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Food and Drug Administration
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**Re: Electronic Cigarettes and the Public Health: A Public Workshop;
Docket No. FDA-2014-N-1936-0003**

The American E-Liquid Manufacturing Standards Association (AEMSA) appreciates this opportunity to respond to the request by the Food and Drug Administration (FDA or Agency) for comments in conjunction with its June 2015 public workshop to gather scientific information about the population-level “public health” impact of electronic cigarettes (e-cigarettes) and e-liquid as announced in Docket No. FDA-2014-N-1936-0003.¹ The purpose of this letter is to provide AEMSA’s responses to several of the issues discussed during that workshop. This comment incorporates by reference AEMSA’s comments (1) dated May 8, 2015, addressing the safety of e-liquid components and the public health benefits of flavored e-liquids, submitted in response to FDA’s December 2014 and March 2015 public workshops², and (2) dated August 8, 2014, to the Notice of Proposed Rulemaking (NPRM) for the Deeming Regulation (FDA Docket No. FDA-2014-N-0189).³

I. Background on AEMSA

AEMSA is the first and only manufacturers’ trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of e-liquids used in e-cigarettes. AEMSA is an all-volunteer 501(c)(6) organization, formed by U.S. manufacturers of e-liquids, to promote safety and responsibility through self-regulation. Our Members believe we have a responsibility to self-regulate the e-liquid manufacturing process using professional criteria. One of AEMSA’s primary goals is to provide consumers and government regulators

¹ See <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-1936-0003>.

² See Comment ID FDA-2014-N-1936-0408 and tracking number 1jz-8iq1-lzcz, available online at: <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-1936-0408>.

³ See Comment ID FDA-2014-N-0189-81140 and tracking number 1jy-8dol-z5ml, available online at: <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0189-81140>.

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with confidence that our members' products are manufactured in a safe manner until such time as FDA promulgates Good Manufacturing Practices (GMPs) for e-liquids. In this regard, AEMSA has developed manufacturing standards for of e-liquids, which are available online at: <http://www.aemsa.org/standards/>. AEMSA supports reasonable, responsible and science-based regulation of e-cigarettes, including open-system refillable personal vaporizers and the e-liquids used in those products.

We note that although e-liquid and e-cigarette products manufactured by AEMSA's Member companies may have the corollary benefit of helping tobacco cigarette smokers quit smoking or nicotine use altogether, these products are not intended to be smoking cessation devices or nicotine replacement therapies (NRTs) (and are not marketed as such), but rather are recreational use products.⁴ Although the available evidence demonstrates that most current e-cigarette users are using these products as an aid to help them quit or cut down on their use of traditional cigarettes, no claims to this effect are being made by AEMSA or any of its Member companies about their products.

AEMSA is providing these comments to FDA on behalf of its e-liquid manufacturing Members.

II. The Public Health Requirement

The electronic cigarette is a revolutionary technology that has the ability to greatly benefit the public health, as it provides the first viable recreational alternative to tobacco for cigarette smokers. Assuming solely for the purposes of these comments that e-cigarettes and their e-liquid components (that contain tobacco-derived nicotine) are deemed to be *regulated* tobacco products,⁵ these products will be subject to, among other things, the "public health" requirement of the Tobacco Control Act. Specifically, the Tobacco Control Act requires new

⁴ See *Sottera Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010).

⁵ First and foremost, AEMSA's position is that e-cigarettes are technology products, not tobacco products, and that Congress should consider separate legislation specifically giving FDA authority over e-vapor products separate from the Agency's tobacco and drug authorities. We believe that attempting to force the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) requirements onto these tobacco-free products is not an effective regulatory strategy. Nevertheless, for purposes of these comments, we assume, *arguendo*, that e-cigarettes and their e-liquid components will be "covered tobacco products" subject to the Tobacco Control Act requirements, assuming they are used with or contain nicotine derived from tobacco.

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covered tobacco products (i.e., products that are not “grandfathered” or determined to be substantially equivalent to a grandfathered product) demonstrate via the Premarket Tobacco Product Application (PMTA) pathway that they are “appropriate for the protection of the public health” in order to be marketed. In assessing whether a tobacco product meets this governing public health standard, FDA must consider the product’s risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products, and the increased or decreased likelihood that those who do not use tobacco products will start using such products. This process could cost millions of dollars and is not feasible for the hundreds of small businesses in the e-vapor industry.

As detailed below, based on the extensive existing literature on the safety and public health benefit of e-cigarettes (compared to conventional cigarettes) the Agency should acknowledge that a less rigorous implementation of premarket documentation is appropriate for non-combusted non-tobacco products such as e-cigarettes. Specifically, FDA should find that, as a class of products, the availability of e-cigarettes and their e-liquid components provides an overall positive impact on the health of the population. Accordingly, e-cigarette and e-liquid manufacturers should not have to consider the potential population-level impact of their individual products, but should instead only be required to demonstrate that their products are not unnecessarily harmful to the health of individual consumers by, for example, complying with product standards and Good Manufacturing Practices.

III. Requiring E-Cigarette Manufacturers to Assess the Potential Population-Level Impact of their Products is Unnecessary and Redundant

AEMSA’s position is that individual e-cigarette and e-liquid manufacturers should not be responsible for assessing the *potential* population-level impact of their product. Rather, the development and testing of new e-cigarette and e-liquid products should address the safety and effectiveness of the product’s features, as well as demonstrating that the device or e-liquid meets industry norms and standards, as well as FDA regulatory and guidance requirements when they become available. Furthermore, post-market research should demonstrate that marketing materials employed with the specific product are demonstrated to target current smokers and vapers, and not adolescents.

It would be unnecessarily redundant, costly, and would serve to further complicate the daunting task which FDA faces in defining how e-cigarettes are regulated to require individual e-cigarette companies address the potential population-level impact posed by their products. Rather, the population-level impact of these products is a general regulatory policy issue for this *category* of product, not a product-specific issue, and FDA is already addressing this general regulatory issue via a variety of activities, including sponsored research (e.g., the Population Assessment of Tobacco and Health (PATH) study, a national longitudinal study of tobacco use

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and how it affects the health of people in the United States), public workshops, consumer surveys, etc. Accordingly, FDA should create a streamlined PMTA process for new e-cigarette and e-liquid products that focuses on product-specific risks and benefits.

To illustrate the logical underpinning of this proposed focus on assessing product-specific: safety, performance and marketing in individuals, rather than needing to address all of the risks and merits of e-cigarettes across the entire population, we offer an analogy. What if FDA required individual sponsors seeking licenses for new vaccines to prove in their applications that adaptive immunity can be elicited by vaccination, to address all of the concerns of the vaccine denier/autism advocacy community, or to demonstrate the benefit of vaccination to the entire population at large? That would be unduly burdensome, and contrary to public health interests. Rather, what is well established by regulatory precedent is that the specific risks and benefits of the product are what need to be addressed in any application to the Agency. Moreover, such assessment needs to occur at the level of representative samples of individual users, not at the general public level. Vaccines clearly work better when herd immunity is factored in, rather than efficacy and effectiveness at the level of the individual, but they are tested and licensed by demonstrating appropriate risk/benefit at the level of groups of tested individuals to whom the vaccine has been administered (relative to control groups). So to, should the risks and benefits of a specific e-cigarette product be demonstrated at the level of adequately powered groups of tested individuals, rather than at the general population level. Population-level analyses concerning an entire product category or technology are subject to many confounding variables which can obscure and complicate risk/benefit assessments for individual products. In the case of the potential population-level impact of e-cigarettes in general, even though Congress required FDA consider the public impact of new tobacco products, it is critical for the Agency to recognize that this is a regulatory policy issue, separate from the risks and benefits of a specific product.

IV. Evidence Exists in the Public Literature that E-Cigarettes are “Appropriate for the Protection of the Public Health”

Another reason why FDA need not place the burden on individual manufacturers to assess the population-level impact of their product is because there is sufficient evidence in the public literature supporting that, as a class of products, e-cigarettes are “appropriate for the protection of the public health” based on their overall population-level impact. This body of data indicates that e-cigarettes and the e-liquids used in them:

- Provide a much less harmful alternative to tobacco leaf-containing products (especially combustible cigarettes) for current tobacco users;

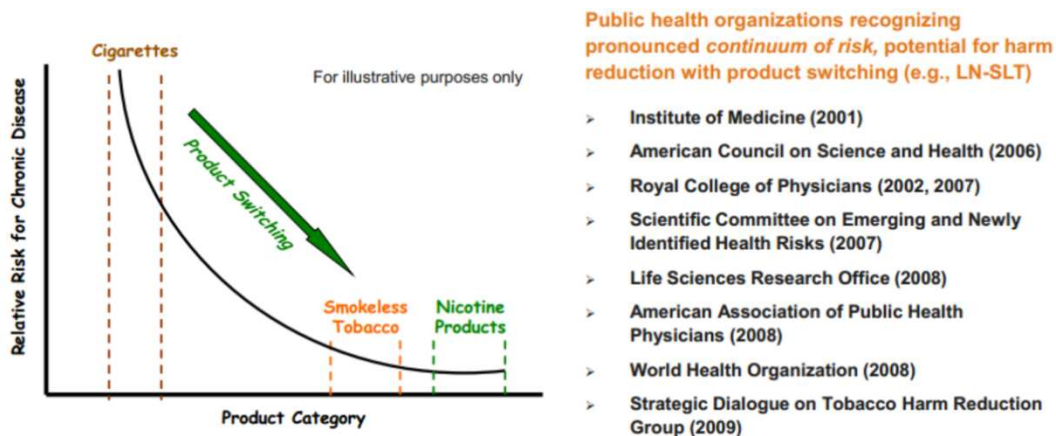
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- Do not have an adverse impact on smoking initiation and cessation rates (i.e., the evidence indicates that the products have contributed to the continuing decline in the percentage of the population that smokes cigarettes); and
- Have not resulted in an increase in adolescent cigarette smoking rates, there is sufficient evidence in the scientific literature for FDA to find that, generally, the availability of these products on the market is “appropriate for the protection of the public health”.

We review the science supporting each of these public health factors below.

