeds the displacement of combustibles at the population level.

Figure 1 illustrates a continuum of harm, with no use at all and toxic combustible use, at opposite extremes.

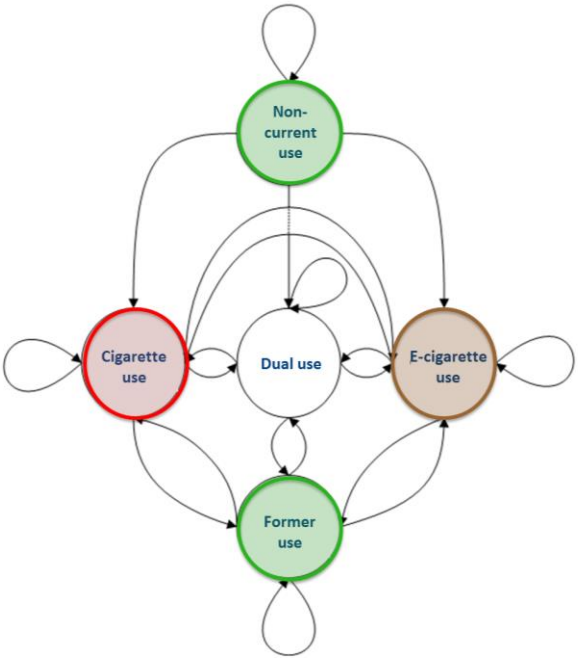
Figure 1. Continuum of harm: Combustible tobacco products to no use at all



Nutt DJ et al Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach – European Addiction Research March 2014

ENDS must be considered in the context of the full spectrum of tobacco use.
Figure 2 below presents a critical framework to identify the shifts in tobacco use that can alter the ultimate population impact. While appearing complicated, the core elements are straightforward. At the top of the model are never-users (in green for no harm). Some will remain never-users, but a proportion will try other tobacco products, and some lesser proportion will transition to long-term use, either to most harmful combustibles in red or to comparatively less harmful ENDS in brown. Dual use may be a static state or a transitional state either toward exclusive ENDS use and lesser harm (from left to right) or toward exclusive combustible cigarette use and greater harm (from right to left). Finally, users may transition to cessation and remain a former user, in green, or relapse to any of the three use states. The utility of this model is that it can be altered to include any number of products, including other potentially reduced harm tobacco products, and the transitions between them, but it keeps use of a single product (e.g., ENDS) within the context of a broader dynamic system.

Figure 2. Markov model of the various states of e-cigarette and cigarette use[10]



In the context of the multiple pathways described in Figure 2, FDA will have the greatest impact on population health through a regulatory scheme informed by three over-arching goals: (1) preventing non-tobacco users, especially youth, from initiating tobacco use in the first place; (2) deterring or reversing progression to combustible use as early in the user's lifetime as possible; and (3) helping combustible users quit entirely *or* switch to less harmful regulated products. The third goal recognizes that once established, quitting tobacco products, particularly combustible products, is not easy and for some, proves nearly impossible. As a result, for those unable to quit combustible products, Legacy supports harm minimization, meaning the displacement of the use of combustibles as soon as possible by moving those who cannot or will not quit the most harmful combustible products to exclusive use of less harmful, non-combustible products.

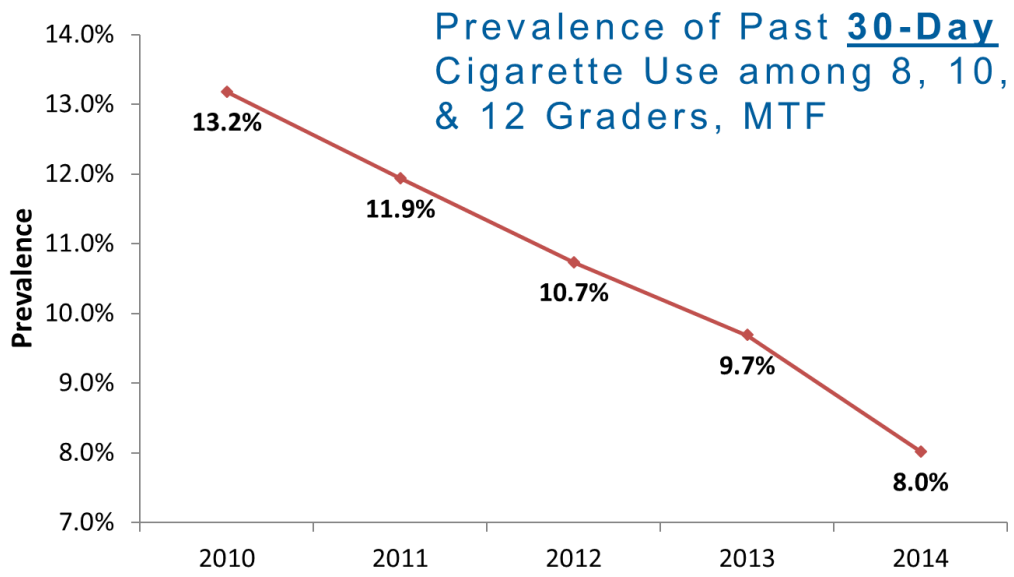
With weighing population-based risks and benefits as the proper criterion, it is essential not only to determine whether ENDS, or any other tobacco product FDA may regulate, encourages uptake of tobacco products, but also whether the product helps those who use the most dangerous by far combustible tobacco products move to less harmful products, and possibly to ceasing use of any and all tobacco or nicotine delivery products.[1,2,4,9] Only when the full picture of the impact a product is having on public health is taken into account can regulations be developed that best protect youth from initiating tobacco use and help those succeed in quitting.

SECTION 2: Recommendations for Reviewing and Interpreting the Science on ENDS

2.A. State of the Science: Uptake of E-cigarette Use by Non-Users of Tobacco Products

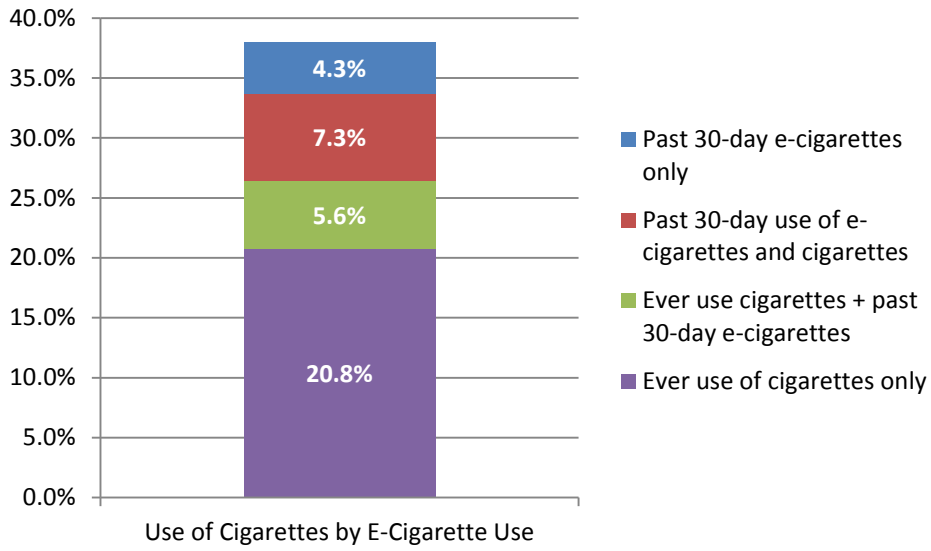
Using our Markov model roadmap (Figure 2), we examine selected examples from the state of the science to show how easily omission of pathways or over interpreting causality can mislead and cloud prudent decision making. According to Monitoring the Future (MTF) data, almost 70.0% of youth have remained non-users of any tobacco product at all and cigarette use declined steeply down to an all-time low in 2014 (Figure 3).

Figure 3. Prevalence of past 30-day cigarette use among 8, 10, & 12th graders (MTF)[11]



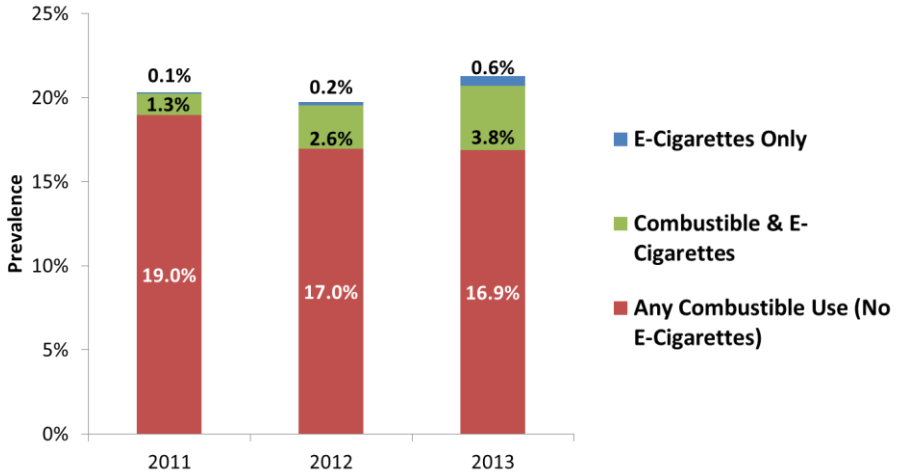
In 2014, 17.2% of 12th graders reported trying an e-cigarette in the past 30 days (Figure 4). Looking closer, 76.0% of those, or 12.9% overall, were dual users and also still smoked cigarettes. Conversely, about a quarter of them – 5.6% of the total – were former cigarette smokers and are now ONLY using ENDS. Still of concern is that 4.3% of never smokers are ENDS experimenters; however, there is no evidence yet to indicate that they are transitioning to more harmful combustible products. These data are cross sectional, so we cannot infer causality.

Figure 4. Ever use and past 30-day use of cigarettes by past 30-day e-cigarette users (12th grade)[12,13]



Like MTF, the National Youth Tobacco Survey (NYTS) has rich data to use to get a fuller picture of use states and trajectories. In 2014, past 30-day e-cigarette use among high school students was at 13.4% and 9.4% of high school students reported past 30-day cigarette use; these data do not provide information on polytobacco use among youth.[14] As such, total combustible product use is not yet analyzed for 2014, but in 2013, it stood at 16.9% exclusively, and at 20.7% combined with e-cigarette use (Figure 5). Across 2011-2013, exclusive e-cigarette use remained below 1%, with the bulk of youth using both an e-cigarette and another tobacco product.

Figure 5. Past 30-day tobacco use among high school students (NYTS 2011 - 2013)[15-17]

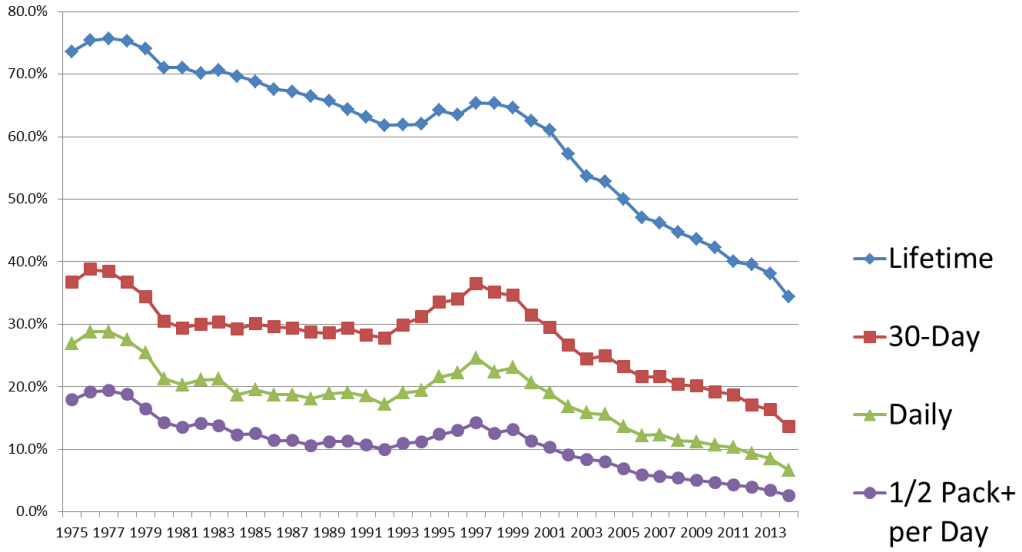


E-cigarettes clearly attract youth, as do regular and mentholated cigarettes, flavored cigars, and hookah. Our roadmap in Figure 2 reminds us not to forget uptake of all combustible products simultaneously with uptake of ENDS when considering how to protect our youth from the most harmful exposures. The take-home point is to avoid narrow and over-reaching interpretation of any one number. All the trajectories and states are needed to inform the net population impact. The roadmap ensures a

balanced perspective, and informs what existing data can be mined even further. Gaps alert us to what specific questions and types of future studies we need to improve overall decision-making.

Ever or past 30-day use can be fleeting in mapping a trajectory into or out of harm from regular use. Recent studies by Kozlowski and Giovino and by Warner strongly reinforce that past 30-day use is a very weak predictor of regular use.[18,19] The raw MTF data from 1975 to 2014 makes the point as clearly as anything. Conversion rates fall off dramatically, from ever/lifetime cigarette use to past 30 days to regular use (Figure 6). Even less is known about conversion from trial e-cigarette use to regular e-cigarette use and into regular use of combustibles. While it is critical to understand progression from ENDS to the combustibles, there are no clear longitudinal data on this issue as yet.

Figure 6. Trends in prevalence of cigarette use in Grade 12, Monitoring the Future 1975 - 2014[11]



Other contextual considerations are important. The concern about youth e-cigarette use is often based on the gateway construct: e-cigarette use will lead to combustible use. However, the common liability model has largely replaced the gateway theory as an explanation of multiple product use.[20,21] Youth have qualities like curiosity, sensation seeking and other risk-taking vulnerabilities, which drive all the substance use behaviors with different implications for overall public health impact. Which substances are used first may simply be an indicator of the shared underlying vulnerability; causal direction cannot be inferred from cross-sectional data, and longitudinal data may not necessarily imply a gateway because the counterfactual cannot be proven. The vulnerable person may have used another substance anyway, even if the first substance had not been available on the market.[22]

Many studies are being published based on observational designs that are largely cross-sectional, such as on youth uptake patterns (e.g. NYTS) in the U.S., that imply ENDS promotes the progression and the use of more harmful combustible cigarettes. As described in recent commentaries by Abrams and Niaura,[23] and Niaura, Glynn and Abrams[22] one of the most prominent of these studies, by Dutra and Glantz, using data from a large representative cross-sectional study of U.S. school students, reported experimental e-cigarette use was associated with more use of combustible cigarettes.[24] The authors acknowledged the correlational, rather than causal, nature of the study design, but then stated: “Use of e-cigarettes does not discourage and may encourage, conventional cigarette use among U.S. adolescents” and “e-cigarette use is aggravating rather than ameliorating the tobacco epidemic among

youths."[24] The data do not support the conclusions.[22] Niaura, Glynn and Abrams[22] explain that it is "equally plausible that use of combustible cigarettes leads to use of e-cigarettes, because they are perceived as a less harmful alternative for smokers who are not able or willing to go without smoking or are simply experimenting with a new and novel product out of curiosity."[22,23] Dutra and Glantz also noted a positive correlation between use of e-cigarettes and time spent using tobacco products, which they believe "… call[s] into question claims that e-cigarettes are effective as smoking cessation aids."[24] The authors fail to note that e-cigarette users also had higher intention to quit,[22,23,24] indicating that e-cigarette users may have adopted e-cigarettes to assist with quitting. Similar studies to this one "appear to replicate one another and thus seem on the surface to strengthen what amounts to the same premature and possibly misleading conclusions."[22,23]

In summary, it is necessary to be mindful of the transition of use among the various states and the limits of current data to accurately predict net public health impact and thus provide a roadmap for science-informed regulation and policy. As a recap, existing data are uninformative or insufficient to determine:

- Causal paths and longitudinal trajectories
- Conversion rates into/out of: trial to regular to combustible – above the counterfactual
- Common vulnerability: travel with other risk behaviors
- Context of combustibles: Menthol, flavored cigars, hookah – TOTAL combustibles - appeal, toxicity, addiction
- Prevention - no sales/marketing and flavors that appeal to youth in any way of any tobacco or nicotine delivery product.

2.B. State of the Science: Impacts on Current Users of Tobacco Products (Cessation/Dual Use/Exclusive Use)

Here we turn to patterns of use among current users of tobacco, especially the most harmful combustible products, and in particular, the current state of knowledge on the impact of e-cigarettes on cessation and dual use behavior. In our view, the current state of the scientific literature is inadequate to draw significant conclusions about this issue. This is because most of the current literature is based on cross-sectional observations that have significant flaws making them of limited or no value in assessing this question.

Sources of concern include:

- Approach is blind: vulnerable to heterogeneous studies that lack sufficient commonality of measures, methods, rigor
- Poor exposure measures: inappropriate/insufficient duration (e.g. ever used an e-cigarette; no duration indicated; no reason for use, type of product, or co-use with other quit aids indicated)
- Selection, indication bias: cannot rule out[25]
- Replication myth: multiple uninformative studies create a false negative impression and are over interpreted.

Evidence to Assess the Effect of E-cigarette Use on Smoking Cessation

Below we detail our concerns regarding the state of the evidence of e-cigarettes on smoking cessation and expand the presentation of Dr. Jennifer Pearson at FDA's third e-cigarette workshop.

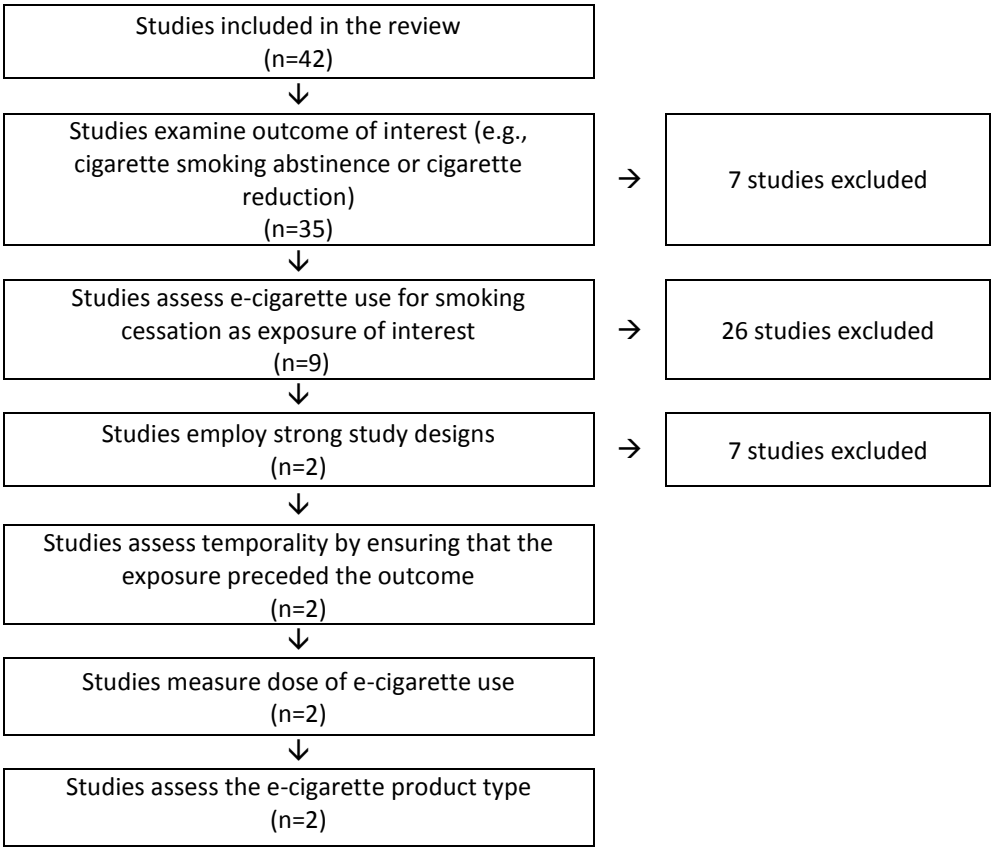
We conducted a review of the scientific evidence related to the effect of e-cigarette use on smoking cessation. We identified 42 studies that purport to report on the relationship between e-cigarette use

and smoking cessation. We present the strengths and weaknesses of these studies, and highlight the best available evidence. Take-home points for each section are noted in bold.

Most existing observational studies related to the effect of e-cigarette use on smoking cessation are uninformative and are marred by poor measurement of exposures and unmeasured confounders.

We established a hierarchy to organize studies according to their methodological strengths. Studies that "fall out" of this hierarchy towards the top are weaker – and uninformative – compared to those that "fall out" towards the bottom. **Figure 7** illustrates this hierarchy. We found that most of the existing studies related to the effect of e-cigarette use on smoking cessation are uninformative. An assessment of the included studies is outlined in detail below. Information about specific studies can be found in **Table 2** (included at the end of this section). We include three randomized, controlled trials published on this topic in the flowchart for completeness, while noting that their design preempts some of the categories listed in Figure 7.

Figure 7. Hierarchy of Methodological Consideration and Evidence. Studies included towards the bottom of the flowchart have the strongest methodologies and provide the best evidence.



It is important to note that the existing observational studies do not constitute reliable scientific evidence and therefore, meta-analyses of these studies are inappropriate for several reasons. First, as noted above and detailed below, the majority of studies that purport to address the relationship between e-cigarette use and smoking cessation do not provide evidence to answer that question. Second, as noted in the Cochrane Handbook for Systematic Reviews of Interventions,[26] the use of meta-analysis is not appropriate in all reviews and the first step to deciding whether to undertake a meta-

analysis is to evaluate the similarity of studies with respect to population, intervention, comparison group, and outcome. The initial determination of heterogeneity should be evaluated qualitatively by the authors and evidence of statistical heterogeneity in the model should be presented ONLY after it is determined that the studies are comparable enough to warrant pooling of data. The observational studies identified in our review were determined to be sufficiently heterogeneous that they should not be pooled in such an analysis. The recent Cochrane review on the use of e-cigarettes for smoking cessation reached a similar conclusion. The Cochrane reviewers examined data from both randomized controlled trials and cohort studies, but conducted limited meta-analyses using data from *only* the two randomized controlled trials where the designs and populations were deemed sufficiently similar to compare.[27] Third, non-randomized studies which use "different study designs (or which have different design features)…should not be combined in a meta-analysis" (p. 422).[26] A key issue related to pooling non-randomized studies is adjustment for confounding which is not captured in simple numerators and denominators or means and standard errors. **The Cochrane Handbook warns: "Meta-analyses of studies that are at risk of bias may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce a 'wrong' result that may be interpreted as having more credibility" (p. 247).**[26] As detailed below, the existing observational studies suffer from measurement bias, selection bias, and confounding that render meta-analysis inappropriate at this time.

Hierarchy of Methodological Considerations and Evidence (top to bottom):

(1) Studies must examine the outcome of interest (i.e., cigarette smoking abstinence or reduction).

To provide information regarding whether e-cigarettes can be used as an effective tool for smoking cessation, a study must appropriately operationalize the outcome of interest (smoking cessation). We considered smoking abstinence and cigarette reduction to be the most relevant/highest-quality outcomes. Of the 42 studies we reviewed, seven did not examine the outcome of interest.[28-34] These studies assessed outcomes that are related to smoking cessation, such as intention to smoke,[28] withdrawal-related symptoms,[28] nicotine levels,[31] reason for e-cigarette use,[30] and other descriptive information about people who use e-cigarettes for cessation.[33,34]

(2) Studies must assess e-cigarette use for smoking cessation as the exposure of interest.

For observational studies, it is crucial to confirm that participants are using e-cigarettes for the purpose of cessation. People use e-cigarettes for a multitude of reasons, e.g., because they are cheaper than cigarettes, they are less harmful, or they are only experimenting with the product. If smokers are not using e-cigarettes to help them quit it does not make sense that we should expect them to help smokers quit. Pearson et al. addressed this issue by asking, "What quit methods have you used in the past 3 months?"[35] Participants who used an e-cigarette as a quit method were classified as "exposed" and those who did not were classified as "unexposed" regardless of other e-cigarette use.

For randomized controlled trials (RCTs), where participants are assigned by the researchers to either use e-cigarettes or abstain and followed for the cessation outcomes of interest, reasons for use are balanced across the exposed and unexposed study groups through randomization. As such, reason for use is unlikely to confound the relationship between e-cigarette exposure and cessation and, similar to studies of NRT on cessation, does not need to be directly assessed in order for study findings to be generalizable.

Of the remaining 35 studies in the hierarchy, three were RCTs.[36-38] Of the other 32 studies in the hierarchy, 26 did not assess the reason for e-cigarette use as an exposure.[39-64]

(3) Studies must employ strong study designs.

Apart from RCTs, the strongest epidemiologic studies examining whether e-cigarette use leads to smoking abstinence or cigarette reduction should be longitudinal and have appropriate comparison groups. Of the nine remaining studies in the hierarchy, seven did not have appropriate study designs.[35,37,65-69] Four of these studies were cross-sectional[65,66,68,69] and one was a case series.[66] One study was longitudinal;[35] however, in its assessment of the association between e-cigarette use and smoking cessation outcomes, it only employed cross-sectional data. One study randomly assigned participants to e-cigarette use or control during the initial lab phase of the study, but then provided the control group with e-cigarettes during the follow-up period.[37] Since there was no longer an unexposed control group during the phase of the study in which the smoking cessation outcomes were obtained, this study was excluded at this point as well.

After considering whether studies assessed the outcome of interest, e-cigarette use for smoking cessation as an exposure, and study design, only two studies – both RCTs – remain in the hierarchy.[36,38] These studies met all of the additional criteria described below.

(4) Studies must precisely measure the exposure of interest (i.e., e-cigarette use).

In order to precisely measure the exposure of interest (e-cigarette use), studies should:

(a) *Establish temporality by ensuring that the exposure preceded the outcome.*

(b) *Measure dose of e-cigarette use.*

Some studies report ever or past 30-day use of e-cigarettes at baseline.[44,46,49,54,62] As measures, neither ever use nor past 30-day use accurately capture individuals who regularly use e-cigarettes. Amato et al. investigated this measurement issue in a 2014 survey of over 9,300 participants and found that, among current smokers who reported past 30 day e-cigarette use, 59% were infrequent e-cigarette users (use on 5 or fewer of the past 30 days), 28.7% were intermediate users (use between 6 and 29 (inclusive) of the past 30 days), and 12.3% were daily users (use 30 out of the past 30 days).[30] Based on this finding, the authors concluded that defining adult prevalence as any e-cigarette use in the past 30 days may include individuals who are experimenting with e-cigarette and are unlikely to progress to regular use.

One study, conducted by Biener and Hargraves, illustrates the importance of measuring e-cigarette dose for studies investigating smoking cessation outcomes.[45] They measured e-cigarette dose and found that intensive e-cigarette use (daily use for at least one month) was associated with a 6.07 (95% CI: 1.11 – 33.18) increase in the odds of smoking abstinence, while there was no significant difference in cessation for intermittent users (e-cigarette use more than 1-2 times but not daily for a month) or for individuals who had never used e-cigarette or who had used e-cigarette only once or twice.[45] Studies using weaker measures of ever or past 30-day e-cigarette use at baseline do not provide sufficient information on exposure to e-cigarettes to understand the relationship between e-cigarette use and cessation.

(c) *Assess the e-cigarette product type.*
E-cigarettes are diverse.[70] They vary by device type,[71] performance,[71] flavor[52] and other characteristics.[70] It is important to assess the e-cigarette product type because products may have different levels of effectiveness when used for smoking cessation. This phenomenon was seen by Hitchman et al., who examined differences between cigalike and tank e-cigarettes and found differential results based on product type.[55]

Many of the observational studies that "fall out" of the hierarchy before reaching the bottom report negative correlational findings between e-cigarettes and smoking cessation.[29,35,39,41,43,50,52,53,55,56,61,63-65,67-69 44,46,54,62,72] These studies are uninformative and do not tell us how e-cigarette use affects cessation due to their inherent methodological limitations. To make inferences about the impact of e-cigarette use on cessation based on these studies would be akin to repeating well-documented errors regarding the negative effect of nicotine replacement therapy on smoking cessation that is the result of confounding with dependence. That is, more dependent individuals are more likely to try multiple cessation treatments, and they are also more likely to fail because of their higher dependence.[25] Similarly, e-cigarette users may be more likely to try any number of cessation treatments and to fail because of the influence of a third variable, such as dependence. This does not imply that the treatments are ineffective overall, but rather that other, extra-treatment factors need to be taken into account when highly dependent smokers try to quit and that perhaps treatment dose was insufficient to address their needs. Like the observational studies of use of nicotine replacement therapies (NRT), selection and indication bias are important considerations and very difficult to eliminate from analysis of the negative correlation between NRT use and cessation outcomes.[25] Research indicates smokers who used e-cigarettes consume more cigarettes per day, are more nicotine dependent, make more quit attempts, make longer quit attempts, and use more cessation aids than otherwise similar smokers who have not used e-cigarettes to quit. Most of these characteristics are associated with poor cessation outcomes in observational studies of NRT.[25,26] So, it's not surprising that smokers who use e-cigarettes to quit have worse outcomes due to selection and indication bias in observational studies.

While the majority of the studies we reviewed are marred by poor measurement of exposures and unmeasured confounders, many of them have been included in a meta-analysis that claims to show that smokers who use e-cigarettes are less likely to quit smoking compared to those who do not.[73] This meta-analysis simply lumps together the errors of inference from these correlations. As described in detail above, quantitatively synthesizing heterogeneous studies is scientifically inappropriate and the findings of such meta-analyses are therefore invalid.

A Cochrane systematic review published in 2014, which used the highest methodological standards, examined the efficacy of e-cigarettes for smoking cessation and reduction.[74] Of the 594 records screened, only two randomized trials were included in the meta-analysis.[36,38] We also identified these two studies as the only ones that met all of the methodological specifications described in our hierarchy.

Findings from the studies with the strongest methodologies suggest that e-cigarettes are effective in helping adult smokers to quit or to reduce their cigarette consumption and that rates of smoking cessation with e-cigarettes are similar to rates of cessation with nicotine replacement therapy.

Three randomized controlled trials (RCTs) were included in our review of the literature. Two of these studies met all of the methodological specifications outlined above.[36,38] The other study did not have an unexposed control group when assessing the relationship between e-cigarette use and the outcome.[37] We discuss the two remaining randomized controlled trials in detail below.

- Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013;382(9905):1629-37.[36]

  Design: Bullen et al. conducted a randomized controlled trial from 2011-2013 among current adult smokers interested in quitting in New Zealand (N=657). Participants randomized to the treatment arm were given an Elusion e-cigarette with a nicotine cartridge that contained 10-16 mg nicotine per mL. Participants randomized to one of the control arms were given either an Elusion e-cigarette with a placebo cartridge that contained no nicotine or a nicotine patch.

  Abstinence outcomes: Biochemically-verified continuous abstinence at six-month follow up was higher in the treatment arm (7.3%) compared to two control arms (placebo e-cigarette, 4.1%; nicotine patch, 5.8%), but these differences were not significantly different. Participants received vouchers for nicotine patches or e-cigarette study products for a 13-week use period (1 week prior and 12 weeks post quit day), and some have suggested that differential adherence may be a confounder that could have weakened the potential efficacy of the NRT patch arm if it was delivered under ideal conditions of adherence. Bullen et al. did, however, also report that the 7-day point prevalence abstinence (ppa) outcomes at six months were similar in the nicotine e-cigarette group (21.1%) and the placebo e-cigarette group (21.9%), and both e-cigarette arms were arithmetically but not statistically significantly higher compared to nicotine patch group (15.6%). Bullen et al. pointed to insufficient statistical power as a probable cause to this lack of effect, but this may also be due to the use of three groups that were not very different in terms of treatment delivery (i.e., no true placebo control group).

  Cigarette reduction outcomes: Bullen et al. found significant differences in smoking reduction by ≥50% at 6 months between the treatment arm (nicotine e-cigarette, 57%) and NRT patch (41%; $p = 0.0002$) but not compared to placebo e-cigarette (45%; $p = 0.08$).

- Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 2013;8(6):e66317.[38]

  Design: Caponnetto et al. conducted a randomized controlled trial from 2010-2011 among current smokers in Italy who were not interested in quitting (N=300). Participants either received 1) a Categoria e-cigarette with 7.2 mg nicotine cartridges for 12 weeks, 2) a Categoria e-cigarette with 7.2 mg nicotine cartridges for 6 weeks, followed by 5.4 mg nicotine cartridges for 6 weeks, or 3) a Categoria e-cigarette with no-nicotine cartridges for 12 weeks.

  Abstinence outcomes: At six-month follow-up, 11% of participants in the nicotine-containing e-cigarette groups had quit smoking compared to 5% in the placebo e-cigarette group. Across groups, 8.7% quit smoking and 10.3% reduced their smoking by ≥50% at 52 weeks, with 11% of those in the nicotine-containing e-cigarette groups reporting quitting compared to 4% in the placebo group. Quit rates were not statistically different whether given e-cigarettes with or without nicotine.

  Cigarette reduction outcomes: Eighteen percent of participants in the nicotine-containing e-cigarette groups (19% in the 7.2 mg group and 17% in the 5.4 mg group) reduced their smoking by ≥50% at six months compared to 15% of those in the placebo e-cigarette group.[38] At one-year follow-up, 9.5% of those in the nicotine-containing e-cigarette groups (10% in the 7.2 mg group

and 9% in the 5.4 mg group) reduced their smoking by ≥50% compared to 12% in the placebo e-cigarette group. Differences in cigarette reduction were not statistically significant at either time point. Overall, 10.3% of participants reduced their cigarette smoking by at least 50% at the one-year follow-up.

Table 1 presents findings from meta-analyses of the impact of smoking cessation medications, including nicotine replacement therapy presented in the 2008 update to the PHS guidelines for Treating Tobacco Use and Dependence.[75] Bullen et al.'s result [36] of 7-day point prevalence abstinence of 21.1% (nicotine e-cigarette) and 21.9% (placebo e-cigarette) at six months are in line with the combined results of 32 randomized controlled trials of short-term (6-14 weeks) use of the nicotine patch among smokers interested in quitting which found six-month abstinence of 23.4% (95% CI 21.3-25.8) and six trials of use of the nicotine inhaler (24.8%). Caponnetto et al.'s results[38] are also similar to findings from meta-analyses of the impact of smoking cessation medications among smokers not willing to quit .[75] Specifically, the 8.7% of smokers using placebo and nicotine-containing e-cigarettes and the 11% using nicotine-containing e-cigarettes who quit at one-year in this study compares favorably to the 8.4% abstinence rate among nicotine replacement users in five randomized controlled trials among smokers unmotivated to quit.

Table 1. Findings from meta-analysis of smoking cessation studies with six-month outcomes in "Treating Tobacco Use and Dependence: 2008 Update"[75]

Intervention	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Among smokers not willing to quit (but willing to change their smoking patterns or reduce their smoking)			
Placebo	5	1.0 (ref.)	3.6
Nicotine replacement (gum, inhaler, or patch)	5	2.5 (1.7–3.7)	8.4 (5.9–12.0)
Among smokers interested in quitting			
Placebo	80	1.0 (ref.)	13.8
Nicotine Patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nicotine Inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)

NOTE: Data extracted from Tables 6.26 (http://www.ncbi.nlm.nih.gov/books/NBK63958/table/A29582/?report=objectonly) and 6.29 (http://www.ncbi.nlm.nih.gov/books/NBK63943/table/A29585/?report=objectonly)

Two of the non-randomized observational studies met all but two of the methodological specifications described in the hierarchy: assessing the reasons for e-cigarette use and assessing e-cigarette product type.[45,47] Compared to the RCTs, we consider these two observational studies as providing the next strongest set of evidence on e-cigarette use and smoking cessation. These two prospective, population-based studies used appropriate comparison groups, measured frequency of ENDS use at baseline, and controlled for key confounders. The studies showed that *daily* e-cigarette users are more likely to report cessation behavior (i.e., quitting smoking[45] or quit attempts[47]) at follow-up compared to non-users, with no relationship seen between *non-daily* e-cigarette use and cessation outcomes. The study conducted

by Biener and Hargraves[45] examined adult smokers at baseline (2011/2012) and follow up (January – March 2014). At follow-up, quit rates among *intensive* users of e-cigarettes was 20.4% (95% CI: 7.3%-45.5%). This is comparable with abstinence rates among smokers interested in quitting who used a nicotine patch or nicotine inhaler, as described in **Table 1**. The study conducted by Brose et al.,[47] which examined smokers at baseline (November/December 2012) and at a one year follow-up time point (December 2013), reported that *daily* e-cigarette use at baseline was associated with increased odds of a quit attempt (AOR = 2.11, p=0.006) and increased odds of a more than 50% reduction in cigarettes smoked per day (AOR = 2.49, p = 0.022) at follow-up compared to no e-cigarette use at baseline, but no difference in cessation at follow-up among daily e-cigarette users compared to non-users. In this study, non-daily cigarette use at baseline was not associated with quit attempts, cessation, or cigarette reduction at follow-up compared to no use at baseline.

Research with strong methodology, while limited, suggests that e-cigarettes show promise as smoking cessation or reduction tools for some adults. However, most existing studies on this topic are uninformative. More high-quality research is needed to investigate this issue further.

The two randomized controlled studies show that e-cigarettes are effective in helping some adult smokers to quit or to reduce their cigarette consumption.[36,38] In these studies, rates of smoking cessation in the e-cigarette study groups were similar to rates of cessation seen in previous clinical trials of nicotine replacement therapy.[75] The two observational studies with the strongest methodologies found that daily e-cigarette users are more likely to report cessation behavior at follow-up compared to non-users, with no relationship seen between non-daily e-cigarette use and cessation outcomes.

As we stated previously, the majority of observational studies reporting findings relating e-cigarettes to smoking cessation are uninformative due to issues with the measurement of the exposure at the same time as the outcome,[29,35,39,41,43,50,52,53,55,56,61,63-65,67-69] lack of information on the dose of ENDS exposure (e.g., past 30-day or ever use as the exposure measure versus frequency and intensity of ENDS use at baseline),[44,46,54,62,72] and assessment of e-cigarette use specifically for cessation.[45,47,48,57-59] Another key concern in existing observational studies is the possibility of selection bias (e.g., smokers who are more nicotine dependent are more likely to try e-cigarettes).[35]

Of note, the two strongest observational studies provide examples of the ways in which future studies can better assess dose of e-cigarette use to evaluate the impact of e-cigarettes on smoking cessation. Biener and Hargraves measured dose of e-cigarette use by using three categories to describe e-cigarette use in their sample: daily use for at least 1 month; regular use, but not daily for more than 1 month; and non-use/use of e-cigarettes at most once or twice.[45] Brose et al. also measured e-cigarette dose, categorizing participants as daily e-cigarette users, non-daily e-cigarette users, or non-users.[47]

More research – especially independent, high quality randomized controlled trials with appropriate control groups and better measurement of exposure – is needed to further determine whether and how e-cigarettes can be an effective cigarette cessation or harm reduction aid, but results so far are promising for some adult smokers.

There is an urgent need for FDA to develop a comprehensive nicotine regulation strategy across the CDER and CTP branches of FDA in order to maximize the use of ENDS both for cessation of combustibles as an approved indication as a therapeutic cessation aid and as a modified risk reduced harm indication to displace combustibles and prevent relapse back to combustibles. As discussed in detail in Abrams[2] and in Cobb and Abrams[4], the popularity of e-cigarettes has spawned discussion over their usefulness in harm reduction as well as a medicinal therapeutic aid. **The discussion may have obscured a key point**

established over the past 20 years: carefully constructed, clean nicotine delivery devices, such as NRT including nicotine patches, chewing gums, lozenges and inhalers are safe and can effectively drive smoking cessation. Published evaluations of some products suggest that ENDS can be manufactured with levels of both efficacy and safety similar to those of NRT products, resulting in profoundly reduced risk compared to cigarettes.[76] If ENDS (and other refined-nicotine products) are thoughtfully regulated, they could play a similar role as NRT but at a national, population scale. Their use could shift smokers permanently away from lethal cigarettes to cleaner, safer nicotine products, saving innumerable lives.[4]

In summary, we need more rigorous studies, but current research suggests that ENDS can increase quit attempts, reduce cravings and dual use can be a transitional pathway to cessation and prevent relapse. To maximize benefits we need employ the two pronged approach discussed earlier in this submission. First, we need to make combustibles less appealing, toxic and addictive. This will speed obsolescence of combustibles that cause the most deaths. Second, we need a regulatory strategy that supports fast track approvals for products that increase cessation and harm minimization, with limited impact on uptake among non-users, to maximize the potential population benefits of lower harm tobacco products.

Table 2. Hierarchy of Studies Included in the Review. The studies with the strongest methodologies (best evidence) are located towards the top of the table. Gray shading indicates that the study "falls out" of the hierarchy; after answering "No" for each study, subsequent questions were not answered.

Study	Study design	Outcome of interest?	Assessed E-cigarette use for smoking cessation as exposure of interest?	Strong study design?	Measurement: Exposure precedes outcome? (Timing)	Measurement: Assessed Dose of E-Cigarette Use? (Dose)	Assessed E-cigarette Product Type?
Bullen (2013)[36]	Randomized controlled trial	Yes	N/A	Yes	Yes	Yes	Yes
Caponnetto (2013)[38]	Randomized controlled trial	Yes	N/A	Yes	Yes	Yes	Yes
Adriens (2014)[37]	Randomized controlled trial	Yes	N/A	No			
Brown (2014)[65]	Cross-sectional survey	Yes	Yes	No			
Caponnetto (2011)[66]	Case series	Yes	Yes	No			
Dawkins (2013)[65]	Cross-sectional survey	Yes	Yes	No			
Pearson (2014)[35]	Longitudinal study with comparison group	Yes	Yes	No			
Rutten (2015)[68]	Cross-sectional survey	Yes	Yes	No			
Tackett (2015)[69]	Cross-sectional survey	Yes	Yes	No			
Adkison (2013)[39]	Longitudinal study with comparison group	Yes	No				
Al-Delaimy (2015)[44]	Longitudinal study with comparison group	Yes	No				
Biener (2014)[45]	Longitudinal study with comparison group	Yes	No				
Borderud (2014)[46]	Longitudinal study with comparison group	Yes	No				
Brose (2015)[47]	Longitudinal study with comparison group	Yes	No				
Caponnetto (2013b)	Longitudinal study with no comparison group	Yes	No				
Choi (2014)[49]	Longitudinal study with comparison group	Yes	No				
Christensen (2014)[50]	Cross-sectional survey	Yes	No				
Etter (2014)[51]	Longitudinal study with no comparison group	Yes	No				
Farsalinos (2013b)[52]	Cross-sectional survey	Yes	No				
Goniewicz (2012)[53]	Cross-sectional survey	Yes	No				
Grana (2014)[54]	Longitudinal study with comparison group	Yes	No				
Hitchman (2015)[55]	Longitudinal study with comparison group	Yes	No				
Lee (2013)[56]	Cross-sectional survey	Yes	No				
Nides (2014)[57]	Longitudinal study with no comparison group	Yes	No				
Polosa (2014)[58]	Longitudinal study with no comparison group	Yes	No				
Polosa (2011)[59]	Longitudinal study with no comparison group	Yes	No				

Polosa (2014)[60]	Longitudinal study with no comparison group	Yes	No
Popova (2013)[61]	Cross-sectional survey	Yes	No
Prochaska (2014)[62]	Longitudinal study with comparison group	Yes	No
Ramo (2014)[63]	Cross-sectional survey	Yes	No
Siegel (2011)[64]	Cross-sectional survey	Yes	No
Sutfin (2015)[40]	Longitudinal study with no comparison group	Yes	No
Vickerman (2013)[41]	Longitudinal study with comparison group	Yes	No
Wagener (2013)[42]	Clinical laboratory study	Yes	No
Zhu (2013)[43]	Cross-sectional survey	Yes	No
Amato (2015)[30]	Cross-sectional survey	No	
Copp (2015)[28]	Clinical laboratory study	No	
Farsalinos (2013)[31]	Cross-sectional survey	No	
Pepper (2014)[32]	Cross sectional survey	No	
Pokhrel (2014a)[33]	Cross-sectional survey	No	
Pokhrel (2014b)[34]	Cross-sectional survey	No	
Pulvers (2014)[29]	Cross-sectional survey	No	

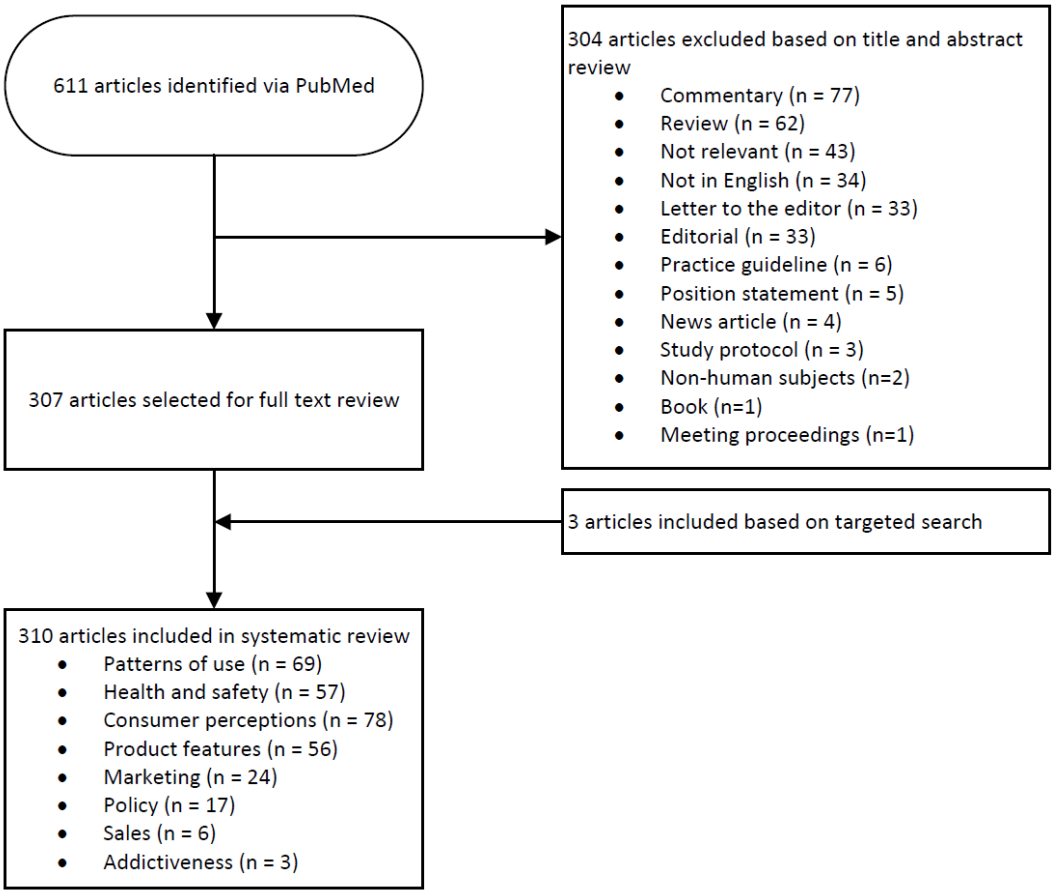
SECTION 3: Review of Scientific Literature and Responses to FDA Questions

Below we present our findings from a review of scientific literature responsive to the questions the FDA posed in its three e-cigarette workshops. The findings were compiled from an in-progress comprehensive systematic review of all published scientific literature on e-cigarettes conducted via a PubMed search through February 19, 2015.[77] Selections from this report are included below as they are relevant to FDA's questions. The search strategy consisted of the following keywords: "e-cigarette*" OR "electronic cigarette" OR "electronic cigarettes" OR "electronic nicotine delivery." Eligible studies were experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross sectional studies), case reports, case series, qualitative studies and mixed methods studies providing empirical data on e-cigarettes. Other sources were obtained by emailing experts and internal discussion of studies underway at Legacy.