V. E-Cigarettes Are a Significantly Less Harmful Alternative to Tobacco Leaf-Containing Products, Especially Combustible Cigarettes for Current Tobacco Users

The data indicate that, when compared to tobacco-leaf products, and especially those that are combusted, e-cigarettes and the e-liquids used in them are dramatically less harmful for individual tobacco users, especially cigarette smokers. This is why when tailoring the regulatory requirements for the tobacco products FDA chooses to deem as regulated, the Agency should recognize the wide disparity of risk posed by different types of products. This risk disparity can be described on a “continuum of risk,” whereby the products that pose the greatest harm and risk of tobacco-related disease (i.e., the traditional, combustible cigarette) is on one end of the continuum, and new product forms (such as e-cigarettes) that do not contain or combust tobacco leaf are on the other end, as depicted in the following diagram⁶:



⁶ Mark Greenwold, Senior Consultant, Campaign for Tobacco Free Kids, Embracing the Continuum of Risk, Presentation at FDLI Conference in Washington, D.C. (Apr. 24, 2013), <http://www.fdl.org/docs/default-document-library/6---tobacco---combined.pdf?sfvrsn=0>.

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Tobacco leaf-containing products, especially those that are combusted, are the most harmful and dangerous products on the continuum of risk and should be treated as such. It is well established that the more pyrolyzed tobacco constituents a user inhales from a combustible tobacco product, such as a cigarette, the greater the risk of tobacco-related disease that product poses⁷. Of the approximately 5,300 chemicals identified in tobacco smoke, at least 60 are known human carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs)⁸.

E-cigarettes are far less risky to individual users than combustible cigarettes because they do not result in the inhalation of pyrolyzed chemicals. As discussed more fully in our comments submitted in response to FDA's December 2015 and March 2015 public workshop, one area of concern for e-liquids is the potential formation of aldehydes (e.g., formaldehyde and acetaldehyde) during use. Although these substances are not intentionally added ingredients, studies have shown that at excessively high temperatures propylene glycol and vegetable glycerin in e-liquids can decompose to low molecular carbonyls compounds, including harmful aldehydes. It is important to understand, however, that during actual e-cigarette use, the potential for human exposure to these substances is quite low because consumers are unlikely to allow their devices to reach such high temperatures. More specifically, the excessive heat required to generate these harmful compounds results in what is known as the "dry puff" phenomenon – the unpleasant, burning taste experienced by the user when the heater coil overheats – which makes the vapor uninhalable. Because a user can immediately detect and avoid dry puffs when vaping (by decreasing puff duration and increasing the inter-puff interval, or refilling the tank if the e-liquid level is low) the potential for exposure to any generated carbonyls is low. Under normal vaping conditions, the aldehyde emission levels are minimal and by far lower than the levels found in tobacco cigarette smoke.

Public health experts around the world have come out in support of tobacco harm reduction through the use of e-cigarettes. More than 50 tobacco and nicotine and public health specialists from 15 countries recently sent a letter to the World Health Organization (WHO) Director General Margaret Chan emphasizing the importance of tobacco harm reduction through the use of "low risk non-combustible tobacco products (which includes e-cigarettes). These products "could be among the most significant health innovations of the 21st Century—perhaps

⁷ See Richard R. Baker & Louise J. Bishop, *The Pyrolysis of Tobacco Ingredients*, 71 J. ANAL. APPL. PYROLYSIS 223-311 (2004).

⁸ See Alan Rodgman & Thomas A. Perfetti, *The Chemical Components of Tobacco and Tobacco Smoke* (2d ed. 2013).

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saving hundreds of millions of lives.”⁹ Similarly, with respect to the impact on the individual consumer, the American Legacy Foundation, a not-for-profit organization dedicated to preventing teen smoking and encouraging smokers to quit, recently published a position statement on e-cigarettes, in which it stated: “Legacy recognizes that, on an individual level, there is a continuum of risk across tobacco products with combustible products (e.g., cigarettes, cigars, hookah) posing the most danger and Food and Drug Administration (FDA) approved nicotine replacement therapies (NRT’s) posing the least harm. Harm reduction is a valuable public health strategy with the potential to reduce, although not eliminate, the preventable disease and death caused by tobacco. Electronic cigarettes may hold great promise in this regard. While they are not without risk, initial scientific evidence suggests that, for the individual smoker, they are likely less harmful than smoking cigarettes, and they likely have significant lower levels of known tobacco toxicants than combusted tobacco products.”¹⁰

The potential for e-cigarettes to be used as a valuable tool for harm reduction must be considered, especially in light of the effectiveness (or lack thereof) of FDA-approved NRT products. The Alpert et al. study casts serious doubt on the efficacy of FDA-approved NRT treatments, such as patches, gum, and drugs, such as Zyban and Chantix.¹¹ As Michael Marlow noted in his public comment on behalf of the Mercatus Center at the George Mason University: “This study concludes that persons who have quit smoking relapsed at equivalent rates, whether or not they used NRT to help them in their quit attempts. In other words, FDA-approved NRT may not be any more effective in helping smokers quit their smoking habits than going ‘cold turkey.’ The possibility that e-cigarettes represent a market response that attempts to fill the need for harm reduction by smokers is worth pursuing. This is especially true given concerns over the efficacy of NRT.”¹²

⁹ See David Abrams et al., *Statement from Specialists in Nicotine Science and Public Health Policy* (2014), <http://www.nicotinepolicy.net/documents/letters/MargaretChan.pdf>.

¹⁰ See Legacy, *E-Cigarette Policy: The FDA Should Promptly Exercise Regulatory Authority over E-Cigarettes* (2014), http://www.legacyforhealth.org/content/download/3962/56088/version/1/file/LEG-Policy_Statement-ECigarette-JAN2014.pdf.

¹¹ Hillel R. Alpert et al., *A Prospective Cohort Study Challenging the Effectiveness of Population-Based Medical Intervention for Smoking Cessation*, 22 TOB. CONTROL 32-37 (2013), available at <http://tobaccocontrol.bmj.com/content/22/1/32.abstract>.

¹² Public Comment from Michael L. Marlow on Deeming Tobacco Products to be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and (continued ...)

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There are dozens of studies in the public literature (and growing) that demonstrate that e-cigarettes and the e-liquid used in them are significantly less harmful for individual consumers compared to tobacco leaf-containing products. We highlight some of these studies below:

- A team of researchers led by Dr. Thomas Eissenberg, co-director of the Center for the Study of Tobacco Products at Virginia Commonwealth University, reviewed 81 prior studies of the pharmacodynamics, pharmacokinetics, and health impact of e-cigarettes including chemicals in the liquids and aerosols and use among smokers and non-smokers.¹³ The purpose of the study, which was partly funded by the U.S. National Institutes of Health and published in the journal *Addiction* on July 30, 2014, was to assess the potential for harm or benefit of e-cigarettes and to obtain evidence to guide future policy. The researchers determined that while e-cigarette aerosol can contain some of the toxicants present in tobacco smoke, the levels are much lower. Moreover, while long-term health effects of e-cigarette use are unknown, compared with combustible tobacco cigarettes, e-cigarettes are likely to be much less, if at all, harmful to users or bystanders. The study authors concluded that allowing e-cigarettes to compete with tobacco cigarettes in the market place might decrease smoking-related morbidity and mortality. Regulating these as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted based on the current evidence.
- Similarly, Drs. Konstantinos Farsalinos and Riccardo Polosa of the Centro per la Prevenzione e Cura del Tabagismo (CPCT) and Institute of Internal Medicine, Università di Catania, Catania, Italy, conducted a systematic review of existing laboratory and clinical research on the potential risks from e-cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes.¹⁴ The researchers

(...continued)

Required Warning Statements for Tobacco Product Packages and Advertisements Docket ID: FDA-2014-N-0189 (July 8, 2014), <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0189-39318>.

¹³ See Peter Hajek et al., *Electronic Cigarettes: Review of Use, Content, Safety, Effects on Smokers and Potential for Harm and Benefit*, 109 ADDICTION 1801-1810 (2014), available at <http://onlinelibrary.wiley.com/doi/10.1111/add.12659/full>.

¹⁴ See Konstantinos E. Farsalinos & Riccardo Polosa, *Safety Evaluation and Risk Assessment of Electronic Cigarettes as Tobacco Cigarette Substitutes: A Systematic Review*, 5 THERAPEUTIC ADVANCES IN DRUG SAFETY 67-86 (2014), available at <http://taw.sagepub.com/content/5/2/67>.

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concluded that currently available evidence indicates that e-cigarettes are by far a less harmful alternative to smoking cigarettes, and significant health benefits are expected in smokers who switch from tobacco to e-cigarettes. Research will help make e-cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.

- An international expert panel convened by the Independent Scientific Committee on Drugs recently demonstrated that use of e-cigarettes is far less risky compared to the use of traditional combustible tobacco, and only slightly more risky than FDA-approved nicotine replacement products that are recognized as being safe for their intended use.¹⁵ More specifically, the expert panel developed a multi-criteria decision analysis model of the relative importance of different types of harm related to the use of nicotine-containing products (*e.g.*, cigarettes, cigars, water pipes, smokeless tobacco, electronic nicotine delivery systems, nicotine patch and nasal spray). After defining the products and the harm criteria the group scored all the products based on each criterion to determine the product's average harm worldwide. The products were compared to each other using a scale with 100 defined as the most harmful product on a given criterion, and a score of zero defined as no harm. The panel found that the weighted averages of the scores provided a single, overall score for each product. Cigarettes (overall weighted score of 100) emerged as the most harmful product, with small cigars in second place (overall weighted score of 64). After a substantial gap to the third-place product, pipes (scoring 21), all remaining products, including e-cigarettes, scored 15 points or less. The panel concluded that cigarettes cause by far the most harm and attempts to encourage smokers to switch to non-combusted sources of nicotine should be encouraged.
- According to a new study published in the International Journal of Environmental Research and Public Health, asthmatic smokers who use e-cigarettes experience an improvement in their asthma symptoms and lung function, even if they remain dual users.¹⁶ The study examined 18 smokers with significant asthma who switched to

¹⁵ See Nutt, D.J. et al., *Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach*, 20 EUR. ADDICTION RES. 218 (2014), available at <http://www.karger.com/article/fulltext/360220>.

¹⁶ See Riccardo Polosa et al., *Effect of Smoking Abstinence and Reduction in Asthmatic Smokers Switching to Electronic Cigarettes: Evidence for Harm Reversal*, 11(5) INT'L J. ENVIRON. RES. PUB. HEALTH 4965-4977 (2014), available at <http://www.mdpi.com/1660-4601/11/5/4965>.

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electronic cigarettes. Ten of the patients switched completely and 8 became dual users (both smoking and using e-cigarettes). Among the dual users, the average cigarette consumption dropped from 22.4 to 3.9 cigarettes per day. After one year follow-up, both the ex-smokers and dual users experienced a significant improvement in asthma symptoms and lung function, especially small airways obstruction. Although the improvements in lung function were small, the improvements in asthma symptoms were clinically relevant. The study authors concluded that by substantially reducing the number of cigarettes smoked per day and exposure to their hazardous toxicants, e-cigarettes may not only improve asthma symptoms and pulmonary function but may also confer an overall health advantage in smokers with asthma.