Upon retrieval from PubMed, studies were catalogued based on title and abstract review to one or more of the following topic areas (see Figure 8): 1) Product features; 2) Health and safety; 3) Consumer perceptions; 4) Patterns of use; 5) Marketing; 6) Sales; and 7) Policies. Reviews were catalogued separately and are not included in the detailed summary of study findings; similarly, commentaries and editorials on e-cigarettes were not included in this review. A flowchart depicting the inclusion and cataloguing of articles is presented in Figure 8.

In line with expertise at Legacy's Schroeder Institute for Tobacco Research and Policy Studies, we evaluated the quality of studies that reported on the association between e-cigarette use and cigarette smoking cessation using a standardized rubric (see Section 2.B.). For those studies, we note the methodological strengths and weaknesses of each study and of the body of evidence. The responses to questions posed for the three workshops include a qualitative summary of literature on a number of topics, but do not provide similar assessment of the quality of these studies.

Figure 8. Flowchart of studies included in the ENDS systematic review



Note: Many included articles were relevant to more than one section; however, they are numbered here by the section of our in-progress review where they first appear.

Workshop 3: Prevalence and Patterns of Use – 1. What is the prevalence of e-cigarette ever use, current use, and established use in the U.S.?

1. ***What is the prevalence of e-cigarette use among population subgroups, such as youth and young adults?***
2. ***What proportion of e-cigarette users are current tobacco users, including cigarette smokers?***
3. ***What proportion of e-cigarette users are former tobacco users, including cigarette smokers?***
4. ***What proportion of e-cigarette users are never tobacco users, including never cigarette smokers?***

PATTERNS OF USE

Overview

Existing studies demonstrate rapid increases in ever use and current use of e-cigarettes in the U.S. The largest increase in current use of e-cigarettes has been among high school students,[14] but the prevalence among young adults and adults overall remains low at around 2%.[15,78] Multiple studies

confirm that the greatest use of e-cigarettes is among current cigarette smokers. More research is needed to understand the relationship between ever use and current use, extent of use of e-cigarettes (e.g., daily or occasional use), length of use of e-cigarettes over time and how these impact patterns of cigarette use.

EVER E-CIGARETTE USE

National data indicates that ever use of e-cigarettes in the U.S. has increased in youth and adult populations. Current national estimates are 6.8% (2012) among youth,[79] 7.8% (2013) among young adults,[78] and 8.5% (2013) among adults.[78]

Youth

National Population

Data from the National Youth Tobacco Survey show that from 2011 to 2012, among all students in grades 6–12 in the U.S., ever e-cigarette use increased from 3.3% to 6.8%.[17,79,80] In 2012, ever use was more common among boys (8.1% vs. 5.5% in girls) and older youth: 9-12 years (1.5%), 13-16 years (6.3%), and 17-18 years (12.8%).[81,82] Ever use was highest among non-Hispanic Native American youth (9.6%), followed by non-Hispanic White respondents (8.2%) and Hispanic respondents (6.2%).[81] In 2013, 3.0% of middle school students and 11.9% of high school students had ever used e-cigarettes.[83] 2014 NYTS data on ever use are not yet available in the published literature; however, since 3.9% of middle school students and 13.4% of high school students reported currently using (≥1 day during the past 30 days) e-cigarettes in 2014, ever use can be estimated to be at least the same as, but likely higher than, these rates.[14]

State/Local Population

Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), 25.2% of high school students were ever e-cigarette users, and 3.5% of middle school students were ever e-cigarette users.[84] Older students, males, and White respondents were more likely to have tried e-cigarettes than their respective counterparts in this sample.[84] Data from a 2013 survey of 9th and 10th graders (both public and private) in Oahu, Hawaii (n=1,941) show that 29% had ever used e-cigarettes compared to 15% for ever use of cigarettes, 27% for alcohol, and 18% for marijuana.[85] Data from a longitudinal cohort study of children with alcoholic parents (n=136 families) showed that 36.9% of adolescents (middle and late adolescence) reported using an e-cigarette at least once.[86]

Current Smokers

A study using only the 2011 NYTS data also showed that the odds of lifetime e-cigarette use were 58 times higher among current cigarette smokers (OR = 58.44, 95%CI: 34.71-98.39) compared to nonsmokers, controlling for age, gender, race/ethnicity, disposable income, living with a smoker and having a smoking friend.[80] According to 2012 NYTS data, 42.2% to 60.2% of current smokers had ever used e-cigarettes.[79,81]

Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), ever cigarette smokers and current cigarette smokers were more likely to have tried e-cigarettes than their respective counterparts.[84] Among a sample of 3,912 students from four U.S. high schools, a higher proportion of current e-cigarette users (n=72), reported occasional (44.7%) compared with daily cigarette smoking (30.3%).[87]

Former Smokers

According to 2012 NYTS data, 48.3% of former smokers had ever used e-cigarettes.[81] Among students in southeast Connecticut in 2013 who reported that they had tried cigarettes in the past but were not current smokers, 59.8% reported having tried e-cigarettes.[84]

Never Smokers

According to 2012 NYTS data, 0.9% of never smokers had ever used e-cigarettes.[79,81] Among students in southeast Connecticut in 2013 who reported never having tried cigarettes, 2.1% of middle school students and 13.2% of high school students reported having tried e-cigarettes.[84]

Young Adults

National Population

One national study showed a doubling of ever e-cigarette use (5.0% to 10.3%) from 2011 to 2012 in U.S. young adults aged 18-34 (n=2,144).[88] Findings from the Legacy Young Adult Cohort Study, which using a nationally representative sample of young adults aged 18-34, reported 6.0% ever use of e-cigarettes in 2011.[89] Another national study showed that ever use of e-cigarettes in young adults aged 18-24 did not increase from 2010 to 2013, with prevalence estimates of 7.0% in 2010, 6.9% in 2011, 4.1% in 2012 and 7.8% in 2013 (n=4,033).[78] Other data from a probability sample of U.S. adults, ever use of e-cigarettes in young adults ages 18-24 increased from 2.5% in 2010 to 21.0% in 2013.[90] Among a nationally representative sample of U.S. young adults (18-34 years) (n=1,247), 25.3% had ever used e-cigarettes in 2014.[91]

State/Local Population

A 2009 study of North Carolina college students showed 4.9% ever use of e-cigarettes.[92] In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 29.9% were ever users of e-cigarettes in the fall of 2013.[93] In this sample, lower odds were seen among those aged 20-23 years, females, non-Hispanic non-Whites, and those reporting better than average school performance, and higher odds were seen among those who were current users of other tobacco products or marijuana.[93] In a convenience sample of college students from Oahu, Hawaii (n=307), 43% had ever used e-cigarettes in fall of 2013, which was more prevalent in younger respondents, Filipinos, current cigarette smokers, and respondents with greater numbers of friends/family who used e-cigarettes.[94] Another sample of students at two universities in Southeastern U.S. states (n=2,002) from 2013 showed that ever use was 13.2%.[95] Data from a sample of college students in Oklahoma (n=1,304) in 2012-2013 show that 13.5% had ever used an e-cigarette and 6.8% occasionally used an e-cigarette (0% reported daily use).[96]

Current Smoker

In 2009-2010, 1.2% young adults aged 18-25 years in the U.S. who had smoked at least one cigarette in the past month (study 1: n=1,987) reported ever using e-cigarettes to quit smoking cigarettes, which increased to 2.7% in 2010-2011 (study 2: n=595) and 38.0% in 2013 (study 3: n=79).[63] In the U.S., in a broad sample of current smokers from the ITC four country survey (n=6,110), 2.9% of young adult respondents (18-24 years) had ever used an e-cigarette from 2002-2011.[97] Data from a probability-based sample of U.S. adults show 31.5% ever use of e-cigarettes in 2011 among young adults ages 18-29 years.[61] A web-survey of current and former smokers (n=2,136) in 2013 found that 57.8% currently used e-cigarettes.[98]

A population-based, prospective cohort study in the Midwest found that 28.5% of current smoking young adults (ages 20-28) were ever users of e-cigarettes in 2010-2011.[99] In a convenience sample of college students from Oahu, Hawaii (n=307), ever use among current cigarette smokers was 68.2% in fall of 2013.[94] Another sample of students at two universities in Southeastern U.S. states (n=2,002) from 2013, among cigarette smokers, 20.0% also used e-cigarettes.[95] Among a sample of college students (n=4,444), current daily smokers (AOR=5.6; 95% CI 2.70, 11.60), current non-daily smokers (AOR=6.6; 95% CI 3.81, 11.2), and former smokers (AOR=5.7; 95% CI 3.37, 9.51) had higher odds of ever using e-cigarettes compared with non-smokers.[92]

Former Smokers

In a convenience sample of college students from Oahu, Hawaii (n=307), ever use among former cigarette smokers was 47.7% in fall of 2013.[94] A population-based, prospective cohort study in the Midwest found that 9.7% of young adults (ages 20-28) who were former smokers were ever users of e-cigarettes in 2010-2011.[99]

Never Smokers

In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 10.1% of never cigarette smokers (n=862) had ever used e-cigarettes in 2013.[93] In a convenience sample of college students from Oahu, Hawaii (n=307), ever use among never cigarette smokers was 18.4% in fall of 2013.[94] A population-based, prospective cohort study in the Midwest found that 2.7% of young adults (ages 20-28) who were never established smokers were ever users of e-cigarettes in 2010-2011.[99]

Adults

National Population

Ever use of e-cigarettes in adults aged 18 and over rose from 0.6% in 2009 to 2.7% in 2010.[100] Data from 2012 show ever use at 8.1% among all adults,[43,101] and rates in 2012-13 from the National Adult Tobacco Survey (NATS) show ever use at 14.1%.[15] In a different national study with data from 2010-2013, ever use almost doubled from 3.3% in 2010 to 6.2% in 2011,[102] then increased to 8.1% in 2012 and 8.5% in 2013.[78,103] Females had greater odds than males (2013), college educated respondents had greater odds than those with a high school diploma (2012), and younger respondents (18-24) had greater odds than older respondents (25-44 in 2010 and 2013; 45-64 and 65+ in 2010, 2011, and 2013) of ever use of e-cigarettes.[78] Among another probability sample of U.S. adults, ever use of e-cigarettes increased from 1.8% in 2010 to 13.0% in 2013.[90] Rate of increase in ever use was highest among non-smokers (although absolute increase was highest for current smokers), young adults, less educated respondents, and those respondents living in the South Census region.[90]

State/Local Population

A population-based telephone survey of adults in Montana (n=5,000) conducted in 2013 found that 11.2% had ever used e-cigarettes.[104] A population-based, prospective cohort study in the Midwest found that 7.0% of young adults (ages 20-28) were ever users of e-cigarettes in 2010-2011.[99]

Current Smokers

Ever use among adult current smokers has grown substantially in the U.S. from around 9.8% in 2010 to 21.2% in 2011, 31.4% in 2012, and 36.5% in 2013.[78]

Increased use of e-cigarettes among current cigarette smokers has been documented in a number of national samples. One study using a consumer-based mail-in survey of U.S. adults in 2009 (n=10,587)

and 2010 (n=10,328) found that current smokers and tobacco users were more likely than nonsmokers to have used e-cigarettes.[100] This same survey (now web-based) found from 2010-2013 ever use of e-cigarette was higher among current cigarette smokers than former and never smokers in every survey year; ever use among current smokers increased from 9.8% in 2010 to 36.2% in 2013.[78,102] Similarly, a U.S. nationally representative cross-sectional survey conducted in 2010 among 2,649 participants aged 18 and older found that between 6.4% and 7.1% of current smokers have ever used an e-cigarette.[105] Data from a probability-based sample of U.S. adults show 18.3% ever use of e-cigarettes in 2011.[61] National data from 2012 show ever use of e-cigarettes at 32.2% among current smokers.[43,101] In the U.S., in a broader U.S. sample of the ITC four country survey (n=6,110) 11% of respondents had ever used an e-cigarette in 2002-2011,[97] while other data from Wave 8 of this study (2010-11) report that 14.9% of current and former tobacco users had done so (n=1,520).[39] In the same wave and sample, among current cigarette smokers (n=1,262), 18% had ever used e-cigarettes.[106] Another U.S. nationally representative survey (The Tobacco Control in a Rapidly Changing Media Environment) of current smoking adults in 2013 (n=6,607) found that half of the sample had ever tried e-cigarettes.[107] A web-survey of current and former smokers (n=2,136) found that 46.8% had ever used e-cigarettes in 2013.[98] In a U.S. representative sample of 519 current smoking adults in 2014, 27.8% were ever users of e-cigarettes.[108]

In a sample of callers to six U.S. state quitlines in 2011-12 (n=2,476), 30.9% reported using an e-cigarette.[41] A longitudinal study of daily smokers in the San Francisco Bay area with serious mental illness (n=956) found 11.0% had ever used e-cigarettes over the course of the study; by year: 0% in 2009, 1.0% in 2010, 9.0% in 2011, 19.0% in 2012, and 25.0% in 2013.[62] In a sample of cigarette smokers who were admitted to a hospital in Alabama (n=958), 50.6% reported having ever used e-cigarettes.[109] About half (55.0%) of a small sample (n=112) of preoperative smoking patients aged 18 years and older in Minnesota reported that they had tried e-cigarettes.[110] A population-based telephone survey of adults in Montana (n=5,000) conducted in 2013 found that among current cigarette smokers, 55% had ever used e-cigarettes.[104]

E-cigarette trial may be increasing among non-daily smokers.

Data from a probability sample of U.S. adults show that ever use of e-cigarettes in current smokers increased from 8.2% in 2010 to 47.0% in 2013 for nondaily smokers and from 6.2% in 2010 to 54.2% in 2013 for daily smokers.[90] The 2010-2011 ITC survey found greater e-cigarette trial among non-daily smokers.[39] Among never established cigarette smokers ages 18-29 (n=4,310), 7.9% had ever tried an e-cigarette in 2013.[111] Among a sample of 3912 students from 4 US high schools, a higher proportion of current e-cigarette users (n=72), reported occasional (44.7%) compared with daily cigarette smoking (30.3%).[87]

Former Smokers

National data from 2012 show ever use of e-cigarettes at 2.4% among long-term former (quit more than one year ago) smokers and 26.8% among recent former (quit within past year) smokers.[43,101] HealthStyles, a national survey, found that ever use among former smokers increased from 2.5% in 2010 to 9.6% in 2013.[78,102] Data from a probability sample of U.S. adults show that ever use of e-cigarettes in former smokers increased from 1.5% in 2010 to 13.5% in 2013.[90] In 2010-2011 in the ITC sample, 10% of recent quitters had tried an e-cigarette.[106] A web-survey of current and former smokers (n=2,136) in 2013 found that more every day smokers (49.6%) had ever used e-cigarettes compared with some days smokers (43.6%) and former smokers (38.3%). However, former smokers had over three times the odds of being an established e-cigarette user (with over 50 lifetime uses) compared with current everyday smokers (AOR 3.24 95%CI 1.13, 9.30).[98]

Never Smokers

National data from 2012 show ever use of e-cigarettes at 1.0% among never smokers.[43,101] HealthStyles, a national survey, found that ever use among never smokers remained the same from 2010 (1.3%) to 2013 (1.2%).[78,102] A U.S. nationally representative cross-sectional survey conducted in 2010 among 2,649 participants aged 18 and older found that 1.0% of non-smokers have ever used an e-cigarette.[105] Data from a probability sample of U.S. adults show that ever use of e-cigarettes in never smokers increased from 0.3% in 2010 to 3.5% in 2013.[90]

CURRENT E-CIGARETTE USE

Current use of e-cigarettes is also growing for all age groups. Recent data from national studies indicates that the prevalence of current e-cigarette use among youth is 3.9% (middle school) to 13.4% (high school) (2014),[14] 2.3% among adults overall (2013),[78] and 2.4% among young adults aged 18-24 (2013).[15]

Youth

National Population

During 2011–2012, among all students in grades 6–12 in the U.S., current e-cigarette use increased from 1.1% to 2.1%.[17] In 2012 NYTS data, current e-cigarette use was also highest among students 17 or older (3.6%) and lowest among youth 12 and under (0.7%).[82] Monitoring the Future data from 2014 show past 30 day prevalence of e-cigarette use among adolescents (n=41,600) at 8.7% among 8th grade students, 16.2% among 10th graders, and 17.1% among 12th graders (13.9% among all grades combined).[112] Among middle school students, current e-cigarette use increased from 0.6% in 2011 to 1.1% in 2012, remained at 1.1% in 2013, and increased to 3.9% in 2014.[14,16,83] For high school students, current use increased from 1.5% in 2011 to 2.8% in 2012, to 4.5% in 2013, and again to 13.4% in 2014.[14,16,83] During the 2011-2014 period, among middle school students, increases were seen among females (0.4% to 3.3%), males (0.7% to 4.5%), non-Hispanic Whites (0.6% to 3.1%), non-Hispanic Blacks (0.4% to 3.8%), and Hispanics (0.6% to 6.2%).[14,16] Among high school students, increases were seen among females (0.7% to 11.9%), males (2.3% to 15.0%), non-Hispanic Whites (1.8% to 15.3%), non-Hispanic Blacks (0.8% to 5.6%), and Hispanics (1.3% to 15.3%).[14,16]

State/Local Population

A survey of high school students (grades 9-12) in Connecticut and New York (n=1345) also showed an increase in past 30-day e-cigarette use from February 2010 (0.9%) to June 2011 (2.3%) (p=0.05).[113] Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), 12.0% of high school students were current e-cigarette users, and 1.5% of middle school students were current e-cigarette users.[84] Data from a 2013 survey of 9th and 10th graders (both public and private) in Oahu, Hawaii (n=1,941) show that 18% had used e-cigarettes in the past month.[85]

Current Smokers/Dual Users

None

Former Smokers/Exclusive Users

Among students in southeast Connecticut in 2013 who reported that they had tried cigarettes in the past but were not current smokers, 22.9% reported using an e-cigarette during the past month.[84]

Never Smokers

None

Young Adults

National Population

In a nationally representative survey (NATS) of 60,192 U.S. adults aged 18 and over conducted in 2012-13, the highest rate of current use of e-cigarettes was among young adults aged 18-24 (2.4%) and adults aged 25-44 (2.4%).[15] Among adults classified as using every day, somedays, or rarely, use of e-cigarettes was highest among 18-24 year olds (8.3%), compared to 4.2% among adults overall.[15] These estimates are consistent with measures of past-30 day use of e-cigarettes, particularly 2011 findings from the Legacy Young Adult Cohort Study, which using a nationally representative sample of young adults aged 18-34, reported 7.0% past 30-day use of e-cigarettes.[89] Data from the HealthStyles survey, a consumer-based web survey of U.S. adults (n=8,173), showed that 0.9% of young adults ages 18-24 years reported current (past 30 day) use in 2012/2013.[78] In another probability sample of U.S. adults, current use of e-cigarettes in young adults ages 18-24 increased from 3.4% in 2012 to 14.2% in 2013.[90] Data from another nationally representative sample of U.S. young adults (18-34 years) (n=1,247) showed that 7.9% reported current use of e-cigarettes in 2014.[91]

State/Local Population

Current use of e-cigarettes also increased in a population-based, prospective cohort study in the Midwest which found that 1.2% of young adults (ages 20-28) were current users of e-cigarettes in 2010-2011.[99] Among young adults, college students may have been early adopters of e-cigarettes with a 2009 study of North Carolina college students showing 1.5% past 30-day use of e-cigarettes.[92] In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 14.9% were current users of e-cigarettes in the fall of 2013.[93] In this sample, lower odds were seen for those aged 20-23 years, females, non-Hispanic non-Whites, and those reporting better than average school performance, and higher odds were seen in those reporting current binge drinking and other tobacco product use.[93] In a convenience sample of college students from Oahu, Hawaii (n=307), 28% currently used e-cigarettes in fall of 2013.[94]

Current Smokers/Dual Users

In 2009-2010, 6.2% young adults aged 18-25 years in the U.S. who had smoked at least one cigarette in the past month (study 1: n=1,987) reported past month use of e-cigarettes, which increased to 18.8% in 2010-2011 (study 2: n=595) and 41.0% in 2013 (study 3: n=79).[63] A web-survey of current and former smokers (n=2,136) in 2013 found that 18.9% of young adults (18-29 years) currently used e-cigarettes, and 3.8% reported established use (50 times or more).[98] Another probability-based, web survey found that in April/May 2014, among current smoking adults (n=2,254), 19.6% of young adults were current users of e-cigarettes.[68]

In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), in fall of 2013, those who had experimented with cigarette smoking had 5-fold greater odds of having ever used e-cigarettes, and current/former smokers of cigarettes had nearly 20 times greater odds of ever using e-cigarettes and 6 times greater odds of currently using e-cigarettes.[93]

Former Smokers/Exclusive Users

None

Never Smokers

In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 5.1% of never cigarette smokers were current e-cigarette users in 2013.[93]

Adults

National Population

In a national sample of U.S. adults in 2010, 1.0-1.2% had used e-cigarettes in the past 30 days, increasing slightly to 1.5% in 2011, dropping slightly to 1.3% in 2012, then increasing in 2013 to 2.3%.[78,100] Females had greater odds than males, non-Hispanic White respondents had greater odds than Hispanic respondents, and those with <high school education had greater odds than those with a high school diploma in 2012/2013 of currently using e-cigarettes.[78] In 2012, an nationally representative online survey detailed current use at 1.4%.[43] A 2012-13 national survey (NATS) found that 1.9% of adults noted that they currently use e-cigarettes every day, some days, or rarely.[15] Among another probability sample of U.S. adults, current use of e-cigarettes increased from 0.3% in 2010 to 6.8% in 2013.[90] Rate of increase in current use was highest among young adults, males, less educated respondents, and those respondents living in the South Census region.[90] Another U.S. nationally representative survey (The Tobacco Control in a Rapidly Changing Media Environment) of adults in 2013 (n=6,607) found that 21% of the sample were currently using e-cigarettes.[107]

State/Local Population

A population-based telephone survey of adults in Montana (n=5,000) conducted in 2013 found that 1.3% were current e-cigarette users.[104]

Current Smokers/Dual Users

Another nationally representative online survey of adults 18 years and older found that in 2011 among those reporting current cigarette smoking (n=1,324), 8.0% were dual e-cigarette users.[114] Significant predictors of dual use of cigarettes and e-cigarettes were ever having used a smoking cessation medication, willingness to try smokeless tobacco when unable to smoke, and strong anti-tobacco industry attitudes.[114] National data from 2012 show current use of e-cigarettes at 6.3% among current smokers.[43,101] Data from the HealthStyles survey, a consumer-based web survey of U.S. adults showed that in 2010/2011, current use among current smokers was 4.9% and increased to 9.4% in 2012/2013.[78] In the U.S. in 2010-11, data showed that 6% of current smoking adults were current e-cigarette users.[39,106] Data from a probability sample of U.S. adults show that current use of e-cigarettes in current smokers increased from 1.4% in 2010 to 34.1% in 2013 for nondaily smokers and from 1.4% in 2010 to 30.3% in 2013 for daily smokers.[90] A panel of current smoking adults 25 years and older in the U.S. (n=2,376; non-probability sample) found that in 2012, 9.2% were current e-cigarette users.[29] A web-survey of current and former smokers (n=2,136) found that 16.1% currently used e-cigarettes in 2013, and 3.8% reported established use (50 times or more).[98] In a U.S. representative sample of 519 current smoking adults in 2014, 18.0% were current users of e-cigarettes.[108] Another probability-based, web survey found that in April/May 2014, among current smoking adults (n=2,254), 24.1% reported current e-cigarette use.[68]

Twenty-one percent of a small sample (n=112) of preoperative smoking patients aged 18 years and older in Minnesota reported that they currently used e-cigarettes.[110] A population-based telephone survey of adults in Montana (n=5,000) conducted in 2013 found that among current cigarette smokers, 10% were current e-cigarette users.[104] Among hospitalized current smokers in the U.S. (n=4,660),

prevalence of e-cigarette use (having used ≥1 time in the 30 days before hospital admission) increased over time, from 1.1% in 2010 to 10.3% in 2011, 10.2% in 2012, and 18.4% in 2013, with use varying widely by geographic region (Alabama 20.9%, New York 16.8%, Kansas 12.3%, Massachusetts 5.8%, and Oregon 6.2%).[115] Use was more prevalent among younger, non-Hispanic White, educated (college or more), and heavy smoking (≥10 or more cigarettes/day) patients.[115]

Former Smokers/Exclusive Users

National data from 2012 show current use of e-cigarettes at 0.2% among long-term former (quit more than one year ago) smokers and 6.1% among recent former (quit within the past year) smokers.[43,101] Data from the HealthStyles survey, a consumer-based web survey of U.S. adults showed that in 2010/2011, current use among former smokers was 1.0% and increased to 1.3% in 2012/2013.[78] Data from a probability sample of U.S. adults show that current use of e-cigarettes in former smokers increased from 0.3% in 2010 to 5.4% in 2013.[90]

The majority (96.7%) of customers at four retail "vape stores" in a large Midwestern (U.S.) city (n=215) reported in the summer of 2013 that they had previously used combustible tobacco (0.9% reported using smokeless tobacco and 2.3% refused to report).[69]

Never Smokers

National data from 2012 show current use of e-cigarettes at 0.4% among never smokers.[43,101] Data from the HealthStyles survey, a consumer-based web survey of U.S. adults showed that in 2010/2011, current use among never smokers was 0.2%.[78] Data from a probability sample of U.S. adults show that current use of e-cigarettes in never smokers increased from 0.1% in 2010 to 1.4% in 2013.[90] In the U.S. in 2010-11, data showed that 7% of recent quitters were current e-cigarette users.[106]

Workshop 3: Prevalence and Patterns of Use – 1. What are the reasons individuals try e-cigarettes?