- With respect to the cardiovascular effects of e-cigarette use, a study was recently performed to examine the immediate effects of e-cigarette use on left ventricular (LV) function, compared to the well-documented acute adverse effects of smoking.¹⁷ Specifically, echocardiographic examinations were performed in 36 healthy adult heavy smokers before and after smoking one cigarette, and in 40 electronic cigarette users before and after using the device with “medium-strength” nicotine concentration (11 mg/mL) for 7 minutes. Mitral flow diastolic velocities (E, A), their ratio (E/A), deceleration time (DT), isovolumetric relaxation time (IVRT) and corrected-to-heart rate IVRT (IVRTc) were measured. Mitral annulus systolic (Sm), and diastolic (Em, Am) velocities were estimated. Myocardial performance index was calculated from Doppler flow (MPI) and tissue Doppler (MPIt). Longitudinal deformation measurements of global strain (GS), systolic (SRs) and diastolic (SRe, SRA) strain rate were also performed. Baseline measurements were similar in both groups. In SM, IVRT and IVRTc were prolonged, Em and SRe were decreased, and both MPI and MPIt were elevated after smoking. In ECIG, no differences were observed after device use. Comparing after-use measurements, ECIG had higher Em ($P = 0.032$) and SRe ($P = 0.022$), and lower IVRTc ($P = 0.011$), MPI ($P = 0.001$) and MPIt ($P = 0.019$). The observed differences were significant even after adjusting for changes in heart rate and blood pressure. The study authors concluded that although acute smoking causes a delay in myocardial relaxation, e-cigarette use has no immediate effects.
- Independent university researchers analyzed data from a pilot online survey to determine whether switching to e-cigarettes from combustible cigarettes had any influence on the

¹⁷ See Konstantinos E. Farsalinos et al., *Acute Effects of Using an Electronic Nicotine-Delivery Device (Electronic Cigarette) on Myocardial Function: Comparison with the Effects of Regular Cigarettes*, 14 BMC CARDIOVASCULAR DISORDERS 78 (2014) available at <http://www.biomedcentral.com/1471-2261/14/78>.

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health of the consumer. All respondents previously smoked and 91% had attempted to stop smoking before trying e-cigarettes. Most respondents resided in the United States (72%) and 21% were in Europe. About half (55%) were 31-50 years old, while 32% were >50 years old. Most (79%) of the respondents had been using e-cigarettes for less than 6 months and reported using them as a complete (79%) or partial (17%) replacement for, rather than in addition to (4%), cigarettes. The majority of respondents reported that their general health (91%), smoker's cough (97%), ability to exercise (84%), and sense of smell (80%) and taste (73%) were better since using e-cigarettes and none reported that these were worse. Although people whose e-cigarette use completely replaced smoking were more likely to experience improvements in health and smoking caused symptoms, most people who substituted e-cigarettes for even some of their cigarettes experienced improvements.¹⁸ Although this study was not published in a peer-reviewed journal, it still provides valuable insight into the potential impact of e-cigarettes on the health of individual smokers.

- The International Journal of Environmental Research and Public Health published a study comparing how e-cigarette vapor impacts heart cells compared to cigarette smoke.¹⁹ More specifically, using a standardized ISO protocol, the cytotoxic potential of the vapor of 20 e-liquid samples was tested and compared to that of cigarette smoke extracted from three combustible tobacco cigarettes. The extracts, undiluted (100%) and in four dilutions (50%, 25%, 12.5%, and 6.25%), were applied to myocardial cells (H9c2); percent-viability was measured after a 24 hour incubation period. According to ISO 10993-5 protocol definition, viability of <70% was considered cytotoxic. The cigarette smoke extract showed cytotoxic effects at extract concentrations above 12.5%, while only 2 e-liquid samples were cytotoxic at 100% and 50% extract concentrations and one was cytotoxic at 100% extract concentration only. The study authors concluded that while some e-cigarette vapor samples have cytotoxic properties on cultured cardiomyoblasts, associated with the production process and materials used in flavorings, all e-cigarette vapor extracts were significantly less cytotoxic compared to cigarette

¹⁸ See Karyn Heavner et al., *Electronic Cigarettes (E-Cigarettes) as Potential Tobacco Harm Reduction Products: Results of an Online Survey of E-Cigarette Users* (2009), <http://tobaccoharmreduction.org/wpapers/011v1.pdf>.

¹⁹ See G. Romagna, Alliffranchini 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*. 25(6) INHAL. TOXICOL. 354-61 (2013), available at <http://www.ncbi.nlm.nih.gov/pubmed/23742112>.

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smoke extracts. The flavorings that demonstrated cytotoxicity were natural extracts of tobacco leaf, and to a lesser extent, natural extract of coffee.

- A 2012 study was conducted to assess the content of the aromatic liquid mixture and its vapor and the Particulate Matter (PM) emissions of an Italian brand of e-cigarette and to compare its PM emissions with a conventional cigarette.²⁰ The main components of the liquid were: Propylene glycol (66%) and glycerine (24%), while the flavoring substances comprised less than 0.1%. The same substances were detected in the vapor in similar proportions. Fine and ultrafine PM emissions were higher for the conventional versus the e-cigarette (e.g., PM₁₀=922 vs 52 ug/m³; PM₁=80 vs 14 ug/m³). The researchers found that the e-cigarette seems to give some advantages when used instead of the conventional cigarette, but more studies are needed. More specifically, the researchers found that e-cigarette use could help smokers to cope with some of the rituals associated with smoking gestures and to reduce or eliminate tobacco consumption avoiding passive smoking.
- A 2012 study evaluated the acute effect of active and passive e-cigarette and tobacco cigarette smoking on complete blood count (CBC) markers in 15 smokers and 15 never-smokers, respectively.²¹ Researchers placed smokers under the following conditions: a control session, an active tobacco cigarette smoking session, and an active e-cigarette smoking session. In addition, researchers placed never-smokers under the following conditions: a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Researchers found that CBC indices remained unchanged during the control session and the active and passive e-cigarette smoking sessions ($P > 0.05$). Active and passive tobacco cigarette smoking increased white blood cell, lymphocyte, and granulocyte counts for at least one hour in smokers and never smokers ($P < 0.05$). Accordingly, the researchers concluded that acute active and passive smoking using the e-cigarettes tested in this study did not influence CBC indices in smokers and never smokers, respectively. In contrast, the researchers noted, acute active and passive tobacco cigarette smoking increase the secondary proteins of acute inflammatory load for at least one hour.

²⁰ See Roberto Maria Pelligrino et al., *Electronic Cigarettes: An Evaluation of Exposure to Chemicals and Fine Particulate Matter (PM)*, 24(4) ANN. IG.279-288 (2012), available at <http://www.ncbi.nlm.nih.gov/pubmed/22913171>.

²¹ See Andreas D. Flouris et al., *Acute Effects of Electronic and Tobacco Cigarette Smoking on Complete Blood Count*, 50(10) FOOD CHEM. TOXICOL. 3600-3603 (2012), available at <http://www.ncbi.nlm.nih.gov/pubmed/22858449>.

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- Researchers concluded that e-cigarettes generate smaller changes in lung function after assessing the acute impact of active and passive e-cigarette smoking on serum cotinine and lung function as compared to active and passive tobacco cigarette smoking.²² Specifically, fifteen smokers (≥ 15 cigarettes/day; seven females; eight males) underwent a control session, an active tobacco cigarette (their favorite brand) smoking session and an active e-cigarette smoking session. 15 never-smokers (seven females; eight males) underwent a control session, a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Serum cotinine, lung function, exhaled carbon monoxide and nitric oxide were assessed. Electronic cigarettes and tobacco cigarettes generated similar effects on serum cotinine levels after active and passive smoking. Neither a brief session of active e-cigarette smoking nor a one hour passive e-cigarette smoking significantly affected the lung function. In contrast, active but not passive tobacco cigarette smoking undermined lung function.
- A 2012 study compared the effects of e-cigarette vapor and cigarette smoke on indoor air quality.²³ Researchers assessed the potential health impacts relating to the use of e-cigarettes through a series of studies using e-cigarettes and standard tobacco cigarettes. Researchers vaporized four different high nicotine e-liquids in two sets of experiments by generic 2-piece e-cigarettes to collect emissions and assess indoor air concentrations of common tobacco smoke by products. Tobacco cigarette smoke tests were conducted for comparison. Researchers compared pollutant concentrations between e-cigarette vapor and tobacco smoke samples. Pollutants included VOCs, carbonyls, PAHs, nicotine, TSNA, and glycols. From these results, researchers conducted risk analyses based on dilution into a 40 m³ room and standard toxicological data. The non-cancer risk analysis revealed “No Significant Risk” of harm to human health for vapor samples from e-liquids (A-D). In contrast, for tobacco smoke, researchers noted that most findings exceeded risk limits indicating a condition of “Significant Risk” of harm to human health. With respect to the cancer risk analysis, researchers noted that no vapor sample from e-liquids A-D exceeded the risk limit for either children or adults. The tobacco smoke sample approached the risk limits for adult exposure. The study concluded that for all byproducts measured, e-cigarettes produce very small exposures as compared to tobacco

²² See AD Flouris, *Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function*, 25(2) *Inhal Toxicol.* 91-101 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/23363041>.

²³ See T.R. McAuley *et al.*, *Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality*, 24(12) *Inhal Toxicol.* 850-857 (2012), abstract <http://informahealthcare.com/doi/abs/10.3109/08958378.2012.724728>.

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cigarettes. The study demonstrated that no apparent risk to human health results from e-cigarette emissions based on the compounds analyzed.