Reasons for Use

The most commonly cited reasons for use by e-cigarette users include: 1) they aid in tobacco craving/withdrawal symptoms[116] and are used as a smoking reduction/cessation aid[32,39,41,43,53,58,67,68,104,110,117-129], 2) to evade smokefree policies and/or to avoid disturbing people with secondhand smoke, [32,39,43,67,68,104,110,117,118,120,121,124-133], and 3) the perception that they are less harmful/less toxic than traditional cigarettes. [32,39,43,53,68,104,107,110,116-119,121,123,124,129-131,133]

E-cigarette users also report trying or using e-cigarettes because they are less expensive than regular cigarettes, [43,68,104,110,116,117,120,121,128-130,134] for relapse prevention, [116,117,129] out of curiosity,[32,68,104,130] because they are accessible and convenient,[130,132,135] for social approval and/or the vaping community and/or a family or friend offered,[32,130,132,136] because of taste,[104,121] because they smell better,[117,130] and because they feel the experience is like smoking a regular cigarette but without the lingering odor.[128]

Workshop 3: Prevalence and Patterns of Use – 7. What types of e-cigarette devices are being used (e.g., "cigalike" devices vs. "tank" systems) and by whom? How do patterns of use differ among users of different devices?

<u>Product Type and Nicotine Content</u>

U.S.

Type/Brand

Data from a web-based survey in 2013 of current and former smokers (n=2,136) show that among ever users of e-cigarettes, 41.3% used blu for their first brand tried, 17.6% used NJOY, 5.6% used V2Cigs,

4.7% used Green Smoke, and 3.8% used Logic. Among current users of e-cigarettes, regular brands reported include blu (30.7%), NJOY (0.4%), V2Cigs (3.1%), other cigalike (28.9%), and other vaporizer (19.9%). Among established users of e-cigarettes (50 times or more), regular brands reported include blu (16.5%), NJOY (4.3%), V2Cigs (4.3%), other cigalike (32.8%), and other vaporizer (34.8%). Rechargeable products were typically used by 60.6% of current users and 84.7% of established users, while disposable products were typically used by 28.2% of current users and 3.6% of established users; around 11% of each group uses both types.[98] Vapers (current e-cigarette users) who are former daily cigarette smokers (n=1,434) reported in an online survey in 2013 that 7.8% used cigalike devices, 73.2% used second generation (refillable) devices, and 19.0% used other.[137] In a sample of current e-cigarette users who are former smokers in the U.S. (n=3,609) in 2012-2014, 87.1% were using an e-cigarette device larger than a cigarette, and 13% were using first generation devices. Respondents had tried an average of five different models and almost 75% had switched to their current brand because it gave them a more satisfying hit.[138]

Most customers at four retail "vape stores" in a large Midwestern (U.S.) city (n=215) reported in the summer of 2013 using newer generation devices (77.9%) as opposed to the cigalike devices (11.5%), while 10.6% reported using both.[69] Most initiated with the tank system compared to the cigalike devices (23.3%), but 91.4% of the latter eventually switched to the newer generation devices. One quarter reported dripping their e-liquid.[69]

Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), more students used rechargeable devices than disposable devices.[84]

Nicotine Content/Flavors

In a sample of current e-cigarette users who are former smokers in the U.S. (n=3,609) in 2012-2014, 50.8% used e-cigarette liquid >12 mg/mL.[138] Customers at four retail "vape stores" in a large Midwestern (U.S.) city (n=215) reported a median concentration of 18 mg/mL of nicotine in their liquid and a preference for non-traditional flavors, such as fruity (46.7%) and candy/nuts (12.6%). One quarter reported dripping their e-liquid.[69] Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), ever users of e-cigarettes initiated use mostly with nicotine-free e-cigarettes, while cigarette smokers were more likely to report initiating use with e-cigarettes with nicotine. Current smokers were most likely (compared to never and ever smokers) to consistently use e-cigarettes with nicotine.[84] Most ever e-cigarette users reported that they had tried (70.7%) and preferred (56.8%) sweet flavors. Menthol and tobacco flavors were mostly used by ever e-cigarette users who were also current smokers (tried: 38%; preferred: 18.6%).[84] A sample of 979 hospitalized cigarette smokers ages 19-80 showed that although Whites were more likely to use e-cigarettes, a higher proportion of Blacks reported a preference for menthol flavored e-cigarettes.[118]

Flavors in other tobacco products

Studies cited in this section were not included in our in-progress systematic review of ENDS, but we feel they are relevant to the FDA's question regarding the appeal of flavors.

According to 2000 and 2004 NYTS data, middle school students who had been smoking for less than one years were more likely to smoke menthol cigarettes than those who had been smoking for more than one year.[139] Data from the American Legacy Longitudinal Tobacco Use Reduction Study (ALLTURS) from 2000-2003 suggest that middle and high school students who initiated with menthol cigarettes had greater odds of progressing to established smoking compared to those who initiated with non-menthol cigarettes.[7] Additional national data from the NSDUH (2004-2010) indicate that menthol cigarette use was higher among 12-17 years olds (56.7%) and 18-25 year olds (45.0%) than older adults, while the rate of non-menthol cigarette use decreased.[6]

NYTS data estimate that in 2011, 6.3% of adolescents in the U.S. report past 30 day use of a flavored cigarette or cigar product.[140] Ninety-five percent of youth cigar smokers and 63% of cigar smokers ages 35 and older reported use of a usual cigar brand that manufactures flavored products in 2010-2011, according to the NDSUH.[141]

These studies demonstrate that flavored combustible products have wide appeal to youth and young adults and in line with our two-pronged strategy outlined above, removal of flavors in these highly harmful combustible products is likely to have a great impact on population health.

Other Countries

Type/Brand
A multi-national case-control study comparing dual users of e-cigarettes and cigarette to those who have completely substituted smoking with e-cigarette use ("non-smoking vapers") found that more non-smoking vapers were using newer generation devices and "do-it-yourself" preparation compared to dual users.[120] Among a sample in 2012-2014 of daily e-cigarette users who had quit smoking cigarettes in the past two months (n=374) throughout France, Switzerland, U.S., Belgium, U.K., Canada, and "other countries", 95% used refillable tank systems, 5% used pre-filled cartridges, and 44% used modular systems.[142] The most frequently used brands were Joye/Joyetech (20%), Ego (17%), Kanger (9%), Innokin (8%), and other (46%).[142]

Nicotine Content/Flavors
A 2013 province-wide survey in Ontario, Canada found that overall, 10.5% of students reported ever using an e-cigarette without nicotine while 4.1% reported using an e-cigarette with nicotine; 18% of ever e-cigarette users who had never used a conventional cigarette used an e-cigarette with nicotine as compared to 49% who had smoked a conventional cigarette in the past year.[143]

The ITC survey in 2013 found that among current e-cigarette users, 42.5% in Australia reported that their current brand contained nicotine compared to 73.1% in the U.K.; 21.1% in Australia and 9.0% in the U.K. did not know whether their brand contained nicotine.[144] This survey also found that in the Netherlands in 2013 and 2014, most (66.4% and 84.9%, respectively) current e-cigarette users reported using a nicotine-containing e-cigarette.[121]

A multi-national case-control study comparing dual users of e-cigarettes and cigarette to those who have completely substituted smoking with e-cigarette use ("non-smoking vapers") found that as time of use progressed (for both groups), lower nicotine levels in e-cigarette liquid were reported (median of 17-18 mg/mL at initiation to 10-12 mg/mL at time of survey).[120]

Among a sample in 2012-2014 of daily e-cigarette users who had quit smoking cigarettes in the past two months (n=374) throughout France, Switzerland, U.S., Belgium, U.K., Canada, and "other countries", 93% used e-cigarettes containing nicotine, and the most used flavors were tobacco (39%), mint-menthol (20%), various fruits (12%), coffee (5%), caramel/toffee (3%), and RY4 (3%; mixed caramel/tobacco).[142] A longitudinal study from 2011-2013 of users of e-cigarettes, or "vapers" (n=367), found that at baseline 96% were using e-cigarettes containing nicotine.[51]

Workshop 3: Prevalence and Patterns of Use – 8. What is the volume of e-cigarette retail sales by type of sales route, including online sales, specialty retail ("vape") shops, and traditional outlets? What are the product attributes of products sold via these routes? What proportion of sales is accounted for by

products using tobacco flavors, menthol or other flavors? What types of non-tobacco or menthol flavors are most frequently sold?

SALES

There have been approximately 9 studies addressing the sales of e-cigarette products. [70,145-152]

Retail Availability

The e-cigarette market is expanding[70,145] and accessible to consumers in most traditional tobacco outlets.[146,148,149] Traditional tobacco outlets were found to sell e-cigarettes in studies that assessed retail availability.[146,148,149] Studies that examined growth trends of the e-cigarette market demonstrated significant expansion over time.[70,145,151] Research is mixed on whether retail availability is associated with neighborhood demographics, with one study demonstrating no significant association, and one indicating a greater likelihood of e-cigarette retailers in communities with higher median incomes.[146,148]

Pricing

Information is limited on the impact of pricing on e-cigarette sales, with one study indicating that e-cigarettes are 2-3 times more sensitive to price than conventional cigarettes.[147] As a result of e-cigarettes not being regulated by the FDA, e-cigarette products can be sold at an estimated 200-400% markup in vape shops.[150] One study, however, suggests that e-cigarettes are very sensitive to price changes. In the one price elasticity study we identified, quarterly prices and sales for e-cigarettes and conventional cigarettes (n=1,043) from 2009 to 2012 were constructed from store scanner data in 77 Nielsen markets. The estimated own price elasticities for disposable e-cigarettes was found to center around -1.2 and -1.9 for reusable e-cigarettes, approximately 2-3 times larger than the price elasticities of conventional cigarettes. There were no consistent and statistically significant relationships between cigarette prices and e-cigarette sales.[147] There is also evidence that as the price of conventional cigarettes rise, e-cigarettes are a suitable substitute for smokers and may therefore discourage smokers from completely quitting.[152]

Workshop 3: Impacts on the Use of Current Tobacco Products – 1. How does e-cigarette use affect use of other tobacco products among current tobacco product users, including current cigarette smokers?

DUAL USE OF E-CIGARETTES AND OTHER TOBACCO PRODUCTS

Dual use of e-cigarettes and other tobacco products, particularly cigarettes, is high.

Youth

National Population

In a nationally representative sample of U.S. middle and high school students (NYTS 2012), current use of e-cigarettes was 9.7% among youth who currently used cigarettes only, 12.9% among youth who currently used any conventional tobacco product (cigarettes, smokeless tobacco product, or cigars/cigarillos, or little cigars), and 19.0% among youth who currently used a non-conventional tobacco product (hookah, snus, or dissolvable).[153] Among users of alternative tobacco products who completed the NYTS survey in 2012, 22.4% were ever users of e-cigarettes and 7.2% were current users (e-cigarette use among cigar smokers: 24.7% ever, 8.0% current; chewing tobacco users: 32.5% ever, 11.2% current; pipe smokers: 35.3% ever, 14.6% current; hookah users: 37.8% ever, 14.0% current; snus users: 43.9% ever, 15.6% current; dissolvable tobacco users: 42.9% ever, 22.0% current).[82] More 2012 NYTS data show that age (≥18 years), gender (male), race/ethnicity (White, non-Hispanic), trying a cigarette before the age of 12, living with someone who uses tobacco, daily cigarette smoking, use of

flavored products, nicotine dependence, harm perceptions (agreeing that all tobacco products are dangerous and breathing smoke from tobacco products causes harm), tobacco marketing receptivity, and perceived prevalence were significantly associated with polytobacco use relative to exclusive cigarette use.[154] 2013 NYTS data showed that out of the 5.4% of middle school students who reported currently using combustible tobacco products, 0.4% reported using them in conjunction with e-cigarettes, while 0.2% reported using them with both e-cigarettes and other non-combustible products.[83] Out of the 20.7% of high school students currently using combustible tobacco products, 2.7% reported currently using them in conjunction with e-cigarettes, while 1.1% reported using them with both e-cigarettes and other non-combustible products.[83] Data on dual use and polyuse of e-cigarettes and other tobacco products in 2014 from the NYTS are not yet available in the published literature.

State/Local Population
In a sample of youth from four high schools in New York and Connecticut in 2010 and 2011 (n=3102), current e-cigarette users reported a greater mean number of alternative tobacco products (cigars, blunts, hookah, or smokeless tobacco) (mean 1.75, SD. 1.32) than current cigarette smokers who did not use e-cigarettes (1.15, SD 1.03) or never smokers (mean: 0.06, SD: 0.3 p<.0001).[87] In a sample of students at two colleges in Southeastern U.S. states (n=2,002) from 2013, among e-cigarette users, 46.6% also used cigars, 17.0% also used smokeless tobacco, and 54.5% also used hookah.[95]

Young Adults
National Population
In a nationally representative longitudinal study of young adults from 2011-2012, ever use of e-cigarettes rose from 5.0% at Wave 1 to 10.3% at Wave 3. However, most of this use was among dual or poly-tobacco users. Less than 1% of users at each wave used a non-combustible tobacco product exclusively.[88] Data from the second wave (2012-2013) of the Dartmouth Media, Advertising, and Health Study, a nationally representative web-based survey of youth and young adults ages 15-23 (n=1,596), show that nearly as many single product users smoked cigarettes (49%) as consumed hookah (23%), little filtered cigars (17%) and e-cigarettes (5%) combined. Among dual product users, e-cigarettes and cigarettes was the least common pair (13%), after cigarettes and hookah (16%) and cigarettes and little filtered cigars (25%).[155]

State/Local Population
In a sample of college students, ever use of e-cigarettes was associated with ever use of hookah in bivariate, but not multivariate analyses.[92] In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), in fall of 2013, 55.3% of users of tobacco besides cigarettes in the past 30 days had ever used e-cigarettes.[93]

Adults
National Population
Among U.S. adults in 2012 (NATS, n=3,627), 10.6% of respondents reported being dual product tobacco users, and 28.1% of dual users reported using e-cigarettes and another tobacco product. Only 0.4% of the adult population reported using e-cigarettes exclusively while 1.9% reported using e-cigarettes and cigarettes in combination.[156] Among ever e-cigarette users from the NATS survey in 2012-2013, 86.2% had experimented with cigarettes, 14.8% had ever used cigars, 58.5% had ever used hookah, and 18.1% had ever used smokeless tobacco.[111]

Workshop 3: Impacts on the Use of Current Tobacco Products – 3. How do flavors affect the appeal and use of e-cigarettes among current tobacco users, including current cigarette smokers?

Workshop 3: Attitudes, Beliefs, and Product Perceptions – 3. What beliefs and perceptions do e-cigarette users have about e-liquid contents, nicotine amount/concentration, and flavorings?

Some e-cigarette users are drawn to the flavors of the products. Evidence indicates that flavors are viewed as an attractive characteristic of e-cigarettes,[131] and in multiple studies, participants cited flavors as a reason for e-cigarette use.[68,120,130] A survey of ever users of e-cigarettes in 2009 (n=81) found that 18% enjoy the taste and variety of flavors.[129] A multi-national survey of current (n=398) and former (n=4,117) adult smokers found that on average, respondents felt that flavor variability was a very important factor in reducing or quitting smoking. Almost half felt that restricting variability would make quitting less likely and would increase craving for conventional cigarettes.[52] The same study also found that most (68.3%) respondents switch among flavors daily because the taste gets blunt from long-term use of one flavor and would find the experience less enjoyable if variability of flavors was restricted.[52] Former smokers switch more frequently.[52] In a study examining nonsmoking teens and adult smokers, the e-cigarette flavors tested appealed more to adults compared to teens, but interest in flavors was low in both groups.[157]

Workshop 3: Update of E-cigarette Use by Non-Users of Tobacco Products – 2. What proportion of non-smoking youth and young adults who experiment with e-cigarettes as their first tobacco product progress to regular e-cigarette use and to use of combustible tobacco products? **(don't have evidence related to progression to combustible tobacco products)**

<u>Initiation</u>

Few studies measure the impact of e-cigarette use on tobacco use initiation.

Among students in southeast Connecticut in 2013 (high school, n=3,614; middle school, n=1,166), middle school students were more likely to report that an e-cigarette was their first tobacco product tried (51.2%) than high school students (18.5%).[84] Data from the second wave (2012-2013) of the Dartmouth Media, Advertising, and Health Study, a nationally representative web-based survey of youth and young adults ages 15-23 (n=1,596), show that e-cigarettes were rarely reported as a first-use product (initiated at 10-14 years 0%, 15-17 years 0.5%, and 18-24 years 1.0%).[155] Data from a sample of college students in Oklahoma (n=1,304) in 2012-2013 show that among those who initiated with cigarettes (n=326), 33.7% had ever used e-cigarettes, and 2.8% occasionally used them (0% used them daily); among those who initiated with emerging tobacco products (dissolvable products, e-cigarettes, and snus combined; e-cigarettes not separated) (n=59), 30.5% had ever used cigarettes, 3.4% occasionally used them, and 1.7% used them daily.[96]

<u>Converting from Ever to Current Use</u>

Fewer than half of those who try e-cigarettes convert to current use.

Among a nationally representative sample of adolescents in grades 6 to 12, of those who had tried e-cigarettes, 29.3% were currently using.[158]

In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 29.9% were ever users of e-cigarettes in the fall of 2013, and 15.0% were discontinued e-cigarette users (50.0% of ever users).[93]

Studies among U.S. adults indicate that among ever users of e-cigarettes, current use of e-cigarettes ranged from 43% in 2010[100] to 18% in 2012.[43] In the U.S. in 2010-11, data showed that among those who had tried e-cigarettes (6% of sample), 37% were current e-cigarette users.[39] A nationally representative,

cross-sectional study of 3,240 adults in the U.S. found that among those who had tried an e-cigarette, 19.7% were current users in 2010.[159]
In Britain, a quantitative online surveys in 2010 and 2012 found that the proportion of smokers who had tried e-cigs but do not use them anymore increased between 2010 and 2012 (5.5% to 15.0%).[125]

Workshop 3: Update of E-cigarette Use by Non-Users of Tobacco Products – 3. What proportion of youth and young adults report curiosity and susceptibility to e-cigarettes? How does e-cigarette curiosity/susceptibility compare to curiosity/susceptibility to conventional cigarettes or other tobacco products?

Interest
Both young adults[135] and adolescents[160] would be willing or interested to try an e-cigarette if offered by a friend, but fewer adults are willing, except among current smokers.[43] In a 2012 national survey in Great Britain, 51.7% of current smokers who had never tried an e-cigarette were interested in future use, compared to 18.3% of recent ex-smokers who had never tried an e-cigarette.[119] In a nationally representative sample of individuals aged 15+ in Italy, of those who had heard of e-cigarette but never tried one, 10.1% had an intention to try one in the future.[133] In a small US sample of tobacco users who had tried ENDS but were not current users, 50% indicated that they were likely or somewhat likely to try them in the future, while 32% of those who had never tried ENDS reported that they were likely or somewhat likely to try them in the future.[110] Willingness to try e-cigarettes is associated with less negative beliefs about the typical smoker,[160] and among current smokers, younger age, having children in the home, using menthol, and having made a quit attempt in the past year.[161] In a small sample of freshman and college students, smoking status, alternate tobacco use, and acceptability of public use of e-cigarettes were significant predictors of intention to use or try an e-cigarette within the next six months.[162]

One study found that current smokers who reported at least some interest in trying e-cigarettes cited the following reasons for being interested: for use in a place where they cannot smoke cigarettes, as a cheaper alternative to cigarettes, for cessation/reduction/replacement of cigarettes, and for times when they do not want to smoke around others.[163] Another study found that expectancies around taste, negative affect and craving/addiction were the strongest predictors of intention to use ENDS.[109] Additionally, another study found that, when participants believed that their nicotine-free e-cigarette contained nicotine, it reduced their intention to smoke cigarettes.[28]

Workshop 3: Attitudes, Beliefs, and Product Perceptions – 1. What beliefs and perceptions do e-cigarette users and non-users have about the risks of e-cigarettes compared to the risks of other tobacco products (both combustible and noncombustible), NRT, and cessation? How do beliefs and perceptions vary across subgroups by age and by e-cigarette and other tobacco use?

<u>Product Perceptions</u>
E-cigarettes are generally perceived to be less harmful than regular cigarettes.[95,105,128,133,164] This finding was consistent among e-cigarette users[67,79,92,116,117,124,126,129] and current smokers and recent quitters.[108-110,119,120,123,125,137] Studies suggest that e-cigarettes are also perceived as less addictive than cigarettes.[53,99] Evidence suggests that, regardless of smoking status, ever use of e-cigarettes is associated with perceiving e-cigarettes to be less harmful than cigarettes.[79,81,82,94,163] The 2012 National Youth Tobacco Survey found that middle and high school students who lived with a smoker[81] or had a family member who used tobacco[82] were less likely than their peers to report that e-cigarettes were more harmful than regular cigarettes. Findings from this survey also indicated that females were more likely to perceive e-

cigarettes as harmful compared to males,[79,82] that susceptibility to cigarette smoking among never smokers was associated with low harm perceptions of e-cigarettes,[79] and that perception of increased harm from e-cigarettes was highest among those in the oldest age bracket (≥17 year olds).[82] Hispanic participants were also more likely than White participants to perceive e-cigarettes as more harmful than cigarettes.[79] Results from a case study suggest that they may be knowledge gaps regarding the harms of using e-cigarettes during pregnancy.[165] Additionally, an online experimental study found that exposure to warning labels increased participants' perceived harm of e-cigarettes.[166]

Workshop 1: Device Design and Design Characteristics – 3. What are the significant design characteristics of e-cigarettes that modify the delivery of nicotine and other constituents to users? Workshop 1: Device Design, E-Liquid and Aerosol Interactions – 3. What design features may alter the abuse liability of e-cigarettes (e.g., user electronic adjustments, constituent delivery modification)? Workshop 3: Impacts on the Use of Current Tobacco Products – 2. What product features make an e-cigarette more or less appealing to current tobacco users, including cigarette smokers who want to quit?