- A 2011 study assessed the safety of certain cigalike e-cigarettes.²⁴ Specifically, researchers examined 32 smokers who consume more than 20 tobacco cigarettes daily. The cartridge of an e-cigarette tested contains 0.25 g of glycerin aqueous solution. Researchers asked each study participant to consume one cartridge per day (more than 150 puffs per day) for 4 weeks. Following the treatment, researchers noted no abnormal changes in blood pressure, hematological data, or blood chemistry, nor any severe adverse events. Although researchers did detect a trace amount of acrolein in the vapor collected from a single cartridge,²⁵ it was less than the minimum amount in the mainstream smoke from a single tobacco cigarette. Importantly, researchers noted that during the use of the electronic cigarette, participants' daily consumption of tobacco cigarettes decreased significantly. Researchers concluded that electronic cigarettes containing glycerin aqueous solution may be a safe alternative to cigarette smoking.
- A 2011 study published in the *Journal of Public Health Policy* concluded that e-cigarettes "dramatically [expand] the potential for harm reduction strategies to achieve substantial health gains."²⁶ Researchers reviewed 16 studies that characterized the components of e-cigarette liquid and vapor using gas chromatography mass spectrometry and determined that e-cigarettes are "a much safer alternative to tobacco cigarettes."
- In a 2014 BMC Public Health research article, a researcher concluded that there is currently no evidence that exposure to e-cigarette vapor would warrant health concerns

²⁴ See Katsuyuki Miura et al., *Safety Assessment of Electronic Cigarettes in Smokers*, 55(1) SEIKATSU EISEI (J. URBAN LIVING & HEALTH ASS'N) 59-64 (2011), available at https://www.jstage.jst.go.jp/article/seikatsueisei/55/1/55_1_59/article.

²⁵ This is because cartridges like these will not be able to deliver 150 puffs without going dry, and thus decomposing the glycerin.

²⁶ See Zachary Cahn & Michael Siegel, *Electronic Cigarettes as a Harm Reduction Strategy for Tobacco Control: A Step Forward or a Repeat of past Mistakes?*, 32 J. PUB. HEALTH POL'Y 16-31 (2011), available at <http://www.palgrave-journals.com/jphp/journal/v32/n1/abs/jphp201041a.html>.

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under current workplace safety standards.²⁷ The researcher extracted more than 9,000 observations of exposure to the aerosols and liquids from electronic cigarettes by reviewing peer reviewed and “grey” literature available on the chemistry of aerosols and liquids used in electronic cigarettes, then compared the exposure levels to Threshold Limit Values (TLV) for workplace exposure. Specifically, the researcher calculated the concentrations of the ingredients/contaminants in the “personal breathing zone,” either based on measured levels of specific compounds in aerosols or using worst case assumptions regarding the chemical content of aerosol and liquids as well as behavior of vapors. These concentrations were then compared to the 2013 Threshold Limit Values (TLVs) from the American Conference of Governmental Industrial Hygienists to establish whether the exposure levels presented a health concern. The researcher determined that there is no evidence that vaping produces inhalable exposures to aerosol contaminants at levels of public health concern when evaluated against standards for workplace exposure. Most of the predicted exposures were less than one percent of TLV. Predicted exposures to acrolein and formaldehyde were less than five percent of TLV.

- Unlike cigarettes, e-cigarettes are not a source of combustion toxicants. Researchers measured several markers of secondhand exposure, including nicotine, aerosol particles, carbon monoxide, and volatile organic compounds in an exposure chamber by generating e-cigarette vapor from multiple brands of e-cigarette.²⁸ The results showed that e-cigarette vapor is a source of second hand exposure to nicotine, but at 10 times lower concentrations than from secondhand cigarette smoke. Of note, secondhand exposure to nicotine has not been implicated as a cause for any adverse health effect and cannot lead to addiction.
- A 2012 study identified and quantified the chemicals released on a closed environment from the use of e-cigarettes (ClearStream-AIR).²⁹ Researchers conducted this study in a 60m³ closed-room. Researchers organized two 5-hour sessions, the first using 5 smokers and the second using 5 users of e-cigarettes. Between sessions, the room was cleaned

²⁷ Igor Burstyn, *Peering Through the Mist: Systemic Review of What the Chemistry of Contaminants in Electronic Cigarettes Tells Us about Health Risks*, 14 BMC PUB. HEALTH 18 (2014), available at <http://www.biomedcentral.com/content/pdf/1471-2458-14-18.pdf>.

²⁸ See Jan Czogala et al., *Secondhand Exposure to Vapors from Electronic Cigarettes*, 16(6) NICOTINE TOB. RES. 655-662 (2014), available at <http://ntr.oxfordjournals.org/content/16/6/655>.

²⁹ See G. Romagna et al., *Characterization of Chemicals Released to the Environment by Electronic Cigarettes Use* (2012).

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and ventilated for 65 hours. Smokers used cigarettes containing 0.6mg of nicotine while e-cigarette users used commercially available liquid (FlavourArt) with nicotine concentration of 11mg/ml. Researchers measured total organic carbon (TOC), toluene, xylene, carbon monoxide (CO), nitrogen oxides (NOx), nicotine, acrolein, poly-aromatic hydrocarbons (PAHs) glycerin and propylene glycol levels on the air of the room. Researchers observed that during the smoking session, 19 cigarettes were smoked, administering 11.4 mg of nicotine (according to cigarette pack information). During the e-cigarette session, researchers noted that 1.6 ml of liquid was consumed, administering 17.6 mg of nicotine. During the smoking session, researchers found: TOC=6.66 mg/m³, toluene=1.7 µg/m³, xylene=0.2 µg/m³, CO=11 mg/m³, nicotine=34 µg/m³, acrolein=20 µg/ml and PAH=9.4 µg/m³. No glycerin, propylene glycol and NOx were detected after the smoking session. During the e-cigarette session, researchers found: TOC=0.73 mg/m³ and glycerin=72 µg/m³. No toluene, xylene, CO, NOx, nicotine, acrolein or PAHs were detected on room air during the e-cigarette session. The researchers concluded that passive vaping is expected from the use of e-cigarettes, but the quality and quantity of chemicals released to the environment from e-cigarettes are far less harmful for human health as compared to regular tobacco cigarettes. Researchers noted that probable reasons for the difference in results are: evaporation instead of burning, absence of several harmful chemicals from the liquids and absence of sidestream smoking from the use of the e-cigarette.

- In an article published in the Critical Reviews in Toxicology, researchers reviewed the toxicological profiles of propylene glycol (PG), dipropylene glycol (DPG), tripropylene glycol (TPG) and polypropylene glycols (PPG; including tetra-rich oligomers) are collectively reviewed, and assessed considering regulatory toxicology endpoints.³⁰ The authors found that the metabolism of these compounds share common pathways, justifying a read-across approach to describing expected hazard potential from data gaps that may exist for specific oligomers, and a consistent toxicity profile. None of the glycols reviewed presented evidence of carcinogenic, mutagenic or reproductive/developmental toxicity potential to humans. The pathologies reported in some animal studies either occurred at doses that exceeded experimental guidelines, or involved mechanisms that are likely irrelevant to human physiology and therefore are not pertinent to the exposures experienced by consumers or workers. The authors concluded that the existing safety evaluations of the FDA, USEPA, NTP and ATSDR for these compounds are consistent and are evidence that the propylene glycols present a very low risk to human health.

³⁰ See Fowles, Jeff et al., *A Toxicological Review of the Propylene Glycols*, 43(4) CRIT. REV. TOXICOL. 363-390 (2013).

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- A laboratory study presented at the annual meeting of the Society of Toxicology on March 24-27, 2014 provides important new evidence that electronic cigarettes have the potential to deliver nicotine with a high degree of relative safety.³¹ Specifically, the study reports that a high-technology brand of electronic cigarette (VUSE) delivers an aerosol that has no detectable carcinogens or metals - compounds that were of concern in a number of other e-cigarette brands. In the study, researchers from R.J. Reynolds Tobacco Company and the Eurofins-Lancaster Laboratories in Winston-Salem examined the constituents in the aerosol produced by VUSE electronic cigarettes. Of particular concern were a number of carcinogens, metals, and volatile compounds found in previous studies of different electronic cigarette brands. The study chromatographically profiled the chemical constituents of VUSE aerosol. The study reported that chemicals including tobacco-specific nitrosamines, carbonyls, metals, volatile organic compounds, poly-aromatic amines, polyaromatic hydrocarbons were all below either the limit of detection or limit of quantification of the laboratory methods used. In contrast, most of these compounds were detected in tobacco cigarettes in very high levels. The study concluded that the composition of VUSE aerosol is much less complex than that of tobacco smoke, that the main compounds detected are those predicted to be present (i.e., those present in the e-liquid), and that none of the toxicants of specific concern were detectable in the electronic cigarette aerosol.

Accordingly, based on growing evidence from around the world, there is little doubt that e-cigarettes and the e-liquid used in them are demonstrably less harmful for the individual consumer compared tobacco leaf-containing products, especially combusted products.

VI. E-Cigarette Impact on Smoking Initiation and Cessation Rates among Adults and Adolescents

There is also a growing body of evidence that e-cigarette use has no adverse impact on overall smoking initiation and cessation rates, and has actually contributed to the continually declining adolescent smoking rate, which is at an all-time low in the United States. Based on this data it is clear that not only are e-cigarettes and the e-liquids used in them less harmful for

³¹ See Michael Siegel, *Laboratory Study Shows No Detectable Carcinogens or Metals in High-Technology Electronic Cigarette Brand, Suggests that Minimal Risk E-Cigarette is Technologically Feasible* (Mar. 31, 2014), <http://tobaccoanalysis.blogspot.com/2014/03/laboratory-study-shows-no-detectable.html> (citing E. H. Theophilus et al., VUSE Electronic Cigarette Aerosol Characterization (Poster), Presented at the Annual Meeting of the Society of Toxicology (March 24-27, 2014)).

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individual tobacco users compared to tobacco-leaf products, they also provide a net positive population level “public health” impact.

FDA and the Centers for Disease Control and Prevention (CDC) recently highlighted findings from the 2014 National Youth Tobacco Survey (NYTS) showing that the number of middle and high school students who have used an e-cigarette at least once in the past 30 days has tripled since 2011 (from 1.1% to 3.9% of middle school students and 4.5% to 13.4% of high school students).³² What both Agencies failed to focus on was the fact that the survey clearly showed that while e-cigarette use (mainly experimentation³³) has increased among adolescents, the cigarette smoking rate among the same population has declined dramatically, to all-time low levels.³⁴ Rather than focusing on this positive development, the Agencies conflated e-cigarette use with all other tobacco use, and focused on the fact that “overall current use of tobacco products” has not changed. Considering that vaping is significantly less harmful than smoking, as documented above, conflating the use of the two products and implying they are equally harmful could itself have adverse public health consequences. Risk communication expert Peter

³² René A. Arrazola et al., CDC, *Tobacco Use among Middle and High School Students – United States, 2011–2014*, 64 ERRATA 426 (April 24, 2015), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6414a3.htm?s_cid=mm6414a3_w.