E-cigarettes typically fall into three broad categories: disposable "cigalike" products, rechargeable "cigalike" products, both commonly referred to as first-generation devices, and larger rechargeable products, commonly referred to as new- or second-generation devices.

2. Disposable "cigalike" e-cigarettes, or first-generation devices, are designed to look like cigarettes and mimic the act of smoking and can have an indicator light with different colors that glow when activated by inhalation. These products are designed for single use with a non-reuseable battery and/or cartridge and priced competitively with conventional cigarette products. They are sold in various flavors including tobacco and menthol, as well as fruit and candy flavors, and are heavily marketed at the point of sale (e.g., convenience stores) and online. Example brands/products include NJOY King, blu Magnificent Menthol Disposables, and V2Cig.[124,129,167-170]
3. Rechargeable "cigalike" e-cigarettes have similar design features to disposables but allow for re-use with replacement cartridges and chargeable/replacement batteries. Often sold as a "starter kit" that includes a charging device/cord, rechargeable "cigalike" products are more expensive than disposables but are sold heavily in convenience stores as well as online.[134,167,169] Example brands/products include blu Premium E-Cig Starter Kit and Smoking Everywhere Platinum starter kit.
4. Larger rechargeable e-cigarette products, personal vaporizers, or new/second generation devices, differ from "cigalike" products in several ways, including the batteries used (larger/higher voltage, longer battery life), cartridge characteristics (e.g., "tank" for nicotine solution), and other product features (temperature control, adjustable voltage, drip tips).[71,171] Users of these products typically purchase refill nicotine liquid separately in bottles or prepare their own using individual ingredients. Refill liquid comes in a wide variety of flavors and nicotine concentrations including 0 mg/ml (no nicotine). These products and associated accessories usually are obtained from Internet sources or at a specialty brick and mortar "vaping store". [67,168,172] Example brands/products include Tornado Tank eGo-C and ProVari Variable Voltage V2 ECig.[67,116,124,134,167,172,173]

Evidence from user surveys and interviews indicate that new e-cigarette users begin with "cigalike" products, but experienced and long-term e-cigarette users (i.e., "vapers) appear to transition to larger "personal vaporizer" models and prefer to order nicotine liquid online/purchase from "vaping stores" or mix their own concentrations.[67,116,124,134,173] An analysis of e-cigarette packaging of six "cigalike" brand models (NJOY, NCIG; Liberty Stix; Crown Seven, Hydro; Smoking Everywhere, Gold and Platinum;

VapCigs) indicated higher vacuums (suction) were required to smoke e-cigarettes compared to conventional cigarettes.[174] Plasma nicotine levels after use of new-generation products have been found to be equal to those resulting from conventional cigarette use, but not until 35 minutes of use (well after peak levels associated with conventional cigarette use), and first-generation products only reach about 75% of the nicotine levels achieved by smoking conventional cigarettes.[71]

Workshop 1: E-Liquid and Aerosol Constituents – 1. What is the chemical composition of e-liquids?

Workshop 1: E-Liquid and Aerosol Constituents – 6. What are the identities, quantities and origins of the chemical constituents of the e-cigarette aerosols inhaled and exhaled aerosols by users?

Workshop 1: E-Liquid and Aerosol Constituents – 10. What are the potential toxicological risks associated with flavorings?

Workshop 1: Device Design, E-Liquid and Aerosol Interactions – 4. What are the quantitative and qualitative relationships between the chemical contents in e-liquids (e.g., nicotine, humectants, flavorings) and chemical constituents in aerosols inhaled by users?

Workshop 2: Toxicological Considerations – 14. What is known about the toxicities of inhaled flavorings? Are some inhaled flavorings more toxic than others?

Workshop 2: Health Effects in Users – 2. What are the potential short and long-term health effects of inhaling humectants (e.g., propylene glycol, glycerin), flavorings and other e-liquid additives?

Workshop 3: Health Effects of E-Cigarettes in Non-Users – 2. How do exhaled aerosol properties impact potential secondhand and thirdhand exposures?

Workshop 3: Health Effects of E-Cigarettes in Non-Users – 4. What are the potential impacts of e-cigarette use on the levels of particulate matter and chemicals/toxicants from the e-cigarette in enclosed spaces such as cars, homes, office settings, and public buildings?

Nicotine Content

E-cigarette nicotine content in liquid and ENDS aerosol varies across manufacturers, devices, cartridges, and even puff to puff.[168,175-183]

Cartridges contain up to 20 mg of nicotine[184] and are largely sold in denominations of 6-8 mg/ml, 9-12 mg/ml, 13-18 mg/ml (although higher denominations are available). Thus a 10 ml bottle of refill e-cigarette liquid may contain as little as 60 to as much as 180 mg of nicotine. For reference, a lethal dose of nicotine is 30-60 mg for adults and 10 mg in children (unclear where this data was substantiated).[116] Some ENDS solutions and aerosols contain nicotine doses are that not consistent with manufacturer specifications[167,175,177,178,180,185-188] and at levels that are potentially lethal in adults and children if used other than directed.[175]

There is wide variability in nicotine content vaporization efficacy by brand, product type, and user profiles.[168,177,183,186] Mainstream and exhaled ENDS aerosol contains measurable amounts of nicotine,[179,189-191] although at much lower levels than found in conventional cigarette smoke.[179,181,192,193] One study indicates there may be a risk for thirdhand exposure to nicotine from e-cigarettes, with exposure level differing by brand and surface.[194]

Propylene Glycol

E-cigarette liquids[167,182,191,195] and mainstream and exhaled ENDS aerosol[167,187,189-191,195] contain propylene glycol which has not been rigorously studied for long-term safety via inhalation using an e-cigarette.[168]

Some e-cigarette liquid solutions contain high levels of propylene glycol and glycerol[167,189,191] and these proportions are sometimes inconsistent with manufacturer specifications.[167]
A literature base exists on safety and toxicological profile of propylene glycol delivered via fluid or pressurized air[196,197] but it is unclear whether this data applies to the use of propylene glycol delivered using a heated atomizer (i.e., via e-cigarettes) and for an extended period of time. In 1996, the U.S. Agency for Toxic Substances and Disease Registry concluded that repeated exposures to propylene glycol are associated with some irritation, but it is generally considered to be a safe chemical.[197] In 2006, the Environmental Protection Agency as part of a reregistration review concluded that there are no toxicological endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol.[196]

Flavorings and Other Toxicants (VOCs, TSNAs, heavy metals)
Mainstream and exhaled ENDS aerosol contains measurable amounts of flavorings[189,191], and liquids contain small amounts of flavorings.[190] Flavors detected in liquid include vanilla, menthol, raspberry, and apple.[190,191,198]

While several categories of toxic constituents or properties have been measured in ENDS liquid and aerosol including tobacco-specific nitrosamines, heavy metals, and carbonyls, there are generally fewer total constituents at lower levels than that observed in conventional cigarette smoke.[167,179,186,188-193,195,198-205]

Particulate Matter
Mainstream and exhaled ENDS aerosol contain ultrafine and fine particulate matter at similar sizes to that of conventional cigarette smoke, but the amount of particulate matter produced by e-cigarettes is not yet conclusive.[179,189-191,200,206-213] In vitro experiments demonstrate that e-cigarette and combustible cigarettes produce mainstream aerosols with generally similar particle sizes.[190,206-208]

Some studies found that the amount of particulate matter produced by e-cigarettes is significantly lower than that produced by conventional cigarettes,[179,189,192,210] while others found no difference or slightly higher concentrations in e-cigarettes.[206-209] Breath-activated models of e-cigarettes have higher initial aerosol absorbance than button-activated models, but decreases gradually with use.[170]

Workshop 1: Device Design and Design Characteristics – 5. What are the information collecting capabilities of current devices? Can the function of the devices be modified by a 3rd party or software communications? What are the potential benefits and concerns associated with software, data collection and electronic communications in e-cigarettes?

Ongoing studies at Legacy are piloting research with an e-cigarette product (Smokio) that has data collection capabilities (http://us.smokio.com/#). We are happy to share information on our experience using this product for data collection with FDA, if requested.

Workshop 1: E-Liquid and Aerosol Constituents – 10. What are the potential toxicological risks associated with flavorings?
Workshop 2: Toxicological Considerations – 14. What is known about the toxicities of inhaled flavorings? Are some inhaled flavorings more toxic than others?

Several experiments have measured cytotoxicity of liquid and vapor, revealing that particular flavors are more cytotoxic than others, but all are less cytotoxic than cigarette smoke extract.

Particular e-cigarette flavors are more cytotoxic than others, but all are less cytotoxic than cigarette smoke extract.[214-216] Studies found that between 5-43% of e-cigarette flavors samples had a slight/moderate cytotoxic effect on human and mouse stem and myocardial cells and 3-10% of samples had a high cytotoxic effect.[172,214] The most common flavor found to be cytotoxic is cinnamon.[172,214,217,218]

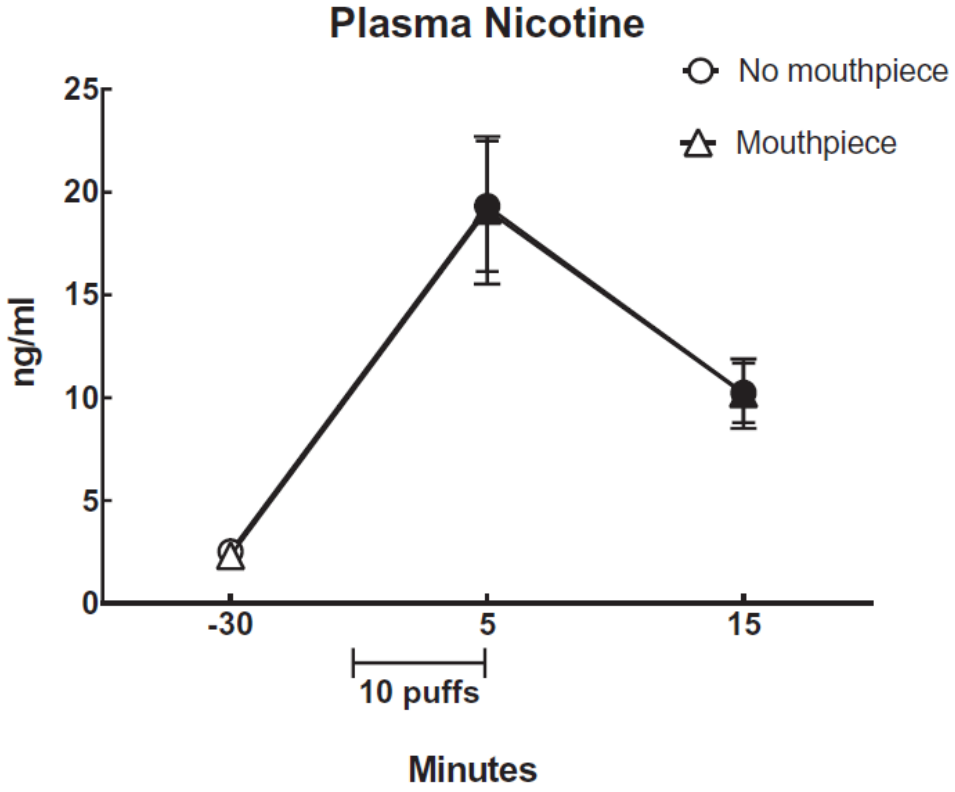
Menthol flavor has also been found to inhibit cell growth.[219] Vegetable glycerin and propylene glycol have been found to be non-cytotoxic at all concentrations for all cell types.[172] Research is mixed on whether nicotine levels are correlated with cytotoxicity.[172,214-216,220]

Workshop 1: Device Design, E-Liquid and Aerosol Interactions – 3. What design features may alter the abuse liability of e-cigarettes (e.g., user electronic adjustments, constituent delivery modification)?
Workshop 2: Clinical Pharmacology and Abuse Liability – 11. What is the impact of e-cigarette use on nicotine addiction (e.g., how may e-cigarette use increase, support or decrease nicotine addiction)?

ADDICTIVENESS
E-cigarettes deliver nicotine, but more research is needed to determine whether the levels of nicotine delivered support the potential for nicotine dependence.

- At least 20 clinical studies have examined nicotine biomarkers resulting from e-cigarette use.[38,71,76,116,173,191,221-234] Acute examinations demonstrate that nicotine delivery is dependent on the e-cigarette device and liquid type, as well as the rate at which the nicotine is delivered and the user's experience with e-cigarette use (i.e., naïve or not naïve).[71,76,221,222,228,229,232-234] Addiction liability is a result of the rapid peak level that is still only found in combustible tobacco products. Three clinical laboratory reports among experienced e-cigarette users indicated 10 puffs of a nicotine-containing e-cigarette reliably increased plasma nicotine within 5-10 minutes but levels were all significantly lower and reached a peak more slowly than that achieved with 10 puffs from a conventional cigarette.[71,173,222] The profile was highly variable and resembled that of NRTs which engender no to minimal nicotine dependence. Another lab study indicated that the same plasma nicotine levels after cigarette use can be achieved after e-cigarette use, dependent upon the puff topography of the user.[76]
    - Spindle et al.[76] measured plasma nicotine levels among experienced e-cigarette users after use of their preferred devices and liquids (none were disposable "cigalike" devices) during two 2.5-hour sessions separated by two days, one during which participants used a mouthpiece-based topography recording device, and one during which they did not. Participants were instructed to take 10 puffs of the device, with each puff separated by 30 seconds, and to use ad lib for the remainder of the time. Plasma nicotine levels after five minutes of use [19.2 ng/ml (SD 2.3)] was significantly greater than at baseline [2.4 ng/ml (SD 0.2)] and ten minutes after use [10.2 ng/ml (SD 1.1)] (see Figure 3). The mean nicotine level achieved after five minutes of use in this study is even greater than what was found after five minutes of cigarette use in a study by Vansickel et al.[228] of 18.8 ng/ml (SD 11.8). Additionally, participants reported reduced urge to use an e-cigarette after five minutes.[76]

Figure 3. Mean plasma nicotine concentrations in two conditions: with no topography mouthpiece and with a topography mouthpiece.[76]



- Twenty-two studies have examined the abuse liability and/or subjective effects of e-cigarette use.[28,38,42,67,76,109,137,138,142,173,221-223,225,227-229,231,235-239] These studies indicate e-cigarette use reliably decreases adverse symptoms related to tobacco abstinence (e.g., urges to smoke, irritability) [76,138,142,221,222,228,229,235-238] and increases ratings of satisfaction/pleasantness.[42,76,137,173,221,228,229] Studies indicate that current smokers find e-cigarettes to be less satisfying than cigarettes,[231,239] but second generation devices are more satisfying than first generation.[237] Among current cigarette smokers who had completed six 10-puff bouts with two types of e-cigarettes, results from a multiple choice procedure to determine the reinforcing efficacy of these products suggested that e-cigarettes were less reinforcing than own brand cigarettes.[229]
- Dependence is a major component of e-cigarettes' abuse liability. No well-validated scales of e-cigarette dependence are available, although at least one measure has been proposed.[138,240] Studies indicate decreased perceived dependence as compared to cigarettes.[138,142] Some characteristics to consider when determining e-cigarette dependence are as follows:[241]

  A. Total dose delivered
  B. Speed of uptake
  C. Amount of behavioral conditioning
  D. Social factors
  E. Taste and other sensations
  F. Adverse effects
  G. Price, availability, etc.

More research is needed to determine whether the levels of nicotine delivered support the potential for e-cigarettes to be sufficiently satisfying to displace combustible tobacco products and to determine what level of nicotine dependence may be acceptable at the population level.

- It is also unclear whether severity of dependence on a cleaner form of nicotine is of as much public health concern if the degree of addiction/dependence is de-coupled from the toxicity in combusted products (i.e., a delivery system that increases addiction liability, but with cleaner nicotine delivery). The net public health benefits versus harms would need to be determined by the degree to which a more addictive clean delivery system can successfully compete with combusted tobacco. That is, the benefits of a product with high addiction liability and with minimal harm (associated with clean nicotine) would outweigh harms associated with combusted tobacco if that product strongly encouraged complete switching away from combusted products. This would contrast with a lower addiction liability product that resulted not in complete switching but rather prolonged dual use (a public health benefit if the comparison is to lethal cigarettes and not to placebo or nothing).

Summary: Addictiveness

Overall, e-cigarettes are associated with lower levels of nicotine exposure relative to cigarettes and bear some similarities to dependence-inducing tobacco products (e.g., cigarettes, smokeless tobacco) in terms of tobacco abstinence symptom suppression and positive subjective effects. To date, these data are inconclusive as to whether the current generation of e-cigarettes do or do not support the potential for nicotine dependence/addiction.

Workshop 2: Toxicological Considerations – 4. What panel of biomarkers of exposure and toxicity in animal studies can be used to evaluate the toxicity of short and long-term e-cigarette use?

Workshop 2: Toxicological Considerations – 5. What panels of biomarkers of exposure and toxicity allow for cross-species comparisons (i.e., between animals and humans)? What are the limitations of scaling from animal to human studies?

Animal studies were not included in our review, but the two below examine biomarkers in mice:[242,243]

1. Romagna, G., Allifranchini, E., Bocchietto, E., Todeschi, S., Esposito, M., & Farsalinos, K. E. (2013). Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. Inhal Toxicol, 25(6), 354-361.
2. Sussan, T. E., Gajghate, S., Thimmulappa, R. K., Ma, J., Kim, J. H., Sudini, K., Biswal, S. (2015). Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. PLoS One, 10(2), e0116861.

Workshop 2: Toxicological Considerations – 6. What panel of biomarkers of exposure and toxicity could be useful for monitoring exposure and toxicity in humans across different tobacco products?

Workshop 2: Health Effects in Users – 4. What biomarkers and clinical endpoints can be used to assess the impact of e-cigarettes on user health?

Outcome	Biomarker
Nicotine	plasma nicotine,[57,71,173,221-223,228,229,244] saliva/serum cotinine,[38,116,224-227] urinary nicotine metabolites[191]
Lung function	exhaled carbon monoxide,[38,48,57,191,226,228,245,246] exhaled nitric oxide,[191,209,247] total respiratory resistances[247]
Cardiovascular function	heart rate,[57,173,223,228,229] myocardial function[248]
Cytotoxicity	cell viability,[172,214,217,242] inhibitory concentration 50 (IC_{50}),[172,214,217,242] human pulmonary fibroblast survival rate,[200] pro-inflammatory cytokines,[215] no observed adverse effects level (NOAEL)[214,217,242]
Others	complete blood count,[226,245] interleukins (IL),[249] vascular endothelia growth factor,[249] tumor necrosis factor alpha (TNFa),[249] monocyte chemotactic protein-1,[249] epidermal growth factor (EGF),[249] carboxyhaemoglobin (COHb),[227] oxygen saturation (SpO_2)[227]

Workshop 2: Toxicological Considerations – 9. What is the impact of local and systemic exposure (of e-liquid and aerosol)?

Workshop 2: Toxicological Considerations – 10. What aerosol constituents (e.g., chemicals, toxicants, flavorants, other additives) are delivered to users?

Workshop 2: Toxicological Considerations – 12. How do levels of toxicant exposure compare to those in users of other tobacco or nicotine containing products (e.g., traditional cigarettes, other combusted tobacco products, smokeless tobacco, nicotine replacement therapy)?

Workshop 2: Health Effects in Users – 1. What are the known short and long-term health effects of e-cigarettes in experienced users?

Workshop 2: Considerations for Health Effects in Specific User Populations – 1. What populations of users may be at lower or higher risk of adverse effects related to e-cigarette use?

Workshop 2: Human Factors – 1. What adverse events have been associated with e-cigarette use in users?

Workshop 3: Health Effects of E-Cigarettes in Non-Users – 1. What chemicals/toxicants are potentially delivered to nonusers who are exposed to e-cigarette aerosols?

Workshop 3: Health Effects of E-Cigarettes in Non-Users – 2. How do exhaled aerosol properties impact potential secondhand and thirdhand exposures?

Workshop 3: Health Effects of E-Cigarettes in Non-Users – 8. What are the potential hazards associated with inadvertent exposure to e-cigarettes by young children (e.g., accidental dermal exposure or oral ingestion of liquid nicotine, choking on e-cigarette components, e-cigarette inhalation)?

HEALTH EFFECTS

There have been approximately 56 studies conducted to examine the impact of e-cigarettes on individuals' health and safety.[38,42,48,57,58,67,71,76,116,126,172,173,191,200,209,214-232,234-236,243-265]

Secondhand ENDS Aerosol Exposure

Data is very limited on the impact of exposure to ENDS aerosol on health, with one study indicating an increase in cotinine level, but no difference in lung function or complete blood count, following exposure to machine-generated ENDS aerosol[226,245] and another study indicating significantly higher cotinine level after exposure to cigarette smoke than ENDS aerosol.[230]

Several studies have been conducted measuring the constituents found in ENDS aerosol generated by both machines and humans; however, only one study has examined the individual health effects of exposure to the secondhand ENDS aerosol itself.[226,245] In this study, participants (N=15) were never-smokers naïve to e-cigarettes and were exposed to air polluted with ENDS aerosol via an air pump for one hour in a chamber set to simulate a bar or restaurant environment.[226,245] Cotinine level was found to be significantly higher than baseline following both secondhand ENDS aerosol and secondhand tobacco smoke exposure, with no significant difference between ENDS aerosol and smoke. Following ENDS aerosol exposure for smokers and non-smokers, there were no differences in lung function or complete blood count.

To our knowledge, there is only one study measuring biomarkers in bystanders, or non-vaping individuals exposed to ENDS aerosol generated by humans, which could be qualitatively different than machine-generated ENDS aerosol.[230] Participants in this study were from a convenience sample of non-smokers from homes with either 1) conventional cigarette smokers, 2) nicotine e-cigarette users, or 3) no tobacco users (control). After one week of exposure to these three conditions (with self-validated lack of exposure to cigarettes or e-cigarettes in other settings), saliva and urinary cotinine were measured (nothing was measured at baseline). No significant differences were observed across the groups for either biomarker except for saliva cotinine between those exposed to ≥7 cigarettes/day and those exposed to e-cigarettes, with levels being significantly higher for those exposed to cigarettes.[230]

Physiologic Effects

Exposure to toxicants is significantly lower for e-cigarettes than for conventional cigarettes. Studies demonstrate modest increases in nicotine biomarkers after e-cigarette use and at much lower levels than for conventional cigarette use. E-cigarette use has no or minimal impact on other physiologic measures, with the impact being generally positive for cigarette smokers switching to e-cigarettes.