³³ A recent study published in *Tobacco Control* evaluated patterns of e-cigarette use by investigating the number of days out of the past 30 days when adults had used e-cigarettes. The analysis found that use ≤ 5 days in the past 30 days demarcated a cluster of infrequent users at the low end of the distribution. Among those with use in the past 30 days, infrequent users were the majorities of current (59%) and never smokers (89.5%), but fewer than half of former smokers (43.2%). Infrequent users were more likely to cite curiosity and less likely to cite quitting/cutting down other tobacco use as reasons for use. The study concluded that defining adult prevalence as any use in the past 30 days may include experimenters unlikely to continue use, and is of questionable utility for population surveillance of public health trends over time. Defining prevalence as > 5 days excludes those infrequent users. See Amato, Michael S., Boyle, Rayond G., and Levy, David, *How to define e-cigarette prevalence? Finding clues in the use frequency distribution*, Tob Control doi:10.1136/tobaccocontrol-2015-052236, abstract available online at: <http://tobaccocontrol.bmj.com/content/early/2015/05/15/tobaccocontrol-2015-052236.abstract>.

³⁴ Please note that neither AEMSA nor any of its Members support the sale of e-cigarettes or e-liquids to anyone under the legal age of purchase. We further agree that marketing imagery, nomenclature, and product naming must not target persons under the legal age of purchase.

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M. Sandman recently noted that in any other context, taking a position akin to this would be laughable³⁵:

- Imagine that teenage pregnancy was down and oral sex was up, and the U.S. government stressed that there was no change in overall teen sexuality and all sexual activity has risks.
- Imagine that sales of energy-wasting appliances were down and sales of energy-saving appliances were up, and the U.S. government pointed out that overall appliance sales were flat and all appliances use energy.
- Imagine that motorcycle riding without helmets was down and motorcycle riding with helmets was up, and a U.S. government report on the trend focused on no change in overall motorcycle riding.
- Imagine that gun battles were down and fisticuffs were up, and the U.S. government stayed steadfastly fixated on no change in overall violent behavior.

Regardless, the absence of any change in overall current use of tobacco products (assuming, *arguendo*, that e-cigarettes use is tobacco use) should not obscure the substantial decline in overall current use of combustible tobacco products. Even with the growing popularity of hookahs, fewer kids are *smoking* tobacco in 2014 than in 2011.³⁶ Indeed, total smoking (e.g., use of hookahs, cigarettes, cigars, pipes and bidis) went down from 2011 to 2014, even though hookah use itself went up:

³⁵ See Peter M. Sandman, *On Kids' Overall Use of Tobacco Products* in *A Promising Candidate for Most Dangerously Dishonest Public Health News Release of the Year* (May 27, 2015), <http://www.psandman.com/col/e-cigs.htm>.

³⁶ See Peter M. Sandman, *On Kids' Overall Use of Tobacco Products* in *A Promising Candidate for Most Dangerously Dishonest Public Health News Release of the Year* (May 27, 2015), <http://www.psandman.com/col/e-cigs.htm#kids>.

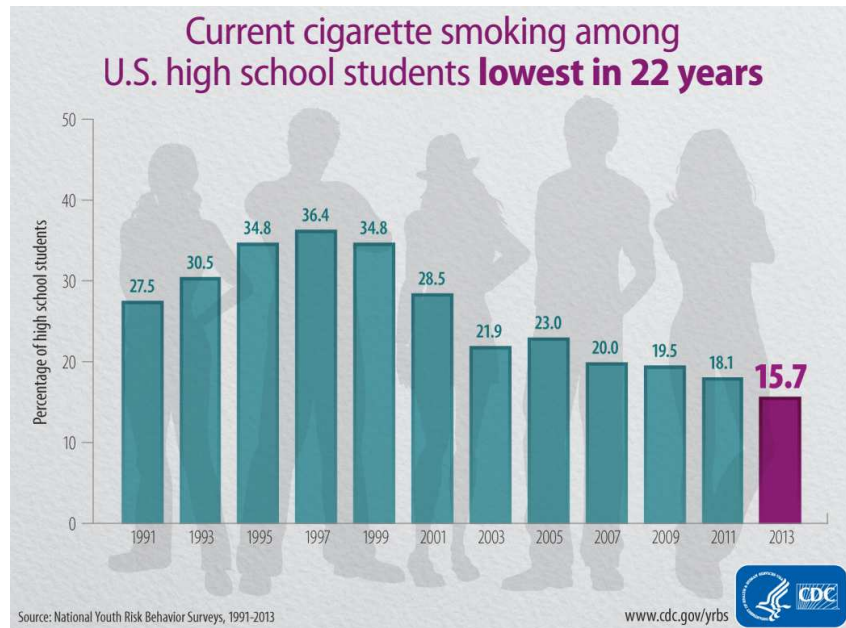
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Combustible Tobacco Product Type	Percentage of High School Users from 2011 to 2014	Percentage Increase or Decrease between 2011 and 2014
Hookahs	4.1% to 9.4%	+5.3%
Cigarettes	15.8% to 9.2%	-6.6%
Cigars	11.6% to 8.2%	-3.4%
Pipes	4.0% to 1.5%	-2.5%
Bidis	2.0% to 0.9%	-1.1%

In 2013, CDC actually highlighted the fact that current cigarette smoking among U.S. high school students was the lowest in 22 years with the following graphic:³⁷

³⁷ CDC, *Current Cigarette Smoking among U.S. high School Students Lowest in 22 Years*, <http://www.cdc.gov/media/releases/2014/images/p0612-YRBS.pdf> (last visited July 1, 2015).

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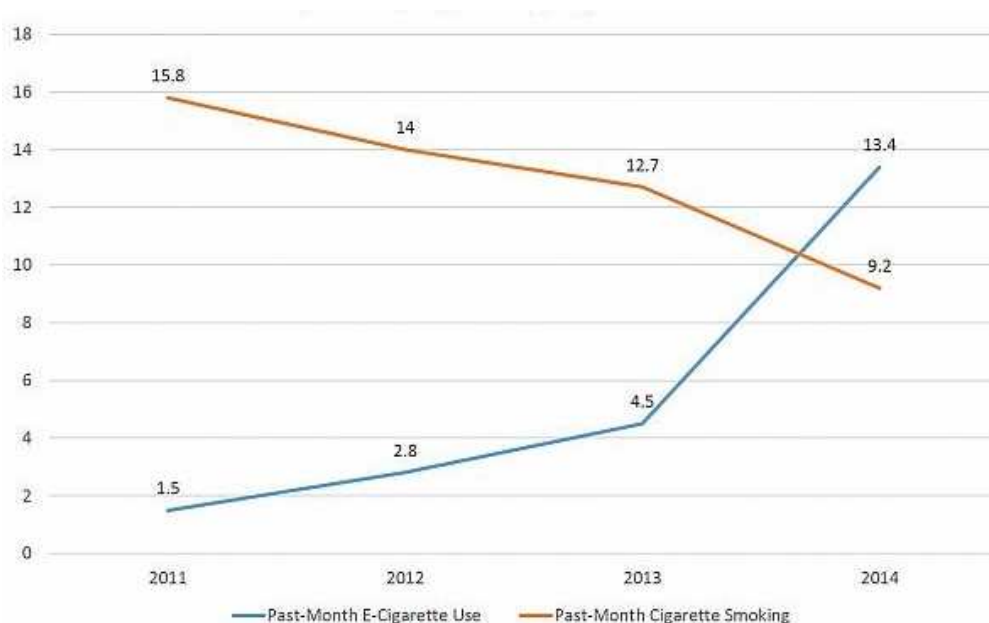


The graphic goes back to 1991, and shows that following a peak of 36.4% in 1997, the high school smoking rate began to decline and plateaued at just under 22% by 2007, and a slower trend downward to 18.1 by 2011. In 2013, when the high school smoking rate dropped to a then record 15.7% – more than a 13% drop in one year – CDC praised the effectiveness of its own anti-tobacco advertising campaign. What CDC did not mention then, and what the above graphic does not show, is that e-cigarettes actually entered the U.S. market beginning in 2007. Many suspected the real reason the smoking rate was suddenly dropping so rapidly was because youth were replacing their cigarettes with e-cigarettes.

The newly released 2014 level for youth smoking at 9.2% represents a 41% drop from 2013, i.e., an even quicker abandonment of smoking. But rather than claiming that their ads have been even more effective than they were last year, CDC is shifting focus by raising the alarm about the dangers of e-cigarette use and the unsubstantiated potential that these products could result in a gateway to smoking.

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We agree that more data is needed to confirm that vaping is replacing smoking for many teenagers, but there is no doubt that as teenage smoking continues to fall so does the viability of the argument that these products are a gateway to smoking³⁸:



Insofar as these results provide evidence about whether e-cigarette use is a gateway to smoking or a *replacement* for smoking, the data suggests that in adolescents, at least so far, the replacement hypothesis is the likelier of the two.

Placed in the proper context, the NYTS actually demonstrates that e-cigarettes can be a tool for tobacco harm reduction. The dramatic decline in both overall and youth smoking rates corresponds directly with the increase in e-cigarette use over the last few years, demonstrating the public health benefit these products provide. Beyond the NYTS, there is a growing body of evidence in the public literature that demonstrates that e-cigarettes and the e-liquid used in them are having a net positive population-level impact by providing a significantly less harmful source of nicotine for current tobacco users and cigarette smokers, and are not having the “gateway” effect to cigarettes feared by many. We highlight some of these studies below:

³⁸ See Jacob Sullum, *E-Cigarettes Are Not Tobacco Products: The CDC Misleads the Public About the Hazards of Vaping*, REASONS.COM (Apr. 27, 2015), <http://reason.com/archives/2015/04/27/e-cigarettes-are-not-tobacco-products#.zmf3lk:fcwT>.

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- A recent survey in England published in the journal of Nicotine and Tobacco Research found that children aged 11 to 16 who have never smoked do not regularly use e-cigarettes. Regular e-cigarette use was found only in children who also smoked tobacco. Experimental e-cigarette use among non-smoking children was low at 3%:

Youth Tobacco Policy Survey - 11-16 year olds, Aug-Sept 2014³⁹

	Prevalence of e-cigarette use in 1,205 UK teenagers
Ever use	12%
More than monthly	2%
More than weekly	1%
Ever use never smokers	3%
Regular use never smokers	0%
*regular use in never smokers was defined as 'at least monthly'	

- A study in England published in the journal *Addiction* found that smokers trying to quit were substantially more likely to succeed if they used e-cigarettes than over-the-counter therapies such as nicotine patches or gum.⁴⁰ Two randomized controlled trials were conducted and suggested that while many factors could influence real-world effectiveness, e-cigarettes can aid smoking cessation. The study included 5,863 adults who had smoked within the previous 12 months and made at least one quit attempt during that period with either an e-cigarette only (n=464), NRT bought over-the-counter only (n=1922) or no aid in their most recent quit attempt (n=3477). About a fifth of those who

³⁹ See Press Release, Cancer Research UK, *Research Shows Most Children Do Not Regularly Use E-Cigarettes* (June 12, 2015), <http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2015-06-12-research-shows-most-children-do-not-regularly-use-e-cigarettes>.

⁴⁰ See Jamie Brown et al., *Real-World Effectiveness of E-Cigarettes When Used to Aid Smoking Cessation: A Cross-Sectional Population Study*, 109 ADDICTION 1531-1540 (2014), available at <http://onlinelibrary.wiley.com/doi/10.1111/add.12623/abstract>.

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said they were using e-cigarettes had stopped smoking at the time of the survey, compared with about a tenth of people who had used patches and gum. More specifically, e-cigarette users were more likely to report abstinence than either those who used NRT bought over-the-counter (odds ratio 2.23, 95% confidence interval 1.70 to 2.93, 20.0% vs. 10.1%) or no aid (odds ratio 1.38, 95% confidence interval 1.08 to 1.76, 20.0% vs. 15.4%). The adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% confidence interval 1.17 to 2.27) times higher compared with users of NRT bought over-the-counter and 1.61 (95% confidence interval 1.19 to 2.18) times higher compared with those using no aid. The study authors concluded that among smokers who have attempted to stop without professional support, those who use e-cigarettes are more likely to report continued abstinence than those who used a licensed NRT product bought over-the-counter or no aid to cessation. This difference persists after adjusting for a range of smoker characteristics such as nicotine dependence.

- Another recent study from England also suggests that e-cigarettes are helping to accelerate smoking cessation, rather than hinder it.⁴¹ According to this study, the prevalence of e-cigarette use began to rapidly increase in 2012 and has continued to climb steadily through the first quarter of 2014. The key finding from the study is that the annual rate of smoking cessation (that is, the percentage of current smokers who quit smoking during the past year), which had reached a low of 4.6% in 2011, increased markedly to 6.2% in 2012, 6.1% in 2013, and 8.7% for the first quarter of 2014, concomitant with the dramatic rise in e-cigarette use among these smokers. The proliferation of electronic cigarettes in England has also been associated with a dramatic increase in the proportion of smokers who tried to stop in the past year (from 33.5% in 2011 to 40.3% in 2014) and an increase in the success rate for smokers who tried to quit (from 13.7% in 2011 to 21.4% in 2014). The proliferation of e-cigarettes was also associated with an acceleration in the decline in smoking prevalence. Taken together, these data suggest that the widespread use of e-cigarettes among smokers in England has advanced the degree of smoking cessation.⁴²

⁴¹ See R. West, J. Brown & E. Beard, *Trends in Electronic Cigarette Use in England*, Smoking Toolkit Study, London: University College London, (April 4, 2014), available at <http://www.smokinginengland.info/latest-statistics/>.

⁴² See Michael Siegel, *New Data from England Suggest that Electronic Cigarettes are Helping to Accelerate Smoking Cessation, Not Hinder It* (Apr. 10, 2014), <http://tobaccoanalysis.blogspot.com/2014/04/new-data-from-england-suggest-that.html> (providing analysis on *Trends in Electronic Cigarette Use in England*).

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- A survey of more than 19,000 vapers from around the world reported in the International Journal of Environmental Research and Public Health found that almost all of the participants (99.5%) were smokers when they started vaping. Four-fifths of them had stopped smoking completely, while the rest had reduced their cigarette consumption, on average, from 20 to four per day.⁴³ This survey clearly demonstrates that e-cigarettes are reducing harm from tobacco/cigarette use and not acting as a gateway to initiation.
- Respondents from three surveys were recruited from a panel of adults in Britain to estimate prevalence and attitudes of e-cigarettes in England.⁴⁴ Preliminary online and face-to-face qualitative research informed the development of a smokers' survey (486 smokers who had used e-cigarettes and 894 smokers who had not). Representative samples of adults in Britain were then constructed from the panel for population surveys in 2010 (12,597 adults, including 2,297 smokers) and 2012 (12,432 adults, including 2,093 smokers), generating estimates of the prevalence of e-cigarette use and trial in Great Britain. Awareness, trial, and current use increased between 2010 and 2012; for example, current use more than doubled from 2.7% of smokers in 2010 to 6.7% in 2012. The proportion of ever-users currently using e-cigarettes was around one-third in both years. In 2012, 1.1% of ex-smokers reported current e-cigarette use, and a further 2.7% reported past use. Approximately 0.5% of never-smokers reported having tried e-cigarettes. The authors concluded that there was evidence supporting the view that e-cigarette use may be a bridge to quitting and that there was little evidence of e-cigarette use among adults who had never smoked.
- In one of the first studies to examine the hypothesis that e-cigarettes are a gateway for youth to become addicted to cigarettes, Dr. Theodore Wagener from the University of Oklahoma Health Sciences Center reports being able to find only one young person who initiated nicotine use with e-cigarettes and then went on to smoke cigarettes, out of a

⁴³ See Konstantinos E. Farsalinos et al., *Characteristics, Perceived Side Effects and Benefits of Electronic Cigarette Use: A Worldwide Survey of More than 19,000 Consumers*, 11(4) INT. J. ENVIRON. RES. PUB. HEALTH 4356-4373 (2014), available at <http://www.ncbi.nlm.nih.gov/pubmed/24758891>.

⁴⁴ See Martin Dockrell et al., *E-Cigarettes: Prevalence and Attitudes in Great Britain*, 15(10) NICOTINE TOB. RES. 1737-1744 (2013), available at <http://www.ncbi.nlm.nih.gov/pubmed/23703732>.

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sample of 1,300 college students.⁴⁵ Overall, 43 students said their first nicotine product was an e-cigarette. Of that group, only one person said they went on to smoke regular cigarettes. And the vast majority who started with e-cigarettes said they weren't currently using any nicotine or tobacco. This study provides preliminary evidence that electronic cigarettes are not currently serving as a major gateway to cigarette smoking.⁴⁶ Similarly, in national survey of 3,240 adults to determine use and awareness of emerging tobacco products (e.g., snus, waterpipe, dissolvable tobacco, and e-cigarettes), only 6 (six) non-smokers, out of a total of 2,000 non-smokers in the sample, had ever used e-cigarettes.⁴⁷

- Self-administered written surveys assessing tobacco use behaviors were conducted in two large U.S. suburban high schools. The surveys demonstrated that, while the use of e-cigarettes increased among the students, such increase was primarily observed in students who were already smoking cigarettes.⁴⁸ Specifically, the prevalence of e-cigarette use during the previous 30 days increased from 0.9% in February 2010 to 2.3% in June 2011 ($p = 0.009$). This is an indication of harm reduction, however, as current cigarette smokers had increased odds of e-cigarette use. When adjusted for school, grade, sex, race and smoking status, students in October 2010 and June 2011 had increased odds of past-30 day use of e-cigarettes compared to February 2010. The

⁴⁵ See Brenda Goodman, *E-Cigarettes May Not Be Gateway to Smoking: Study*, HEALTHDAY.COM (Oct. 29, 2013), <http://consumer.healthday.com/cancer-information-5/tobacco-and-kids-health-news-662/e-cigarettes-may-not-be-gateway-to-smoking-study-681597.html>.

⁴⁶ For more analysis of this study, See Michael Siegel, *First Study to Examine E-Cigarette Gateway Hypothesis Can Find Only One Nonsmoker Who Initiated with E-Cigs and Went on to Smoke* (Oct. 31, 2013), <http://tobaccoanalysis.blogspot.com.au/2013/10/first-study-to-examine-e-cigarette.html>.

⁴⁷ See Robert McMillen, Jeomi Maduka & Jonathan Winickoff, *Use of Emerging Tobacco Products in the United States*, 2012 J. ENVIRON. & PUB. HEALTH (2012), available at <http://www.hindawi.com/journals/jep/2012/989474/>; Michael Siegel, *National Study of Adults Can Find Only Six Nonsmokers Who Have Ever Tried Electronic Cigarettes*, (May 8, 2013), <http://tobaccoanalysis.blogspot.com/2013/05/national-study-of-adults-can-find-only.html> (providing analysis of study referenced in *Use of Emerging Tobacco Products in the United States*).

⁴⁸ See Deepa R. Camenga et al., *Trends in Use of Electronic Nicotine Delivery Systems by Adolescents*, 39 ADDICTIVE BEHAVIORS 338-340 (2014), available at <http://www.sciencedirect.com/science/article/pii/S0306460313002736>.

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prevalence of e-cigarette use doubled in the sample of high school students, but current cigarette smoking was the strongest predictor of current use.

- A prospective 6-month pilot study conducted in Catania, Italy examined the effect of e-cigarettes on smoking reduction and cessation and demonstrated that the use of e-cigarettes helps smokers, not intending to quit, to remain abstinent or reduce their cigarette consumption.⁴⁹ The execution of this study involved monitoring possible modifications in the smoking habits of 40 regular smokers (unwilling to quit) by experimenting the 'Categoria' e-cigarette with a focus on smoking reduction and smoking abstinence. Study participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. At each visit, product use, number of cigarettes smoked, and exhaled carbon monoxide (eCO) levels were all measured. In addition, smoking reduction and abstinence rates were calculated and adverse events and product preferences were also reviewed. The researchers found a sustained 50% reduction and smoking abstinence in 22/40 (55%) participants, with an overall 88% reduction in cigarettes/day. Although mouth (20.6%) and throat (32.4%) irritation, and dry cough (32.4%) were common, these side effects diminished substantially by week-24. Overall, two to three cartridges/day were used throughout the study and participants' perception and acceptance of the product was good. The researchers concluded that the use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit.
- A 2011 study conducted in Philadelphia, Pennsylvania surveyed experienced e-cigarette users in the interest of identifying the e-cigarette products used by experienced e-cigarette users, their pattern of e-cigarette use and the impact on tobacco use. Specifically, the study involved face-to-face surveys of 104 experienced e-cigarette users. Researchers found that 78% of participants had not used any tobacco in the prior 30 days. Researchers noted that these e-cigarette users had previously smoked an average of 25 cigarettes per day and had tried to quit smoking an average of nine times before they started using e-cigarettes. Researchers also observed that two-thirds of e-cigarette users had previously tried to quit smoking using an FDA-approved smoking cessation NRT products. The majority of the sample in this study had used e-cigarettes daily for at least a year and three quarters started using e-cigarettes with the intention of quitting smoking. Notably, almost all participants who identified as e-cigarette users felt that the e-cigarette

⁴⁹ See Riccardo Polosa et al., *Effect of an Electronic Nicotine Delivery Device (E-Cigarette) on Smoking Reduction and Cessation: A Prospective 6-Month Pilot Study*, 11 BMC PUB. HEALTH 786 (2011), available at <http://www.biomedcentral.com/content/pdf/1471-2458-11-786.pdf>.