Most studies found a modest to no increase in plasma nicotine (three included experienced users of e-cigarettes,[76,173,222] four included participants naïve to e-cigarettes,[71,223,229,232] one included both experienced and naïve users,[57] and one did not state participants' prior experience with e-cigarettes[226]) and saliva cotinine (one included experienced users of e-cigarettes,[224] none included participants naïve to e-cigarettes, one included both experienced and naïve users,[116,225] and one did not state participants' prior experience with e-cigarettes[38]) levels after e-cigarette use. When compared to conventional cigarette use, plasma nicotine[71,221,223,228] and saliva cotinine[227,231] levels were significantly lower after switching to e-cigarette use. Two clinical laboratory reports performed among experienced e-cigarette users indicate nicotine-containing e-cigarette use reliably increases plasma nicotine within 5-10 minutes.[173,222] Nicotine-free products had no impact on biomarkers.[38,191,228]

Few studies have examined cardiovascular measures associated with e-cigarette use, and findings are divided with respect to the impact of e-cigarette use on heart rate. Eissenberg[223] measured heart rate continuously among e-cigarette naïve smokers (N=16) in a US Public Health Service funded study and found significant increases in heart rate at five and 15 minutes for participants' own brand of cigarette, but not for e-cigarettes. Vansickel and colleagues' initial cross-over National Cancer Institute funded study[228] did not demonstrate an increase in heart rate (measured every 20 seconds) after five minutes of smoking an e-cigarette, but subsequent experiments[173,229] found an increase in heart rate five minutes after the first puff and an elevated heart rate throughout the puffing period. Nides and colleagues,[57] in a study funded by an e-cigarette company (NJOY, Inc.), found an increased heart rate (measured every 20 seconds) for 10 minutes following the beginning of each of two series of 10 puffs of an e-cigarette, then a gradual decrease toward baseline levels. Farsalinos et al.[248] did not find any significant changes in echocardiographic parameters, but did find significant changes in various other measures of myocardial function, such as a decrease in early diastolic velocity (Em) and an increase in isovolumic relaxation time (IVRT). Average e-cigarette associated increases in heart rate range from 2.4 to 6.2 beats per minute (bpm) within five minutes following a 10-puff smoking bout,[57,173,229] which is much lower than that observed five minutes following a 10-puff smoking bout using a conventional cigarette (mean increase=14.6 bpm).[228] Spindle et al.[76] measured heart rate among experienced e-cigarette users after use of their preferred devices and liquids (none were disposable "cigalike" devices) during two 2.5-hour sessions separated by two days, one during which participants used a mouthpiece-based topography recording device, and one during which they did not. After taking 10 puffs of the device, with each puff separated by 30 seconds, followed by ad lib use for the remainder of the time, mean heart rate was significantly higher relative to baseline.[76] In a study conducted by Yan and colleagues,[232] adult smokers naïve to e-cigarettes used blu eCigs ad lib for one hour, resulting in an increase in heart rate, although lower than when compared to Marlboro cigarettes.

Among smokers, exhaled carbon monoxide (eCO) and nitric oxide (eNO) have been found to decrease after switching to e-cigarettes,[38,48,209,231] and various clinical studies have found no difference in eCO levels following e-cigarette experiments.[57,191,228,232] One study found that lung resistance and airway impedance increased after ad libitum use of an e-cigarette containing nicotine, but use of an e-cigarette with no nicotine has been shown to have no impact on lung function[247]; however, among asthmatic smokers, e-cigarettes have been shown to improve lung function and reduce symptom exacerbations.[259] One study found significantly lower levels of various carcinogen biomarkers among e-cigarette users than cigarette smokers,[263] and another found much lower levels of ethylene (an indicator of oxidative stress) among e-cigarette users compared to cigarette users.[265] A worldwide online survey in 2013 found that the majority (74.5%) of respondents who had initiated e-cigarette use reported better general physical status after initiation, with improvements seen mostly in former smokers.[126] The same survey found that 35.0-75.7% of respondents with chronic conditions (such as diabetes, coronary artery disease, and chronic obstructive pulmonary disorder) experienced improvements in their symptoms following e-cigarette initiation. 18.4% of respondents with lung disease stopped using medications after initiating e-cigarette use.[126]

Cognitive Effects

Few studies have been published on the cognitive effects of e-cigarette use, but these studies indicate a minimal but positive impact on cognitive measures.[126,235,236]

Minimal research has been conducted on the cognitive effects of e-cigarette use. Performance on memory-related tests has been shown to be better among participants who used nicotine-containing e-cigarettes than those using nicotine-free e-cigarettes.[235,236] Among former and current smokers, a

worldwide survey revealed that 32.1% of respondents reported an improvement in mood and 16.2% reported an improvement in memory.[126] One study did not find a difference in cognitive ability (attention/speed of processing and visual-spatial scanning ability) after use of a nicotinic e-cigarette among e-cigarette naïve smokers.[236]

Adverse Events

The most common adverse events reported after use of e-cigarettes are mouth and throat irritation, nausea, headache, and dry cough.[38,48,57,67,126,221,254,264]

There is adequate data on the adverse effects of e-cigarette use. Most common events include mouth and throat irritation,[38,48,57,58,67,126,221,222,254] nausea,[48,221,264] headache,[38,48,58,264] and dry cough.[38,48,58] The majority of survey respondents (94.5%) reported at least partially resolved adverse symptoms over time.[126] A study analyzing online e-cigarette forums revealed more negative than positive effects of e-cigarette use.[254]

FDA CTP reports that the proportion of tobacco product complaints that are e-cigarette related has increased from 1/8 in 2008 to 9/11 in the first quarter of 2012.[253] Chatham-Stephens et al.[252] analyzed calls to US poison centers and found that calls per month related to e-cigarette exposure increased from one in September 2010 to 215 in February 2014. Cigarette exposure calls were more common in children[258] and involved ingestions, whereas e-cigarette exposure calls occurred in all age groups and involved ingestions, inhalations, and eye and skin exposures.[252] Vakkalanka and colleagues[258] also analyzed exposure calls to US poison centers June 1, 2010 through September 30, 2013, and found that slightly more exposures were reported among males, particularly in the 13-19 year age group. In 2010-2012, there were 35 cases of e-cigarette-related poisonings.[251] The American Association of Poison Control Centers reported 3,783 e-cigarette exposures in 2014, and 975 through March 31, 2015.[266] According to the 2013 annual report from the National Poison Data System (NPDS), e-cigarette exposure calls comprised 35% of all nicotine-related single exposure calls at their peak in April 2014. Among children <5 years old, e-cigarette exposures account for around 25% of nicotine single exposure calls, while among other age groups (>5 years old) they comprise 65% of exposures. Following April 2014, there was a decline in exposures, perhaps due to increased state/local regulations.[267] One patient committed suicide via intravenous injection of e-cigarette liquid (serum nicotine was 22-400% greater than a normal level)[256], and there are two documented suicide attempts.[261,262]

Workshop 2: Topography – 1. How are e-cigarettes used in terms of actual use patterns (frequency of use) and topography (number of puffs per session, puff volume, puff duration, velocity)?
Workshop 2: Topography – 3. What factors impact e-cigarette topography? For example, how is topography affected by the type of device, reason(s) for use, or user subpopulation (e.g., polytobacco users, experienced users, youth)?

Here is a list of studies assessing topography-related outcomes for reference:[76,116,171,174,225,229,231,234,268,269]

- Behar, R. Z., Hua, M., & Talbot, P. (2015). Puffing topography and nicotine intake of electronic cigarette users. PLoS One, 10(2), e0117222. doi: 10.1371/journal.pone.0117222
- 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):2500-14.
- Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. Tob Control. 2013;22(2):103-6.

- Norton KJ, June KM, O'Connor RJ. Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. Tobacco induced diseases. 2014;12(1):17.
- Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary Results of an Examination of Electronic Cigarette User Puff Topography: The Effect of a Mouthpiece-Based Topography Measurement Device on Plasma Nicotine and Subjective Effects. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Sep 19 2014.
- Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction (Abingdon, England). 2012;107(8):1493-1500. PMCID: PMC3330136.
- Trtchounian A, Williams M, Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. Nicotine Tobacco Res. 2010;12(9):905-12.
- Williams M, Talbot P. Variability among electronic cigarettes in the pressure drop, airflow rate, and aerosol production. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2011;13(12):1276-1283.
- Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction, 2011;106(11):2017-28.
- Etter JF, Bullen C. Saliva cotinine levels in users of electronic cigarettes. Eur Respir J. 2011;38:1219-1236.

Frequency of E-cigarette Use

There are an increasing number of studies characterizing the extent of e-cigarette use.

U.S. National Population

National data from 2012 show that among current users of e-cigarettes (n=267), 16.3% use them every day (0% among never smokers, 31.0% among long-term former smokers, 45.7% among recent former smokers, and 11.5% among current smokers), and 83.7% use them some days (100% among never smokers, 69.0% among long-term former smokers, 54.3% among recent former smokers, and 88.5% among current smokers).[43] A panel of current smoking adults 25 years and older in the U.S. (n=2,376; non-probability sample) found that in 2012, current e-cigarette users (9.2%) used them on an average of 7.7 days in the past month; 8.7% of current e-cigarette users used e-cigarettes on 30/30 past days averaging 5.8 times per day.[29] Vapers (current e-cigarette users) who are former daily cigarette smokers (n=1,434) reported in an online survey in the U.S. in 2013 that 28.5% used e-cigarettes 1-9 times/day, 41.4% 10-20 times/day, and 30.4% >20 times/day.[137] NATS data from 2012-2013 (n=60,192) show that among ever users of e-cigarettes (14.1%), 5.3% use them every day, 8.3% use them some days, 16.2% use them rarely, and 70.2% use them not at all.[15] A web-survey of current and former smokers (n=2,136) in the U.S. found that 3.8% were established users of e-cigarettes (lifetime use of 50 times) in 2013.[98]

U.S. State/Local Population

In a sample of callers to six U.S. state quitlines in 2011-12 (n=2,476), 8.2% reported using an e-cigarette every day while 22.4% reported using them some days.[41]

Among students in southeast Connecticut in 2013 who reported that they had tried cigarettes in the past but were not current smokers, those who reported using an e-cigarette during the past month did so on an average of 9.77 days.[84] Among high school students who reported current use of e-cigarettes, current cigarette smokers used e-cigarettes on a greater number of days in the past month when compared to never smokers.[84] Data from a 2013 survey of 9th and 10th graders (both public and private) in Oahu, Hawaii (n=1,941) show that 9% have used e-cigarettes 1-2 times, 11% have used 3-4 times, 2%

have used yearly, 3% have used monthly, 2% have used weekly, and 2% have used daily.[85] Data from a sample of college students in Oklahoma (n=1,304) in 2012-2013 0% reported daily use of e-cigarettes.[96]

Other Countries
A web-based study of 179 e-cigarette users in Poland found that 98% of participants used e-cigarettes every day. A total of 25% reported that they were not smoking conventional cigarettes when they started using e-cigs.[53] A convenience sample of smokers (n=1,738) in the Czech Republic in 2012 found that 18.3% of smokers used e-cigarettes regularly and 14% used them daily.[122]
A small cross-sectional survey in 2013 of New Zealand adult smokers and recent quitters (n=267) found that daily use of e-cigarettes was 4.6% among non-attempters (smokers who had not made a quit attempt in the past three months), 3.2% among recent attempters (smokers who had made a quit attempt in the past three months), and 2.3% among serious quitters (former smokers or smokers who quit within the past 30 days and intend to stay quit in the next three months).[270]

The ITC survey found that in the Netherlands, current e-cigarette users used their devices at least once per week in 2008 (59.1%), 2013 (70.6%), and 2014 (64.9%); only 23.5% used them that often in 2010.[121]Data from a representative sample from the EU and member nations in 2012 estimated that 69.9% of European adults used e-cigarettes once or twice, 21.1% used them occasionally, and 9.0% used them regularly.[271]

A longitudinal study from 2011-2013 of users of e-cigarettes, or "vapers" (n=367) in the U.S. (34%), France (24%), U.K. (8%), Switzerland (6%), and other countries (28%), found that at baseline 79% used e-cigarettes daily, and at one year follow-up, 89% of daily users were still using them daily; among daily cigarette smokers who were vaping daily at baseline, 81% were still doing so at one year, and among former smokers who were vaping daily at baseline, 92% were still doing so at one year.[51]

<u>Duration of E-cigarette Use</u>
Few studies characterize the length of e-cigarette use.

U.S. National Population
Vapers (current e-cigarette users) who are former daily cigarette smokers (n=1,434) reported in an online survey in 2013 that 0.5% started using e-cigarettes <1 month ago, 39.5% 1-6 months ago, 25.1% 6-12 months ago, 18.1% 12-24 months ago, and 16.7% >2 years ago.[137]

U.S. State/Local Population
One study conducted surveys among callers to six U.S. state quitlines from June 2011 through March 2012. Results indicated that among those who had tried an e-cigarette, 62% were short term (less than one month) users and 37% had used for less than a week.[41] Customers at four retail "vape stores" in a large Midwestern (U.S.) city (n=215) reported in the summer of 2013 that they had been using e-cigarette products for an average of 7.4 months; 62% had been using them for 6 months or less.[69]

Other Countries
A multi-national case-control study comparing dual users of e-cigarettes and cigarette to those who have completely substituted smoking with e-cigarette use ("non-smoking vapers") found that duration of e-cigarette use was similar for both group, but more dual users were using e-cigarettes occasionally instead of daily compared to non-smoking vapers.[120] A longitudinal study from 2011-2013 of users of e-cigarettes, or "vapers" (n=367) in the U.S. (34%), France (24%), U.K. (8%), Switzerland (6%), and other countries (28%), found that at baseline vapers had been using e-cigarettes for a median of 91 days.[51]

Workshop 2: Clinical Pharmacology and Abuse Liability – 1. What are the pharmacokinetic and the pharmacodynamics effects of nicotine delivered via e-cigarettes?

Workshop 2: Clinical Pharmacology and Abuse Liability – 2. How do pharmacokinetic and pharmacodynamics properties of e-cigarettes differ in specific subpopulations (e.g., experienced users, naïve users, dual users, youth)?

Nicotine Exposure

Most studies found a modest to no increase in plasma nicotine (three included experienced users of e-cigarettes,[76,173,222] four included participants naïve to e-cigarettes,[71,223,229,232] one included both experienced and naïve users,[57] and one did not state participants' prior experience with e-cigarettes[226]) and saliva cotinine (one included experienced users of e-cigarettes,[224] none included participants naïve to e-cigarettes, one included both experienced and naïve users,[116,225] and one did not state participants' prior experience with e-cigarettes[38]) levels after e-cigarette use. When compared to conventional cigarette use, plasma nicotine[71,221,223,228] and saliva cotinine[227,231] levels were significantly lower after switching to e-cigarette use. Two clinical laboratory reports performed among experienced e-cigarette users indicate nicotine-containing e-cigarette use reliably increases plasma nicotine within 5-10 minutes.[173,222] Nicotine-free products had no impact on biomarkers.[38,191,228]

Workshop 2. Clinical Pharmacology and Abuse Liability – 4. What are the primary subjective effects associated with e-cigarette use?
Workshop 2. Clinical Pharmacology and Abuse Liability – 5. How do the subjective effects associated with e-cigarette use differ in specific subpopulations (e.g., experienced users, naïve users, dual users, youth)?
Workshop 2. Clinical Pharmacology and Abuse Liability – 6. What are the reinforcing effects of e-cigarettes? How do these compare to traditional cigarettes in smokers as well as to other combusted products, smokeless tobacco or nicotine replacement therapy?

Performance on memory-related tests was better among participants who used nicotine-containing e-cigarettes than in those using nicotine-free e-cigarettes.[235,236] Dawkins et al.[236] did not find a difference in cognitive ability (attention/speed of processing and visual-spatial scanning ability) after use of a nicotine-containing e-cigarette among e-cigarette naïve smokers (N=60). A worldwide 2013 survey found that 32.1% of respondents who were current or former smokers (N=19,353) reported an improvement in mood and 16.2% reported an improvement in memory.[126]

Abuse Liability and Subjective Effects

Twenty-two studies have examined the abuse liability and/or subjective effects of e-cigarette use.[28,38,42,57,67,76,109,116,137,138,142,173,221-223,225,227-229,231,235-239] Studies measured withdrawal symptoms, desire to smoke, satisfaction, and various other subjective effects. Seven experimental studies included participants naïve to e-cigarettes,[42,223,228,229,231,236,238] while three studies included experienced users.[76,173,222] One study included both experienced and naïve users,[57] and three studies did not state participants' prior experience with e-cigarettes.[38,221,235]

Withdrawal

Eleven studies measured reduction in withdrawal symptoms after use of an e-cigarette.[42,57,116,173,221,222,225,228,229,235,236,238] Wagener and colleagues[42] found, in a study funded by an academic-based tobacco research center, no significant changes in withdrawal symptoms after one

week of e-cigarette use among naïve users (N=20), but the remainder of the studies observed a reduction in symptoms within 5-60 minutes of use of an e-cigarette,[57,76,173,221,222,229,235,236,238] particularly in irritability, restlessness, and anxiety.[57,222] Conventional cigarettes resulted in a greater reduction in symptoms than nicotine-containing e-cigarettes,[221] and nicotine-containing e-cigarettes resulted in a greater reduction in symptoms than nicotine-free e-cigarettes.[116,221,225,228,235,236] Second generation devices resulted in a greater alleviation of nicotine withdrawal symptoms than first generation devices.[238] A greater reduction in symptoms was observed in males[236] and former smokers.[116,225]

Desire/Urge to Smoke

We identified seven studies that measured alleviation of desire or urge to smoke a cigarette after using an e-cigarette.[57,76,221-223,235,236] All studies reported a decrease in desire/urge to smoke after e-cigarette use. Wagener and colleagues[42] found no significant differences in urge to smoke between those using their own brand of cigarette and those using an e-cigarette, but other studies revealed a significantly greater decrease in desire/urge to smoke after conventional cigarette use[221,223] than nicotine-containing e-cigarette use and a greater decrease after nicotine-containing e-cigarette use than nicotine-free e-cigarette use.[221,235] Dawkins et al.[236] found that participants using the nicotine-free e-cigarettes experienced a greater reduction in desire to smoke than those just holding an e-cigarette.

Other Subjective Effects

All other subjective outcomes are reported in Table 2-13. Bullen et al.[221] compared the subjective effects of e-cigarettes and a nicotine inhalator in an industry-funded study and found no difference in embarrassment associated with use between the products, but found a higher rating of pleasantness for the e-cigarette. Generally, e-cigarettes are associated with a high level of satisfaction, with little variation among brands.[38,42,76,137,222,235,239] E-cigarettes are also reported among smokers as improving cough/breathing, taste/appetite, and smell/less phlegm.[67,227] Experiments found an increase in ratings of acceptability[228], feeling awake, calming down, pleasantness, satisfaction[173], and tasting good[229] after e-cigarette use. However, two studies found that participants rated e-cigarettes significantly less enjoyable and satisfying than their own brand of cigarettes,[42,231] but second generation devices are more satisfying than first generation.[237] Among current cigarette smokers who had completed six 10-puff bouts with two types of e-cigarettes, results from a multiple choice procedure to determine the reinforcing efficacy of these products suggested that e-cigarettes were less reinforcing than own brand cigarettes.[229]

Workshop 2: Clinical Pharmacology and Abuse Liability – 7. What measures or methods can be used for assessing the reinforcing effects of e-cigarettes in users?

No well-validated scales of e-cigarette dependence are available, although at least one measure has been proposed.[138,240] Studies indicate decreased perceived dependence as compared to cigarettes.[138,142] Some characteristics to consider when determining e-cigarette dependence are as follows:[241]

A. Total dose delivered
B. Speed of uptake
C. Amount of behavioral conditioning
D. Social factors
E. Taste and other sensations
F. Adverse effects
G. Price, availability, etc

Various studies have used the following validated measures to assess reinforcing/subjective effects of e-cigarette use:

- Minnesota Nicotine Withdrawal Scale[42,57,116,142,221,225]
- Mood and Physical Symptoms Scale[222,235,236]
- Questionnaire of Smoking Urges[57,231]
- Tiffany Drobes Questionnaire of Smoking Urges Brief[173,228,229]
- Drug Effects and Liking Scale[42]
- Fagerstrom Test of Cigarette Dependence[138]
- Hughes-Hatsukami Withdrawal Scale[76]
- Brief Smoking Consequences Questionnaire-Adult[109]

Workshop 2: Health Effect in Users – 5. What evidence is available that e-cigarettes promote current smokers to completely switching as compared to continuing dual or polytobacco use? What data are available that indicate the characteristics of e-cigarettes that may enhance the potential for complete switching and how do these characteristics compare to approved cessation aids?
Workshop 3: Impacts on the Use of Current Tobacco Products – 1. How does e-cigarette use affect use of other tobacco products among current tobacco product users, including current cigarette smokers?

Refer to Section 2.B. on cessation for additional information.

<u>Former Cigarette Smokers</u>

Ever E-cigarette Use among Former Cigarette Smokers

According to 2012 NYTS data, 48.3% of former smokers had ever used e-cigarettes.[81] Among students in southeast Connecticut in 2013 who reported that they had tried cigarettes in the past but were not current smokers, 59.8% reported having tried e-cigarettes.[84] In a convenience sample of college students from Oahu, Hawaii (n=307), ever use among former cigarette smokers was 47.7% in fall of 2013.[94] A population-based, prospective cohort study in the Midwest found that 9.7% of young adults (ages 20-28) who were former smokers were ever users of e-cigarettes in 2010-2011.[99] National data from 2012 show ever use of e-cigarettes at 2.4% among long-term former (quit more than one year ago) smokers and 26.8% among recent former (quit within past year) smokers.[43,101] HealthStyles, a national survey, found that ever use among former smokers increased from 2.5% in 2010 to 9.6% in 2013.[78,102] Data from a probability sample of U.S. adults show that ever use of e-cigarettes in former smokers increased from 1.5% in 2010 to 13.5% in 2013.[90] In 2010-2011 in the ITC sample, 10% of recent quitters had tried an e-cigarette.[106] A web-survey of current and former smokers (n=2,136) in 2013 found that more every day smokers (49.6%) had ever used e-cigarettes compared with some days smokers (43.6%) and former smokers (38.3%). However, former smokers had over three times the odds of being an established e-cigarette user (with over 50 lifetime uses) compared with current everyday smokers (AOR 3.24 95%CI 1.13, 9.30).[98] In Great Britain, ever use was 2.7% in 2012 among former smokers.[125] Among former smokers who were surveyed in the European Union in 2012, 4.4% had ever used an e-cigarette.[271] The ITC survey reported ever use among former smokers in various countries at the following rates (from lowest to highest): China (2009) 2.0%, Mexico (2012) 3.0%, Brazil (2012-2013) 4.0%, Canada (2010-2011) 5.0%, Malaysia (2011-2012) 13.0%, Netherlands (2013) 14.0%, Australia (2013) 16.0%, U.K. (2010-2011) 16.0%, and Republic of Korea (2010) 23.0%.[106]

Current E-cigarette Use among Former Cigarette Smokers

Among students in southeast Connecticut in 2013 who reported that they had tried cigarettes in the past but were not current smokers, 22.9% reported using an e-cigarette during the past month.[84]

National data from 2012 show current use of e-cigarettes at 0.2% among long-term former (quit more than one year ago) smokers and 6.1% among recent former (quit within the past year) smokers.[43,101] Data from the HealthStyles survey, a consumer-based web survey of U.S. adults showed that in 2010/2011, current use among former smokers was 1.0% and increased to 1.3% in 2012/2013.[78] Data from a probability sample of U.S. adults show that current use of e-cigarettes in former smokers increased from 0.3% in 2010 to 5.4% in 2013.[90]

The majority (96.7%) of customers at four retail "vape stores" in a large Midwestern (U.S.) city (n=215) reported in the summer of 2013 that they had previously used combustible tobacco (0.9% reported using smokeless tobacco and 2.3% refused to report).[69]

In Great Britain, current use was 1.1% in 2012 among former smokers.[125] The ITC survey reported current use among former smokers in various countries at the following rates (from lowest to highest): China (2009) 0.0%, Canada (2010-2011) 0.0%, Netherlands (2013) 1.0%, Australia (2013) 2.0%, Malaysia (2011-2012) 6.0%, U.K. (2010-2011) 11.0%, and Republic of Korea (2010) 13.0% (no data for current use was available for Mexico and Brazil).[106] The ITC survey reported that long-term former smokers in the U.K. and in Australia were significantly less likely to be current users of e-cigarettes than smokers.[144] A small cross-sectional survey in New Zealand of adults smokers and recent quitters (n=267) found that current use (use in the past two weeks) of e-cigarettes was 15.0% among serious quitters (former smokers or smokers who quit within the past 30 days and intend to stay quit in the next three months).[270]

DUAL USE OF E-CIGARETTES AND COMBUSTIBLE CIGARETTES

Across all age groups, the majority of ever and current e-cigarette users are current cigarette smokers.