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had helped them to succeed in quitting smoking. Researchers further noted that most participants used advanced vaporizers which are designed to enable the atomizer to more consistently achieve a more satisfying vapor. Researchers concluded that further evidence should be collected regarding the safety and efficacy of e-cigarettes for smoking cessation and that until then, smokers should use proven treatments such as counseling and FDA-approved medicines. Nevertheless, the researchers also concluded that smokers who successfully switch to e-cigarettes, should continue vaping e-cigarettes and not revert to smoking cigarettes.⁵⁰

- A 2011 internet survey in English and French examined 3,587 participants (70% former tobacco smokers, 61% men, mean age 41 years) to assess the profile, utilization patterns, satisfaction and perceived effects among users of e-cigarettes.⁵¹ The researchers observed that the median duration of e-cigarette use was 3 months, users drew 120 puffs/day and used five refills/day. Most participants (96%) said the e-cigarette helped them to quit smoking or reduce their smoking (92%). Reasons for using the e-cigarette included the perception that it was less toxic than tobacco (84%), to deal with craving for tobacco (79%) and withdrawal symptoms (67%), to quit smoking or avoid relapsing (77%), because it was cheaper than smoking (57%) and to deal with situations where smoking was prohibited (39%). Most ex-smokers (79%) feared they might relapse to smoking if they stopped using the e-cigarette. Users of nicotine-containing e-cigarettes reported better relief of withdrawal and a greater effect on smoking cessation than those using non-nicotine e-cigarettes. The researchers concluded that participants used e-cigarettes similar to people who take nicotine replacement medications – by former smokers to avoid relapse or as an aid to cut down or quit smoking.
- A 2012 study examined the effects of the White Super e-cigarette on desire to smoke, nicotine withdrawal symptoms, attention and working memory.⁵² Researchers selected

⁵⁰ See J. Foulds, S. Veldheer & A. Berg, *Electronic Cigarettes (E-Cigs): Views of Aficionados and Clinical/Public Health Perspectives*, 65(10) INT'L. J. CLIN. PRACT. 1037-1042 (2011), available at <http://www.ncbi.nlm.nih.gov/pubmed/21801287>.

⁵¹ See Jean-François Etter & Chris Bullen, *Electronic Cigarette: Users Profile, Utilization, Satisfaction and Perceived Efficacy*, 106(11) ADDICTION 2017-2028 (2011), available at <http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2011.03505.x/abstract>.

⁵² See Dawkins, L., et al., *The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition*, 37(8) ADDICT BEHAV. 970-973 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22503574>.

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eighty-six smokers, and randomly allocated them to either: 18 mg nicotine e-cigarette (nicotine), 0 mg e-cigarette (placebo), or just hold the e-cigarette (just hold) conditions. Participants rated their desire to smoke and withdrawal symptoms at baseline (T1), and five (T2) and twenty (T3) minutes after using the e-cigarette ad libitum for 5 min. A subset of participants completed the Letter Cancellation and Brown-Peterson Working Memory Tasks. Researchers found that after 20 minutes, compared with the just hold group, desire to smoke and some aspects of nicotine withdrawal were significantly reduced in the nicotine and placebo group; the nicotine e-cigarette was superior to placebo in males but not in females. Researchers also determined that the nicotine e-cigarette also improved working memory performance compared with placebo at the longer interference intervals. There was no effect of nicotine on Letter Cancellation performance. Researchers concluded that the White Super e-cigarette alleviated desire to smoke and withdrawal symptoms 20 min after use although the nicotine content was more important for males.

- Based on data gathered from a national online study of 2,649 adults and the Legacy Longitudinal Smoker Cohort study of 3,658 adults, researchers used multivariable models to examine e-cigarette awareness, use, and harm perceptions.⁵³ In the online survey, 40.2% (95% confidence interval [CI] = 37.3, 43.1) had heard of e-cigarettes, with awareness highest among current smokers. Utilization was higher among current smokers (11.4%; 95% CI = 9.3, 14.0) than in the total population (3.4%; 95% CI = 2.6, 4.2), with 2.0% (95% CI = 1.0, 3.8) of former smokers and 0.8% (95% CI = 0.35, 1.7) of never-smokers ever using e-cigarettes. The study authors concluded that awareness of e-cigarettes is high, and use among current and former smokers is evident.
- A study published in 2012 examined e-cigarette use among teenagers and young adults in Poland, and concluded that most youth that tried e-cigarettes and previously smoked.⁵⁴ The researchers conducted a survey with a cluster sample of 20,240 students enrolled at 176 nationally representative Polish high schools and universities between September 2010 and June 2011. To estimate national e-cigarette prevalence among various demographic groups, researchers used population weights. In addition, researchers used

⁵³ See Jennifer L. Pearson et al., *E-Cigarette Awareness, Use, and Harm Perceptions in U.S. Adults*, 102(9) AM. J. PUB. HEALTH 1758-1766 (2012), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474361/>.

⁵⁴ See M.L. Goniewicz & W. Zielinska-Danch, *EleCtronic Cigarette Use among Teenagers and Young Adults in Poland*, 130(4) PEDIATRICS e879-885 (2012), available at <http://www.ncbi.nlm.nih.gov/pubmed/22987874>.

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multiple logistic regression to evaluate which demographic factors were independent predictors of two outcomes: ever use of e-cigarettes and use in the previous 30 days. The researchers found that among high school students, aged 15 to 19 years, 23.5% had ever used e-cigarettes and 8.2% had done so within the previous 30 days. Among those in universities, aged 20 to 24 years, 19.0% had ever used an e-cigarette and 5.9% had done so in the previous 30 days. In multivariate analyses that controlled for covariates, smoking cigarettes, male gender, living in an urban area, and having parents who smoke were associated with ever using e-cigarettes. Overall, 3.2% of students who had never smoked reported ever using e-cigarettes. The researchers concluded that about one-fifth of Polish youth have tried e-cigarettes; most of whom previously smoked cigarettes. This study shows the potential for harm reduction that e-cigarettes provide.

- In another study in Poland conducted in 2013, the patterns and effects of e-cigarette use and user beliefs about safety and benefits were examined.⁵⁵ Researchers recruited 179 e-cigarette users in Poland online and asked about their smoking history, patterns of e-cigarette use, beliefs and attitudes regarding the product and information on concurrent use of conventional cigarettes. Sixty-six percent (66%) were no longer smoking conventional cigarettes and twenty-five (25%) had reduced their consumption to less than five cigarettes a day. Most participants (82%) did not think that e-cigarettes were completely safe, but correctly understood that they are less dangerous than conventional cigarettes. The study found that the participants primarily used e-cigarettes to assist their efforts to stop smoking or as an alternative to conventional cigarettes; the majority of participants reported that they successfully stopped smoking.
- A 2011 study conducted in Italy examined the association between nicotine dependence and depression in two subjects.⁵⁶ Specifically, researchers conducted a case study of two heavy smokers with an established history of depression. Both subjects had previously attempted intensive smoking cessation programs with no success. Researchers found, however, that e-cigarette use led each to successfully quit smoking. Although the researchers acknowledge that the findings cannot be generalized, they note that high quit

⁵⁵ See M.L. Goniewicz et al., *Patterns of Electronic Cigarette Use and User Beliefs About Their Safety and Benefits: An Internet Survey*, 32(2) DRUG ALCOHOL REV. 133-140 (2013), available at <http://www.ncbi.nlm.nih.gov/pubmed/22994631>.

⁵⁶ See Pasquale Caponnetto et al., *Smoking Cessation with E-Cigarettes in Smokers with a Documented History of Depression and Recurring Relapses*, 2(3) INT'L J. CLINICAL MEDICINE 281-284 (2011), available at <http://www.scirp.org/journal/PaperInformation.aspx?PaperID=6134#.U9kbLxCORWw>.

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rates would be desirable among smokers suffering from depression (who generally respond poorly to smoking cessation efforts) and that, therefore, additional studies should be conducted to explore whether e-cigarette use should be considered as a potential tool to aid in smoking cessation.

- A 2013 U.S. population survey revealed that current smokers were more likely than never-smokers to report use of e-cigarettes.⁵⁷ Survey respondents were asked if they had heard of e-cigarettes, where they heard of e-cigarettes, whether and how often they used e-cigarettes, and why. Responses were weighted to represent the entire U.S. population. A high proportion, 75.4%, reported having heard about e-cigarettes. About 8.1% had tried e-cigarettes, and 1.4% were current users. These rates were twice those of snus (4.3% and 0.8%, respectively). Among current smokers, 32.2% had tried e-cigarettes, and 6.3% were current users. Over 80% of current e-cigarette users were non-daily users. Women were significantly more likely to have tried e-cigarettes than men. Those who had tried e-cigarettes were more likely than those who tried snus to report their products being safer than regular cigarettes (49.9% vs. 10.8%). Almost half (49.5%) of current smokers were susceptible to using e-cigarettes in the future. The study authors concluded that e-cigarettes have surpassed snus in adoption rate, even before any promotion by major tobacco companies, suggesting that the former have tapped into smokers' intuitive preference for potentially harm-reducing products, probably due to the product design.
- Researchers from the University of Geneva and the University of Auckland, New Zealand, recruited 477 volunteers from websites devoted to e-cigarettes and/or smoking cessation, and followed their smoking and vaping habits over one-month (477 subjects) and one-year (367 subjects) periods.⁵⁸ At the one-month mark, among the former smokers who were regular e-cigarette users, only 6% had taken up smoking again. Of those who both smoked and used e-cigarettes, 46% had quit smoking by the one-year mark. The study shows that dual use may ultimately lead to smoking cessation.

⁵⁷ See Shu-Hong Zhu et al., *The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population*, 8(10) PLoS ONE e79332 (2013), available at <http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0079332&representation=PDF>.

⁵⁸ See Jean-François Etter & Chris Bullen, *A Longitudinal Study of Electronic Cigarette Users*, 39(20) ADDICT. BEHAV. 491-494 (2014), available at <http://www.sciencedirect.com/science/article/pii/S0306460313003304>.