Youth

U.S. National Population

During 2011-2012, current use of both e-cigarettes and cigarettes increased from 0.8% to 1.6% among U.S. adolescents.[17,79] Another study using 2012 NYTS data (n=24,658) showed an overall dual use (e-cigarettes and cigarettes) rate of 0.4% (9-14 years 0.1%, 15-17 0.6%, ≥18 years 1.1%).[154] Age (15-17 years), gender (male), race/ethnicity (Black, non-Hispanic), use of flavored tobacco products, nicotine dependence, tobacco marketing receptivity, and perceived prevalence of peers using tobacco were significantly associated with dual use.[154] Monitoring the Future data from 2014 found a prevalence of dual lifetime cigarette (ever and current) and current e-cigarette use among 12th grade students (n=7,915) at 12.9% and prevalence of dual current use of both products at 7.3%.[12,13] Data on dual use of e-cigarettes and combustible cigarettes in 2013 and 2014 from the NYTS are not yet available in the published literature.

U.S. State/Local Population

A survey of high school students (grades 9-12) in Connecticut and New York (n=1,345) showed an increase in dual use of cigarettes and e-cigarettes from February 2010 (0.8%) to June 2011 (1.9%). The majority of e-cigarette users were dual users (87.5% in Wave 1, 82.8% in Wave 2, 83.9% in Wave 3).[113] Data from a 2013 survey of 9th and 10th graders (both public and private) in Oahu, Hawaii (n=1,941) show that 12% ever used both e-cigarettes and cigarettes.[85]

Ever E-cigarette Users

Data from the 2011 NYTS indicate that 41.5% of respondents who reported having ever used an e-cigarette were current smokers, and 49.3% had ever tried a cigarette,[80] and data from 2012 indicate

that among ever e-cigarette users, 90.7% reported ever smoking conventional cigarettes. Data from a longitudinal cohort study of children with alcoholic parents (n=136 families) showed that among adolescents (middle and late adolescence) who had ever used an e-cigarette, 68.9% reported having ever used cigarettes as well; among those who had smoked, e-cigarette use was associated with more frequent use of cigarettes over the prior 30 days.[86]

Current E-cigarette Users
During 2011-2012 among U.S. adolescents (NYTS) who were current e-cigarette users, 76.3% reported current smoking.[17] Additional analyses in the 2011 and 2012 NYTS showed that in 2011, 49.7% of current e-cigarette users were current smokers of conventional cigarettes, and increased very little to 49.8% of current e-cigarette users in 2012.[24] Current e-cigarette use was also associated with ever cigarette smoking (OR = 7.42; 95% CI, 5.63-9.79) and current cigarette smoking (OR = 7.88; 95%CI, 6.01-10.32).[24]

Other Countries
Data from the 2011 Korean Youth Risk Behavior survey found that among students aged 13-18 years (n=75,643), 8.0% were ever dual users of e-cigarettes and cigarettes, and 1.4% were former dual users of e-cigarettes and cigarettes, and 3.6% were current dual users of e-cigarettes and cigarettes.[56]

A national school-based survey of youth ages 15-19 in Poland found dual use of e-cigarettes and cigarettes increase from 3.6% in 2010-2011 to 21.8% in 2013-2014.[272]

A school-based province-wide survey in Ontario, Canada found that among high school students, 9.6% reported using both e-cigarettes and conventional cigarettes.[143]

Current E-cigarette Users
A national school-based survey of youth ages 15-19 in Poland found 72.4% of current e-cigarette users also smoked cigarettes in 2013-2014 compared to 65.3% in 2010-2011.[272]

<u>Young Adults</u>
U.S. State/Local Population
In a sample of young adults (ages 18-23) in colleges/universities in upstate New York (n=1,437), 6.4% were dual users of e-cigarettes and cigarettes in the fall of 2013.[93]

Ever E-cigarette Users
Among high school and college students who were ever users of e-cigarettes (n=1,175) in Connecticut in 2012-2013, 28.7% were ever cigarette smokers, and 34.0% were current cigarette smokers.[130]

Current E-cigarette Users
A nationally representative survey of U.S. young adults (18-34 years) (n=1,247) showed that of the 7.9% who reported current use of e-cigarettes in 2014, 18.3% were non-smokers, 63.3% were current smokers, and 18.4% were former smokers.[91] In a sample of students at two universities in Southeastern U.S. (n=2,002) from 2013, among current e-cigarette users, 71.6% also used cigarettes.[95]

<u>Adults</u>
U.S. National Population
Among U.S. adults in 2012 (NATS, n=3,627), 1.9% reported using e-cigarettes and cigarettes in combination.[156]

U.S. State/Local Population
A population-based telephone survey of adults in Montana (n=5,000) conducted in 2013 found that 71.0% of ever e-cigarette users were current cigarette smokers.[104] In a convenience sample of college students from Oahu, Hawaii (n=307), 54.1% of ever e-cigarette users were current cigarette smokers in 2013.[94]

Ever E-cigarette Users
Among ever e-cigarette users in the U.S., 62.6% were current cigarette smokers in 2010, 57.3% in 2011, 66.1% in 2012, and 63.4% in 2013.[78]

Current E-cigarette Users
Among current e-cigarette users, 72.0% were current cigarette smokers in 2010/2011 and 76.8% in 2012/2013.[78]

In closing, these workshops and this docket are an important step in preparing for the regulation of ENDS and we hope FDA will move quickly to protect the public health with appropriate regulation of these products in order reduce the death and disease from tobacco. We look forward to working with FDA to continue moving toward our goal of creating the first tobacco-free generation.

Sincerely,

M. David Dobbins
Chief Operating Officer

References

1. Abrams DB. Potential and pitfalls of e-cigarettes--reply. *JAMA.* May 14 2014;311(18):1922-1923.
2. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA.* Jan 8 2014;311(2):135-136.
3. Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction G. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tobacco control.* Aug 2009;18(4):324-332.
4. Cobb NK, Abrams DB. The FDA, e-cigarettes, and the demise of combusted tobacco. *The New England journal of medicine.* Oct 16 2014;371(16):1469-1471.
5. Levy DT, Pearson JL, Villanti AC, et al. Modeling the future effects of a menthol ban on smoking prevalence and smoking-attributable deaths in the United States. *Am J Public Health.* Jul 2011;101(7):1236-1240.
6. Giovino GA, Villanti AC, Mowery PD, et al. Differential trends in cigarette smoking in the USA: is menthol slowing progress? *Tobacco control.* Jan 2015;24(1):28-37.
7. Nonnemaker J, Hersey J, Homsi G, Busey A, Allen J, Vallone D. Initiation with menthol cigarettes and youth smoking uptake. *Addiction (Abingdon, England).* Jan 2013;108(1):171-178.
8. *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General.* Atlanta GA2014.
9. Fiore MC, Schroeder SA, Baker TB. Smoke, the chief killer--strategies for targeting combustible tobacco use. *The New England journal of medicine.* Jan 23 2014;370(4):297-299.
10. Cobb CO, Villanti AC, Graham AL, et al. Markov modeling to estimate the population health impact of emerging tobacco products: A proof-of-concept study. *Tob Reg Sci.* 2015;1(2):129-141.
11. Monitoring the Future - The University of Michigan. Table 1: Trends in prevalence of use of cigarettes in grades 8, 10, and 12. 2014.
12. Monitoring the Future - The University of Michigan. Table 28: Lifetime use of cigarettes by use of e-cigarettes in last 30 days: Grade 12, 2014. Ann Arbor2015.
13. Monitoring the Future - The University of Michigan. Table 29: Use of cigarettes by e-cigarettes in last 30 days: Grade 12, 2014. Ann Arbor2015.
14. Arrazola RA, Singh T, Corey CG, et al. Tobacco use among middle and high school students - United States, 2011-2014. *Morbidity and Mortality Weekly Report.* Apr 17 2015;64(14):381-385.
15. Agaku IT, King BA, Husten CG, et al. Tobacco product use among adults--United States, 2012-2013. *MMWR. Morbidity and mortality weekly report.* Jun 27 2014;63(25):542-547.
16. Centers for Disease Control Prevention. Tobacco product use among middle and high school students--United States, 2011 and 2012. *Morbidity and Mortality Weekly Report.* Nov 15 2013;62(45):893-897.
17. Corey CG, Wang B, Johnson SE, et al. Notes from the field: electronic cigarette use among middle and high school students - United States, 2011-2012. *Morbidity and Mortality Weekly Report.* Sep 6 2013;62(35):729-730.
18. Kozlowski L, Giovino G. Softening of monthly cigarette use in youth and the need to harden measures in surveillance. *Preventive Medicine Reports.* 2014;1:53-55.
19. Warner K. The remarkable decrease in cigarette smoking by American youth: further evidence. *Preventive Medicine Reports.* 2015;2:259-261.
20. Vanyukov MM, Tarter RE, Kirillova GP, et al. Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. *Drug and alcohol dependence.* Jun 2012;123 Suppl 1:S3-17.

21. Pentz MA, Shin H, Riggs N, Unger JB, Collison KL, Chou CP. Parent, peer, and executive function relationships to early adolescent e-cigarette use: A substance use pathway? *Addictive Behaviors.* Nov 1 2014;42c:73-78.

22. Niaura RS, Glynn TJ, Abrams DB. Youth experimentation with e-cigarettes: Another interpretation of the data. *JAMA pediatrics.* 2014;312(6):1-2.

23. Abrams DB, Niaura R. The importance of science-informed policy and what the data really tell us about e-cigarettes. *Israel journal of health policy research.* 2015;4:22.

24. Dutra LM, Glantz SA. Electronic Cigarettes and Conventional Cigarette Use Among US Adolescents: A Cross-sectional Study. *JAMA pediatrics.* Mar 6 2014.

25. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. *Am J Prev Med.* Feb 2008;34(2):102-111.

26. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* West Sussex, England: Wiley-Blackwell; 2008. Cochrane Book Series.

27. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev.* 2014;12:CD010216.

28. Copp SR, Collins JL, Dar R, Barrett SP. The effects of nicotine stimulus and response expectancies on male and female smokers' responses to nicotine-free electronic cigarettes. *Addict Behav.* Jan 2015;40:144-147.

29. Pulvers K, Hayes RB, Scheuermann TS, et al. Tobacco Use, Quitting Behavior, and Health Characteristics among Current Electronic Cigarette Users in a National Tri-Ethnic Adult Stable Smoker Sample. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Nov 10 2014.

30. Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tobacco control.* Jun 17 2015.

31. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst Abuse.* 2013;7:139-146.

32. Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. *International journal of environmental research and public health.* 2014;11(10):10345-10361.

33. Pokhrel P, Herzog TA. Reasons for Quitting Cigarette Smoking and Electronic Cigarette Use for Cessation Help. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors.* Sep 1 2014.

34. Pokhrel P, Little MA, Fagan P, Kawamoto CT, Herzog TA. Correlates of use of electronic cigarettes versus nicotine replacement therapy for help with smoking cessation. *Addict Behav.* Aug 7 2014;39(12):1869-1873.

35. Pearson JL, Stanton CA, Cha S, Niaura RS, Luta G, Graham AL. E-Cigarettes and Smoking Cessation: Insights and Cautions From a Secondary Analysis of Data From a Study of Online Treatment-Seeking Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Dec 26 2014.

36. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet.* Nov 16 2013;382(9905):1629-1637.

37. Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the Electronic Cigarette: An Eight-Week Flemish Study with Six-Month Follow-up on Smoking Reduction, Craving and Experienced Benefits and Complaints. *International journal of environmental research and public health.* 2014;11(11):11220-11248.

38. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS one.* 2013;8(6):e66317.

39. Adkison SE, O'Connor RJ, Bansal-Travers M, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med.* Mar 2013;44(3):207-215.

40. Sutfin EL, Reboussin BA, Debinski B, Wagoner KG, Spangler J, Wolfson M. The Impact of Trying Electronic Cigarettes on Cigarette Smoking by College Students: A Prospective Analysis. *Am J Public Health.* Jun 11 2015:e1-e7.

41. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 2013;15(10):1787-1791.

42. Wagener TL, Meier E, Hale JJ, et al. Pilot investigation of changes in readiness and confidence to quit smoking after E-cigarette experimentation and 1 week of use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jan 2014;16(1):108-114.

43. Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zoref L. The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population. *PloS one.* 2013;8(10):e79332.

44. Al-Delaimy WK, Myers MG, Leas EC, Strong DR, Hofstetter CR. E-cigarette use in the past and quitting behavior in the future: a population-based study. *Am J Public Health.* Jun 2015;105(6):1213-1219.

45. Biener L, Hargraves JL. A Longitudinal Study of Electronic Cigarette Use in a Population-Based Sample of Adult Smokers: Association With Smoking Cessation and Motivation to Quit. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 9 2014.

46. Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: Characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer.* Sep 22 2014.

47. Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction (Abingdon, England).* Apr 21 2015.

48. Caponnetto P, Auditore R, Russo C, Cappello GC, Polosa R. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *International journal of environmental research and public health.* Feb 2013;10(2):446-461.

49. Choi K, Forster JL. Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. *American Journal of Preventive Medicine.* Feb 2014;46(2):175-178.

50. Christensen T, Welsh E, Faseru B. Profile of e-cigarette use and its relationship with cigarette quit attempts and abstinence in Kansas adults. *Preventive medicine.* Sep 16 2014;69C:90-94.

51. Etter JF, Bullen C. A longitudinal study of electronic cigarette users. *Addict Behav.* Feb 2014;39(2):491-494.

52. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *International journal of environmental research and public health.* Dec 2013;10(12):7272-7282.

53. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an Internet survey. *Drug Alcohol Rev.* Mar 2013;32(2):133-140.

54. Grana RA, Popova L, Ling PM. A Longitudinal Analysis of Electronic Cigarette Use and Smoking Cessation. *JAMA internal medicine.* Mar 24 2014.

55. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in

Great Britain. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Apr 20 2015.

56. Lee S, Grana RA, Glantz SA. Electronic cigarette use among Korean adolescents: a cross-sectional study of market penetration, dual use, and relationship to quit attempts and former smoking. *The Journal of Adolescent Health.* Jun 2014;54(6):684-690.

57. Nides MA, Leischow SJ, Bhatter M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *American Journal of Health Behavior.* 2014;38(2):265-274.

58. Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC public health.* 2014;14:1159.

59. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC public health.* 2011;11:786.

60. Polosa R, Morjaria JB, Caponnetto P, et al. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Internal and emergency medicine.* Aug 2014;9(5):537-546.

61. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health.* May 2013;103(5):923-930.

62. Prochaska JJ, Grana RA. E-Cigarette Use among Smokers with Serious Mental Illness. *PloS one.* 2014;9(11):e113013.

63. Ramo DE, Young-Wolff KC, Prochaska JJ. Prevalence and correlates of electronic-cigarette use in young adults: Findings from three studies over five years. *Addictive Behaviors.* Oct 23 2014;41c:142-147.

64. Siegel MB, Tanwar KL, Wood KS. Electronic cigarettes as a smoking-cessation: tool results from an online survey. *Am J Prev Med.* Apr 2011;40(4):472-475.

65. 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 (Abingdon, England).* May 20 2014.

66. Caponnetto P, Polosa R, Russo C, Leotta C, Campagna D. Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep.* 2011;5(1):585.

67. Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction (Abingdon, England).* Jun 2013;108(6):1115-1125.

68. Rutten LJ, Blake KD, Agunwamba AA, et al. Use of e-Cigarettes among Current Smokers: Associations among Reasons for Use, Quit Intentions, and Current Tobacco Use. *Nicotine & Tobacco Research.* Jan 14 2015.

69. Tackett AP, Lechner WV, Meier E, et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction (Abingdon, England).* Feb 10 2015.

70. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco control.* Jul 2014;23 Suppl 3:iii3-iii9.

71. 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. *Scientific reports.* 2014;4:4133.

72. Choi K, Forster JL. Authors' response. *Am J Prev Med.* Jun 2014;46(6):e58-59.

73. Glantz S. Meta-analysis of all available population studies continues to show smokers who use e-cigs less likely to quit smoking. Accessed June 12, 2015. Available from

https://tobacco.ucsf.edu/meta-analysis-all-available-population-studies-continues-show-smokers-who-use-e-cigs-less-likely-quit-smoking2015.

74. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *The Cochrane database of systematic reviews.* 2014;12:Cd010216.

75. Tobacco Use and Dependence Guideline Panel. *Treating Tobacco Use and Dependence: 2008 Update.* Rockville (MD): US Department of Health and Human Services; 2008.

76. Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary Results of an Examination of Electronic Cigarette User Puff Topography: The Effect of a Mouthpiece-Based Topography Measurement Device on Plasma Nicotine and Subjective Effects. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Sep 19 2014.

77. Glasser AM, Cobb CO, Teplitskaya L, et al. Electronic nicotine delivery devices, and their impact on health and patterns of tobacco use: a systematic review protocol. *BMJ Open.* 2015;5(4):e007688.

78. King BA, Patel R, Nguyen K, Dube SR. Trends in awareness and use of electronic cigarettes among U.S. adults, 2010-2013. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2014;[Epub ahead of print].

79. Ambrose BK, Rostron BL, Johnson SE, et al. Perceptions of the Relative Harm of Cigarettes and E-cigarettes Among U.S. youth. *Am J Prev Med.* Aug 2014;47(2 Suppl 1):S53-60.

80. Lippert AM. Do Adolescent Smokers Use E-Cigarettes to Help Them Quit? The Sociodemographic Correlates and Cessation Motivations of U.S. Adolescent E-Cigarette Use. *American Journal of Health Promotion.* Jun 26 2014.

81. Cardenas VM, Breen PJ, Compadre CM, et al. The smoking habits of the family influence the uptake of e-cigarettes in US children. *Annals of epidemiology.* Jan 2015;25(1):60-62.

82. Amrock S, Zakhar J, Zhou S, Weitzman M. Perception of e-cigarettes' harm and its correlation with use among US adolescents. *Nicotine & Tobacco Research.* Aug 14 2014.

83. Arrazola RA, Neff LJ, Kennedy SM, Holder-Hayes E, Jones CD. Tobacco use among middle and high school students - United States, 2013. *MMWR. Morbidity and mortality weekly report.* Nov 14 2014;63(45):1021-1026.

84. Krishnan-Sarin S, Morean M, Camenga D, Cavallo DA, Kong G. E-cigarette Use among High School and Middle School Adolescents in Connecticut. *Nicotine & Tobacco Research.* Nov 9 2014.

85. Wills TA, Knight R, Williams RJ, Pagano I, Sargent JD. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics.* Jan 2015;135(1):e43-51.

86. Lessard J, Henrie J, Livingston JA, Leonard KE, Colder CR, Eiden RD. Correlates of ever having used electronic cigarettes among older adolescent children of alcoholic fathers. *Nicotine & Tobacco Research.* Dec 2014;16(12):1656-1660.

87. Camenga DR, Kong G, Cavallo DA, et al. Alternate Tobacco Product and Drug Use Among Adolescents Who Use Electronic Cigarettes, Cigarettes Only, and Never Smokers. *The Journal of Adolescent Health.* Jul 29 2014.

88. Richardson A, Williams V, Rath J, Villanti AC, Vallone D. The Next Generation of Users: Prevalence and Longitudinal Patterns of Tobacco Use Among US Young Adults. *American Journal of Public Health.* Aug 2014;104(8):1429-1436.

89. 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. *Journal of Environmental and Public Health.* 2012;2012.

90. McMillen RC, Gottlieb MA, Shaefer RM, Winickoff JP, Klein JD. Trends in Electronic Cigarette Use Among U.S. Adults: Use is Increasing in Both Smokers and Nonsmokers. *Nicotine & Tobacco Research.* Nov 6 2014.

91. Sanders-Jackson AN, Tan AS, Bigman CA, Henriksen L. Knowledge About E-Cigarette Constituents and Regulation: Results From a National Survey of U.S. Young Adults. *Nicotine & Tobacco Research.* Dec 26 2014.

92. Sutfin EL, McCoy TP, Morrell HE, Hoeppner BB, Wolfson M. Electronic cigarette use by college students. *Drug and alcohol dependence.* Aug 1 2013;131(3):214-221.

93. Saddleson ML, Kozlowski LT, Giovino GA, et al. Risky behaviors, e-cigarette use and susceptibility of use among college students. *Drug and alcohol dependence.* Jan 24 2015.

94. Pokhrel P, Fagan P, Kehl L, Herzog TA. Receptivity to E-cigarette Marketing, Harm Perceptions, and E-cigarette Use. *American Journal of Health Behavior.* Jan 2015;39(1):121-131.

95. Berg CJ, Stratton E, Schauer GL, et al. Perceived harm, addictiveness, and social acceptability of tobacco products and marijuana among young adults: marijuana, hookah, and electronic cigarettes win. *Substance use & misuse.* Jan 2 2015;50(1):79-89.

96. Meier EM, Tackett AP, Miller MB, Grant DM, Wagener TL. Which nicotine products are gateways to regular use? First-tried tobacco and current use in college students. *American Journal of Preventive Medicine.* Jan 2015;48(1 Suppl 1):S86-93.

97. Kasza KA, Bansal-Travers M, O'Connor RJ, et al. Cigarette smokers' use of unconventional tobacco products and associations with quitting activity: findings from the ITC-4 U.S. cohort. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jun 2014;16(6):672-681.

98. Giovenco DP, Lewis MJ, Delnevo CD. Factors Associated with E-cigarette Use: A National Population Survey of Current and Former Smokers. *American Journal of Preventive Medicine.* Oct 2014;47(4):476-480.

99. Choi K, Forster J. Characteristics associated with awareness, perceptions, and use of electronic nicotine delivery systems among young US Midwestern adults. *American Journal of Public Health.* Mar 2013;103(3):556-561.

100. Regan AK, Promoff G, Dube SR, Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. *Tobacco control.* Jan 2013;22(1):19-23.

101. Cummins SE, Zhu SH, Tedeschi GJ, Gamst AC, Myers MG. Use of e-cigarettes by individuals with mental health conditions. *Tobacco control.* May 12 2014.

102. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among U.S. adults, 2010-2011. *Nicotine & Tobacco Research.* Sep 2013;15(9):1623-1627.

103. Majeed BA, Dube SR, Sterling K, Whitney C, Eriksen MP. Opinions About Electronic Cigarette Use in Smoke-Free Areas Among U.S. Adults, 2012. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 30 2014.

104. Schmidt L, Reidmohr A, Harwell TS, Helgerson SD. Prevalence and reasons for initiating use of electronic cigarettes among adults in montana, 2013. *Preventing chronic disease.* 2014;11:E204.

105. Pearson JL, Richardson A, Niaura RS, Vallone DM, Abrams DB. e-Cigarette awareness, use, and harm perceptions in US adults. *American Journal of Public Health.* Sep 2012;102(9):1758-1766.

106. Gravely S, Fong GT, Cummings KM, et al. Awareness, Trial, and Current Use of Electronic Cigarettes in 10 Countries: Findings from the ITC Project. *International journal of environmental research and public health.* 2014;11(11):11691-11704.

107. Pepper JK, Emery SL, Ribisl KM, Rini CM, Brewer NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. *Journal of behavioral medicine.* Oct 28 2014.

108. Wackowski OA, Delnevo CD. Smokers' attitudes and support for e-cigarette policies and regulation in the USA. *Tobacco control.* Jan 6 2015.

109. Hendricks PS, Cases MG, Thorne CB, et al. Hospitalized smokers' expectancies for electronic cigarettes versus tobacco cigarettes. *Addictive Behaviors.* Sep 28 2014;41c:106-111.
110. Kadimpati S, Nolan M, Warner DO. Attitudes, beliefs, and practices regarding electronic nicotine delivery systems in patients scheduled for elective surgery. *Mayo Clinic proceedings.* Jan 2015;90(1):71-76.
111. Coleman BN, Apelberg BJ, Ambrose BK, et al. Association Between Electronic Cigarette Use and Openness to Cigarette Smoking Among U.S. Young Adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Nov 4 2014.
112. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. *Monitoring the Future national survey results on drug use: 1975-2014: Overview, key findings on adolescent drug use.* Ann Arbor2015.
113. Camenga DR, Delmerico J, Kong G, et al. Trends in use of electronic nicotine delivery systems by adolescents. *Addictive Behaviors.* Jan 2014;39(1):338-340.
114. Kalkhoran S, Grana RA, Neilands TB, Ling PM. Dual Use of Smokeless Tobacco or E-cigarettes with Cigarettes and Cessation. *Am J Health Behav.* Mar 2015;39(2):277-284.
115. Rigotti NA, Harrington KF, Richter K, et al. Increasing Prevalence of Electronic Cigarette Use Among Smokers Hospitalized in 5 US Cities, 2010-2013. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2015;17(2):236-244.
116. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction (Abingdon, England).* Nov 2011;106(11):2017-2028.
117. Tucker JS, Shadel WG, Golinelli D, Ewing B. Alternative Tobacco Product Use and Smoking Cessation Among Homeless Youth in Los Angeles County. *Nicotine & Tobacco Research.* Aug 21 2014.
118. Baumann AW, Kohler C, Kim YI, et al. Differences in Electronic Cigarette Awareness, Use History, and Advertisement Exposure Between Black and White Hospitalized Cigarette Smokers. *Journal of cancer education : the official journal of the American Association for Cancer Education.* Dec 13 2014.
119. 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. *Addictive Behaviors.* Jun 2014;39(6):1120-1125.
120. Farsalinos KE, Romagna G, Voudris V. Factors associated with dual use of tobacco and electronic cigarettes: A case control study. *The International journal on drug policy.* Jan 19 2015.
121. Hummel K, Hoving C, Nagelhout GE, et al. Prevalence and reasons for use of electronic cigarettes among smokers: Findings from the International Tobacco Control (ITC) Netherlands Survey. *The International journal on drug policy.* Dec 17 2014.
122. 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.* Nov 1 2013;144(5):1609-1614.
123. Li J, Bullen C, Newcombe R, Walker N, Walton D. The use and acceptability of electronic cigarettes among New Zealand smokers. *The New Zealand Medical Journal.* May 31 2013;126(1375):48-57.
124. Foulds J, Veldheer S, Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *Int J Clin Pract.* Oct 2011;65(10):1037-1042.
125. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine & Tobacco Research.* Oct 2013;15(10):1737-1744.
126. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000

consumers. *International journal of environmental research and public health.* 2014;11(4):4356-4373.

127. Harrington KF, Hull NC, Akindoju O, et al. Electronic Cigarette Awareness, Use History, and Expected Future Use Among Hospitalized Cigarette Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* May 13 2014.

128. Richardson A, Pearson J, Xiao H, Stalgaitis C, Vallone D. Prevalence, Harm Perceptions, and Reasons for Using Noncombustible Tobacco Products Among Current and Former Smokers. *American Journal of Public Health.* Jun 12 2014:e1-e8.

129. Etter JF. Electronic cigarettes: a survey of users. *BMC public health.* 2010;10:231.

130. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine & Tobacco Research.* Dec 6 2014.

131. McDonald EA, Ling PM. One of several 'toys' for smoking: young adult experiences with electronic cigarettes in New York City. *Tobacco control.* Jan 6 2015.

132. Peters RJ, Jr., Meshack A, Lin MT, Hill M, Abughosh S. The social norms and beliefs of teenage male electronic cigarette use. *Journal of Ethnicity in Substance Abuse.* 2013;12(4):300-307.

133. Gallus S, Lugo A, Pacifici R, et al. E-Cigarette Awareness, Use, and Harm Perception in Italy: A National Representative Survey. *Nicotine & Tobacco Research.* Jul 31 2014.

134. McQueen A, Tower S, Sumner W. Interviews with "vapers": implications for future research with electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Sep 2011;13(9):860-867.

135. Choi K, Fabian L, Mottey N, Corbett A, Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *American Journal of Public Health.* Nov 2012;102(11):2088-2093.

136. Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. *Addict Sci Clin Pract.* 2013;8(1):5.

137. Harrell PT, Marquinez NS, Correa JB, et al. Expectancies for Cigarettes, E-Cigarettes, and Nicotine Replacement Therapies Among E-Cigarette Users (aka Vapers). *Nicotine & Tobacco Research.* Feb 2015;17(2):193-200.

138. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire to assess dependence on electronic cigarettes in a large sample of ex-smoking e-cig users. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 19 2014.

139. Hersey JC, Ng SW, Nonnemaker JM, et al. Are menthol cigarettes a starter product for youth? *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jun 2006;8(3):403-413.

140. King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* Jan 2014;54(1):40-46.

141. Delnevo CD, Giovenco DP, Ambrose BK, Corey CG, Conway KP. Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tobacco control.* Jul 2015;24(4):389-394.

142. Etter JF. Explaining the effects of electronic cigarettes on craving for tobacco in recent quitters. *Drug and alcohol dependence.* Mar 1 2015;148:102-108.

143. Hamilton HA, Ferrence R, Boak A, et al. Ever Use of Nicotine and Nonnicotine Electronic Cigarettes Among High School Students in Ontario, Canada. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 30 2014.

144. Yong HH, Borland R, Balmford J, et al. Trends in E-Cigarette Awareness, Trial, and Use Under the Different Regulatory Environments of Australia and the United Kingdom. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 30 2014.
145. Bagcchi S. E-cigarette market expands online. *The lancet oncology.* Jul 2014;15(8):e313.
146. Hsu R, Myers AE, Ribisl KM, Marteau TM. An observational study of retail availability and in-store marketing of e-cigarettes in London: potential to undermine recent tobacco control gains? *BMJ open.* 2013;3(12):e004085.
147. Huang J, Tauras J, Chaloupka FJ. The impact of price and tobacco control policies on the demand for electronic nicotine delivery systems. *Tobacco control.* Jul 2014;23 Suppl 3:iii41-iii47.
148. Rose SW, Barker DC, D'Angelo H, et al. The availability of electronic cigarettes in US retail outlets, 2012: results of two national studies. *Tobacco control.* Jul 2014;23 Suppl 3:iii10-iii16.
149. Seidenberg AB, Hong W, Liu J, Noel JK, Rees VW. Availability and range of tobacco products for sale in Massachusetts pharmacies. *Tobacco control.* Nov 2013;22(6):372-375.
150. Lee YO, Kim AE. 'Vape shops' and 'E-Cigarette lounges' open across the USA to promote ENDS. *Tobacco control.* Apr 11 2014.
151. Giovenco DP, Hammond D, Corey CG, Ambrose BK, Delnevo CD. E-Cigarette Market Trends in Traditional U.S. Retail Channels, 2012-2013. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Dec 26 2014.
152. Grace RC, Kivell BM, Laugesen M. Estimating Cross-Price Elasticity of E-Cigarettes Using a Simulated Demand Procedure. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Dec 28 2014.
153. Wang B, King BA, Corey CG, Arrazola RA, Johnson SE. Awareness and Use of Non-conventional Tobacco Products Among U.S. Students, 2012. *American Journal of Preventive Medicine.* Aug 2014;47(2 Suppl 1):S36-52.
154. Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Youth Tobacco Product Use in the United States. *Pediatrics.* Feb 2 2015.
155. Soneji S, Sargent J, Tanski S. Multiple tobacco product use among US adolescents and young adults. *Tobacco control.* Oct 31 2014.
156. 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. *Preventive medicine.* Jan 16 2014.
157. Shiffman S, Sembower MA, Pillitteri JL, Gerlach KK, Gitchell JG. The Impact of Flavor Descriptors on Nonsmoking Teens' and Adult Smokers' Interest in Electronic Cigarettes. *Nicotine & Tobacco Research.* Jan 7 2015.
158. Agaku IT, Ayo-Yusuf OA. The Effect of Exposure to Pro-Tobacco Advertising on Experimentation With Emerging Tobacco Products Among U.S. Adolescents. *Health education & behavior : the official publication of the Society for Public Health Education.* Dec 16 2013.
159. McMillen R, Maduka J, Winickoff J. Use of emerging tobacco products in the United States. *J Environ Public Health.* 2012;2012:989474.
160. Pepper JK, Reiter PL, McRee AL, Cameron LD, Gilkey MB, Brewer NT. Adolescent males' awareness of and willingness to try electronic cigarettes. *The Journal of Adolescent Health.* Feb 2013;52(2):144-150.
161. Berg CJ, Haardoerfer R, Escoffery C, Zheng P, Kegler M. Cigarette Users' Interest in Using or Switching to Electronic Nicotine Delivery Systems or Smokeless Tobacco for Harm Reduction, Cessation, or Novelty: A Cross-Sectional Survey of U.S. Adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jun 20 2014.
162. Trumbo CW, Harper R. Use and Perception of Electronic Cigarettes Among College Students. *Journal of American College Health.* Apr 2013;61(3):149-155.

163. Czoli CD, Hammond D, White CM. Electronic cigarettes in Canada: Prevalence of use and perceptions among youth and young adults. *Canadian Journal of Public Health.* 2014;105(2):e97-e102.

164. Camenga DR, Cavallo DA, Kong G, et al. Adolescents' and young adults' perceptions of electronic cigarettes for smoking cessation: A focus group study. *Nicotine & Tobacco Research.* Feb 2 2015.

165. Farquhar B, Mark K, Terplan M, Chisolm MS. Demystifying Electronic Cigarette Use in Pregnancy. *Journal of addiction medicine.* Jan 22 2015.

166. Popova L, Ling PM. Nonsmokers' responses to new warning labels on smokeless tobacco and electronic cigarettes: an experimental study. *BMC public health.* 2014;14:997.

167. Cheah NP, Chong NW, Tan J, Morsed FA, Yee SK. Electronic nicotine delivery systems: regulatory and safety challenges: Singapore perspective. *Tobacco control.* Mar 2014;23(2):119-125.

168. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette". *Am J Public Health.* Dec 2010;100(12):2340-2342.

169. Trtchounian A, Talbot P. Electronic nicotine delivery systems: is there a need for regulation? *Tobacco control.* Jan 2011;20(1):47-52.

170. Williams M, Ghai S, Talbot P. Disposable Electronic Cigarettes and Electronic Hookahs: Evaluation of Performance. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Aug 6 2014.

171. 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. *International journal of environmental research and public health.* 2013;10(6):2500-2514.

172. Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol.* Dec 2012;34(4):529-537.

173. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jan 2013;15(1):267-270.

174. Trtchounian A, Williams M, Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Sep 2010;12(9):905-912.

175. Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tobacco control.* Jan 2014;23(1):77-78.

176. Etter JF, Zather E, Svensson S. Analysis of refill liquids for electronic cigarettes. *Addiction (Abingdon, England).* Sep 2013;108(9):1671-1679.

177. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jan 2013;15(1):158-166.

178. Kubica P, Kot-Wasik A, Wasik A, Namiesnik J. "Dilute & shoot" approach for rapid determination of trace amounts of nicotine in zero-level e-liquids by reversed phase liquid chromatography and hydrophilic interactions liquid chromatography coupled with tandem mass spectrometry-electrospray ionization. *J Chromatogr A.* May 10 2013;1289:13-18.

179. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jun 2014;16(6):655-662.

180. Davis B, Dang M, Kim J, Talbot P. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2015;17(2):134-141.

181. Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. *Addiction (Abingdon, England).* Mar 2014;109(3):500-507.

182. Hahn J, Monakhova YB, Hengen J, et al. Electronic cigarettes: overview of chemical composition and exposure estimation. *Tobacco induced diseases.* 2014;12(1):23.

183. Talih S, Balhas Z, Eissenberg T, et al. Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predictions. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Sep 3 2014.

184. Cobb NK, Abrams DB. E-cigarette or drug-delivery device? Regulating novel nicotine products. *The New England journal of medicine.* Jul 21 2011;365(3):193-195.

185. Hadwiger ME, Trehy ML, Ye W, Moore T, Allgire J, Westenberger B. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A.* Nov 26 2010;1217(48):7547-7555.

186. Westenberger B. Evaluation of e-cigarettes. *St Louis, MO: Food and Drug Administration.* 2009:1-8.

187. Geiss O, Bianchi I, Barahona F, Barrero-Moreno J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. *International journal of hygiene and environmental health.* Jan 2015;218(1):169-180.

188. Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Jan 30 2015.

189. Pellegrino RM, Tinghino B, Mangiaracina G, et al. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). *Ann Ig.* Jul-Aug 2012;24(4):279-288.

190. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air.* Feb 2013;23(1):25-31.

191. 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. *International journal of hygiene and environmental health.* Jul 2014;217(6):628-637.

192. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhalation toxicology.* Oct 2012;24(12):850-857.

193. Tayyarah R, Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. *Regulatory toxicology and pharmacology : RTP.* Oct 24 2014.

194. Goniewicz ML, Lee L. Electronic Cigarettes Are a Source of Thirdhand Exposure to Nicotine. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Aug 30 2014.

195. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco control.* Mar 2014;23(2):133-139.

196. Environmental Protection Agency. Reregistration eligibility decision for propylene glycol and dipropylene glycol. 2006.

197. Agency For Toxic Substances and Disease Registry. *Toxicological profile for propylene glycol.* Atlanta, GA: U.S. Department of Health and Human Services, Public Health Services;1997.

198. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. *Archives of toxicology.* Jul 2014;88(7):1295-1308.

199. Kim HJ, Shin HS. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *J Chromatogr A.* May 24 2013;1291:48-55.

200. 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(3):e57987.

201. 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. *Analytical sciences : the international journal of the Japan Society for Analytical Chemistry.* 2013;29(12):1219-1222.

202. Kosmider L, Sobczak A, Fik M, et al. Carbonyl Compounds in Electronic Cigarette Vapors-Effects of Nicotine Solvent and Battery Output Voltage. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* May 15 2014.

203. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Sep 1 2014.

204. Lerner CA, Sundar IK, Watson RM, et al. Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols. *Environmental pollution (Barking, Essex : 1987).* Mar 2015;198:100-107.

205. Oh JA, Shin HS. Identification and Quantification of Several Contaminated Compounds in Replacement Liquids of Electronic Cigarettes by Gas Chromatography-Mass Spectrometry. *Journal of chromatographic science.* Nov 16 2014.

206. Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. *Environmental pollution (Barking, Essex : 1987).* Jan 2014;184:523-529.

207. Ingebrethsen BJ, Cole SK, Alderman SL. Electronic cigarette aerosol particle size distribution measurements. *Inhalation toxicology.* Dec 2012;24(14):976-984.

208. Zhang Y, Sumner W, Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2013;15(2):501-508.

209. Marini S, Buonanno G, Stabile L, Ficco G. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. *Toxicology and applied pharmacology.* Apr 13 2014.

210. Ruprecht AA, De Marco C, Pozzi P, et al. Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. *Tumori.* Jan-Feb 2014;100(1):24e-27e.

211. Bertholon JF, Becquemin MH, Roy M, et al. [Comparison of the aerosol produced by electronic cigarettes with conventional cigarettes and the shisha]. *Revue des maladies respiratoires.* Nov 2013;30(9):752-757.

212. Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. *International journal of environmental research and public health.* 2014;11(11):11177-11191.

213. Manigrasso M, Buonanno G, Fuoco FC, Stabile L, Avino P. Aerosol deposition doses in the human respiratory tree of electronic cigarette smokers. *Environmental pollution (Barking, Essex : 1987).* Oct 29 2014;196c:257-267.

214. Farsalinos KE, Romagna G, Allifranchini E, et al. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *International journal of environmental research and public health.* Oct 2013;10(10):5146-5162.

215. Cervellati F, Muresan XM, Sticozzi C, et al. Comparative effects between electronic and cigarette smoke in human keratinocytes and epithelial lung cells. *Toxicology in vitro : an international journal published in association with BIBRA.* May 5 2014;28(5):999-1005.

216. Misra M, Leverette RD, Cooper BT, Bennett MB, Brown SE. Comparative in vitro toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. *International journal of environmental research and public health.* 2014;11(11):11325-11347.

217. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicology in vitro : an international journal published in association with BIBRA.* Mar 2014;28(2):198-208.

218. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PloS one.* 2015;10(2):e0116732.

219. Willershausen I, Wolf T, Weyer V, Sader R, Ghanaati S, Willershausen B. Influence of E-smoking liquids on human periodontal ligament fibroblasts. *Head & face medicine.* 2014;10:39.

220. Wu Q, Jiang D, Minor M, Chu HW. Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. *PloS one.* 2014;9(9):e108342.

221. 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. *Tobacco control.* Apr 2010;19(2):98-103.

222. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology.* Jan 2014;231(2):401-407.

223. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tobacco control.* Feb 2010;19(1):87-88.

224. Etter JF. Levels of saliva cotinine in electronic cigarette users. *Addiction (Abingdon, England).* Jan 8 2014.

225. Etter JF, Bullen C. Saliva cotinine levels in users of electronic cigarettes. *The European respiratory journal.* Nov 2011;38(5):1219-1220.

226. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation toxicology.* Feb 2013;25(2):91-101.

227. van Staden SR, Groenewald M, Engelbrecht R, Becker PJ, Hazelhurst LT. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* Nov 2013;103(11):865-868.

228. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* Aug 2010;19(8):1945-1953.

229. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction (Abingdon, England).* Aug 2012;107(8):1493-1500.

230. Ballbe M, Martinez-Sanchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environmental research.* Sep 25 2014;135c:76-80.

231. Norton KJ, June KM, O'Connor RJ. Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. *Tobacco induced diseases.* 2014;12(1):17.

232. Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regulatory toxicology and pharmacology : RTP.* Nov 22 2014.

233. Velez de Mendizabal N, Jones DR, Jahn A, Bies RR, Brown JW. Nicotine and Cotinine Exposure from Electronic Cigarettes: A Population Approach. *Clinical pharmacokinetics.* Dec 12 2014.

234. Behar RZ, Hua M, Talbot P. Puffing topography and nicotine intake of electronic cigarette users. *PloS one.* 2015;10(2):e0117222.

235. Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacology.* Jun 2013;227(3):377-384.

236. Dawkins L, Turner J, Hasna S, Soar K. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict Behav.* Aug 2012;37(8):970-973.

237. Dawkins L, Kimber C, Panwanesarasa Y, Soar K. First versus second generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. *Addiction (Abingdon, England).* Nov 18 2014.

238. Lechner WV, Meier E, Wiener JL, et al. The Comparative Efficacy of 1 vs. 2 Generation Electronic Cigarettes in Reducing Symptoms of Nicotine Withdrawal. *Addiction (Abingdon, England).* Feb 1 2015.

239. Martinez-Sanchez JM, Ballbe M, Fu M, et al. Electronic cigarette use among adult population: a cross-sectional study in Barcelona, Spain (2013-2014). *BMJ open.* 2014;4(8):e005894.

240. Penn State Electronic Cigarette Dependence Index. http://smokingcessationleadership.ucsf.edu/webinar_40_final_presentation_042314.pdf.

241. Fagerstrom KO. Nicotine - relative addictiveness of different products. *Presentation at: Global Forum on Nicotine.* June 2014;Warsaw, Poland.

242. Romagna G, Allifranchini E, Bocchietto E, Todeschi S, Esposito M, Farsalinos KE. Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. *Inhalation toxicology.* May 2013;25(6):354-361.

243. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PloS one.* 2015;10(2):e0116861.

244. Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after four weeks of regular use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Aug 13 2014.

245. Flouris AD, Poulianiti KP, Chorti MS, et al. Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol.* Oct 2012;50(10):3600-3603.

246. Farsalinos KE, Romagna G. Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: a case report. *Clin Med Insights Case Rep.* 2013;6:15-21.

247. 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.* Jun 2012;141(6):1400-1406.

248. Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC cardiovascular disorders.* 2014;14(1):78.

249. Tzatzarakis MN, Tsitoglou KI, Chorti MS, et al. Acute and short term impact of active and passive tobacco and electornic cigarette smoking on inflammatory markers. [Abstract]. *Toxicology Letters.* 2013;221S:S86.

250. Camus M, Gallois G, Marteau P. Ulcerative colitis and electronic cigarette: What's the matter? *The American journal of gastroenterology.* Apr 2014;109(4):608-609.
251. Cantrell FL. Adverse effects of e-cigarette exposures. *Journal of community health.* Jun 2014;39(3):614-616.
252. Chatham-Stephens K, Law R, Taylor E, et al. Notes from the field: calls to poison centers for exposures to electronic cigarettes--United States, September 2010-February 2014. *MMWR. Morbidity and mortality weekly report.* Apr 4 2014;63(13):292-293.
253. Chen IL. FDA summary of adverse events on electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2013;15(2):615-616.
254. Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *Journal of medical Internet research.* 2013;15(4):e59.
255. McCauley L, Markin C, Hosmer D. An unexpected consequence of electronic cigarette use. *Chest.* Apr 2012;141(4):1110-1113.
256. Thornton SL, Oller L, Sawyer T. Fatal intravenous injection of electronic nicotine delivery system refilling solution. *Journal of medical toxicology : official journal of the American College of Medical Toxicology.* Feb 6 2014.
257. Thota D, Latham E. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. *The Journal of emergency medicine.* Jan 21 2014.
258. Vakkalanka JP, Hardison LS, Jr., Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers. *Clinical toxicology (Philadelphia, Pa.).* May 5 2014.
259. Polosa R, Morjaria J, Caponnetto P, et al. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *International journal of environmental research and public health.* 2014;11(5):4965-4977.
260. Monroy A, Hommel E, Smith S, Raji M. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. *Clin Geriatr.* 2012;20(3):28-32.
261. Eberlein CK, Frieling H, Kohnlein T, Hillemacher T, Bleich S. Suicide attempt by poisoning using nicotine liquid for use in electronic cigarettes. *The American journal of psychiatry.* Aug 1 2014;171(8):891.
262. Schipper EM, de Graaff LC, Koch BC, et al. A New Challenge: Suicide Attempt using Nicotine Fillings for Electronic Cigarettes. *British journal of clinical pharmacology.* Aug 12 2014.
263. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of Toxicant and Carcinogen Metabolites in the Urine of e-Cigarette Users Versus Cigarette Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 21 2014.
264. Ordonez JE, Kleinschmidt KC, Forrester MB. Electronic Cigarette Exposures Reported to Texas Poison Centers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Oct 25 2014.
265. Popa C. Infrared spectroscopy study of the influence of inhaled vapors/smoke produced by cigarettes of active smokers. *Journal of biomedical optics.* May 2015;20(5):051003.
266. American Association of Poison Control Centers. E-Cigarette Devices and Liquid Nicotine. 2015; http://www.aapcc.org/alerts/e-cigarettes/. Accessed May 13, 2015.
267. Mowry JB, Spyker DA, Cantilena LR, Jr., McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clinical toxicology (Philadelphia, Pa.).* Dec 2014;52(10):1032-1283.
268. Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tobacco control.* Mar 2013;22(2):103-106.

269. Williams M, Talbot P. Variability among electronic cigarettes in the pressure drop, airflow rate, and aerosol production. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Dec 2011;13(12):1276-1283.

270. Li J, Newcombe R, Walton D. The use of, and attitudes towards, electronic cigarettes and self-reported exposure to advertising and the product in general. *Australian and New Zealand journal of public health.* Dec 2014;38(6):524-528.

271. Vardavas CI, Filippidis FT, Agaku IT. Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries. *Tobacco control.* Jun 16 2014.

272. Goniewicz ML, Gawron M, Nadolska J, Balwicki L, Sobczak A. Rise in electronic cigarette use among adolescents in Poland. *The Journal of Adolescent Health.* Nov 2014;55(5):713-715.