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- A prospective 12-month double-blind, controlled, randomized clinical study with two different nicotine strengths of a very popular e-cigarette brand was conducted to evaluate smoking reduction, smoking abstinence and adverse events in smokers who were not otherwise intending to quit.⁵⁹ The authors concluded that the use of e-cigarettes, with or without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects. Three hundred smokers were recruited and placed into three equal study groups: Group A received 7.2 mg nicotine cartridges for 12 weeks; Group B received 6-weeks of 7.2 mg nicotine cartridges followed by a further 6-weeks of 5.4 mg nicotine cartridges; and Group C received no-nicotine cartridges for 12 weeks. The study consisted of nine visits during which cigarette day use and exhaled carbon monoxide (eCO) levels were measured. Declines in cigarette per day use and eCO levels were observed at each study visits in all three study groups, with no consistent differences among study groups. Smoking reduction was documented in 22.3% and 10.3% at week 12 and week 52 respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week 12 and week 52 respectively, leading to the conclusion that the use of e-cigarettes helped to reduce cigarette consumption and in some cases resulted in tobacco abstinence.
- A year-long study of 14 smokers (not intending to quit) with schizophrenia was conducted to determine impact of e-cigarettes on their smoking behavior and condition.⁶⁰ The study authors concluded that the use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients. Product use, number of cigarettes smoked, carbon monoxide in exhaled breath (eCO) and positive and negative symptoms of schizophrenia levels were measured. Sustained 50% reduction in the number of cigarettes per day at week 52 was shown in 50% of participants, with their median of 30 cigarettes per day decreasing significantly to 15 cigarettes per day. Sustained smoking abstinence at week 52 was observed in 2 participants with combined sustained 50% reduction and smoking abstinence in 9 participants. Overall, one to two e-cigarette cartridges per day were used throughout the

⁵⁹ See Pasquale Caponnetto et al., *Impact of an Electronic Cigarette on Smoking Reduction and Cessation in Schizophrenic Smokers: A Prospective 12-Month Pilot Study*, 10(2) INT'L. J. ENVIRON. RES. PUB. HEALTH 446-461 (2013), available at <http://www.mdpi.com/1660-4601/10/2/446/htm>.

⁶⁰ See Caponnetto P, et al, *Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study*, 10(2) Int J Environ Res Public Health 446-461 (2013), available online at: <http://www.mdpi.com/1660-4601/10/2/446/htm>.

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study. The authors concluded that positive and negative symptoms of schizophrenia are not increased after smoking reduction/cessation in patients using e-cigarettes.

- In a study that sought to characterize e-cigarette use, users, and effects in a sample of Electronic Cigarette Company (TECC) and Totally Wicked E-Liquid (TWEL) users, the authors concluded that e-cigarettes are used primarily for smoking cessation, but for a longer duration than nicotine replacement therapy, and users believe them to be safer than smoking.⁶¹ Respondents (1347) completed a questionnaire regarding their e-cigarette use, and 74% reported not smoking for at least a few weeks since using the e-cigarette and 70% reported a reduced urge to smoke. E-cigarettes were generally considered to be satisfying to use, elicit few side effects, be healthier than smoking, improve cough/breathing, and resulted in low levels of craving. Among ex-smokers, ‘time to first vape’ was significantly longer than “time to first cigarette,” suggesting a lower level of dependence to e-cigarettes. Ex-smokers reported significantly greater reduction in craving than current smokers although few other differences emerged between these groups. Compared with males, females opted more for chocolate/sweet flavors and liked the e-cigarette because it resembles a cigarette.
- A qualitative study was conducted to determine how e-cigarettes compare to NRTs in maintaining cigarette abstinence.⁶² Using focus groups, e-cigarette users discussed their perceptions of e-cigarette efficacy for smoking cessation compared to NRTs. The study sought to explain the popularity of these devices and to shed light on the factors which influence the efficacy of different smoking cessation products. Five themes emerged that describe users’ perceptions of why e-cigarettes are efficacious in quitting smoking: 1) bio-behavioral feedback, 2) social benefits, 3) hobby elements, 4) personal identity, and 5) distinction between smoking cessation and nicotine cessation. The authors concluded that tobacco control practitioners must pay increased attention to the importance of the behavioral and social components of smoking addiction. By addressing these components, in addition to nicotine dependence, e-cigarettes appear to help some cigarette smokers transition to a less harmful replacement tool, thereby maintaining cigarette abstinence.

⁶¹ See Lynne Dawkins et al., *Vaping' Profiles and Preferences: An Online Survey of Electronic Cigarette Users*, 108(6) ADDICTION 1115-1125 (2013), available at <http://onlinelibrary.wiley.com/doi/10.1111/add.12150/abstract>.

⁶² See Amanda M. Barbeau et al., *Perceived Efficacy of E-Cigarettes Versus Nicotine Replacement Therapy among Successful E-Cigarette Users: A Qualitative Approach*, 8(1) ADDICT. SCI. CLIN. PRACT. 5 (2013), available at <http://www.biomedcentral.com/content/pdf/1940-0640-8-5.pdf>.

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- In a survey study conducted across four countries (Canada, U.S., U.K. and Australia), the authors examined patterns of e-cigarette awareness, use, and product-associated beliefs among current and former smokers, concluding that e-cigarettes may have the potential to serve as a smoking cessation aid.⁶³ The study showed that 79.8% reported using e-cigarettes because they were considered less harmful than traditional cigarettes, 75.4% stated that they used e-cigarettes to help them reduce their smoking, and 85.1% reported using e-cigarettes to help them quit smoking.
- A study conducted in 2009 by the Northern Sweden cohort of the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) concluded that the use of e-cigarettes was a significant factor in the low prevalence of smoking, especially among younger men and women in Northern Sweden.⁶⁴
- A 2014 study documented the prevalence of e-cigarette ever use, current use, and established use in a nationally representative survey of 2,236 current and former cigarette smokers in the U.S.⁶⁵ Participants completed a web-based survey in June 2013. The data from that survey was analyzed using multivariate logistic regression, which identified demographic and smoking-related factors associated with each use category. Researchers observed that almost half of the study participants had tried e-cigarettes (46.8%), but prevalence of established use remained low (3.8%). Researchers further observed that although trial of e-cigarettes was highest among daily smokers, it was much more likely for former smokers to identify as an established e-cigarette user. Importantly, the results demonstrated that most/all of the survey's established e-cigarette users who were also former smokers became former smokers by switching to e-cigarettes.

⁶³ See S.E. Adkison et al., *Electronic Nicotine Delivery Systems: International Tobacco Control Four-Country Survey*, 44(3) AM. J. PREV. MED. 207-215 (2013), available at <http://www.ncbi.nlm.nih.gov/pubmed/23415116>.

⁶⁴ See B. Rodu, J.H. Jansson & M. Eliasson, *The Low Prevalence of Smoking in the Northern Sweden MONICA Study*, 41(8) SCAND. J. PUB. HEALTH. 808-811 (2013), available at <http://www.ncbi.nlm.nih.gov/pubmed/24052339>.

⁶⁵ See Daniel P. Giovenco et al., *Factors Associated with E-cigarette Use, a National Population Survey of Current and Former Smokers*, AM. J. PREV. MED. (2014), available at <http://www.ncbi.nlm.nih.gov/pubmed/24880986>.

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- A single-blind randomized trial measured the short-term effects of an e-cigarette on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects.⁶⁶ Study participants included 40 adult dependent smokers of 10 or more cigarettes per day. Researchers randomized study participants to use e-cigarettes containing 16 mg nicotine or 0 mg capsules, Nicorette nicotine inhalator or their usual cigarette on each of four study days 3 days apart, with overnight smoking abstinence before use of each product. Researchers found that over 60 minutes, participants using 16 mg an e-cigarette recorded 0.82 units less desire to smoke than the placebo e-cigarette ($p=0.006$). Researchers did not observe a difference in desire to smoke between the 16 mg e-cigarette and the Nicorette nicotine inhalator. Study participants found e-cigarettes to be more pleasant to use than the inhalator ($p=0.016$) and produced less irritation of mouth and throat ($p<0.001$). Researchers observed that, on average, the e-cigarette increased serum nicotine to a peak of 1.3 ng/mL in 19.6 min, the Nicorette nicotine inhalator to 2.1 ng/ml in 32 min and cigarettes to 13.4 ng/ml in 14.3 min. Researchers concluded that the 16 mg Ruyan V8 e-cigarette alleviated desire to smoke after overnight abstinence, was well tolerated among study participants, and had a pharmacokinetic profile more like the Nicorette nicotine inhalator than a tobacco cigarette.
- Three quarters of e-cigarette users surveyed in a 2012 study reported that using e-cigarettes helped them quit smoking.⁶⁷ The study participants smoked an average of 25 cigarettes per day prior to the study and tried to quit smoking an average of nine times before using e-cigarettes (two-thirds of the participants had previously tried to quit smoking using an FDA-approved smoking cessation product). The majority of the e-cigarette users involved in the study had used e-cigarettes daily for at least a year. Most of the study participants did not use the type of e-cigarette that are commonly sold, i.e., those powered by a single 3.7 volt battery; these users represented only 8% of the study participants. Two-thirds of the participants used e-cigarettes designed to enable the atomizer to achieve hotter, more intense vapor with e-liquids containing medium to high concentrations of nicotine (13 mg +). Due to the results of the survey the study authors have concluded that those who already have switched to e-cigarettes should focus on staying off cigarettes, rather than quitting e-cigarettes.

⁶⁶ See C. Bullen et al., *Effect of an Electronic Nicotine Delivery Device (E Cigarette) on Desire to Smoke and Withdrawal, User Preferences and Nicotine Delivery: Randomised Cross-Over Trial*, 19 TOB. CONTROL 98-103 (2010), available at <http://tobaccocontrol.bmj.com/content/19/2/98.abstract>.

⁶⁷ See M. Leelavathi & S. Das, *Electronic Cigarettes: New Kit on the Rack*, 66(4) INT'L J. CLIN. PRACT. 417 (2012), available at <http://www.ncbi.nlm.nih.gov/pubmed/22420500>.

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- Over two hundred smokers who had tried e-cigarettes were surveyed online to examine the effectiveness of e-cigarettes as a smoking cessation tool.⁶⁸ The primary outcome of interest in the study was the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase. In summary, the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase was 31.0% (95% CI=24.8%, 37.2%). A large percentage of respondents reported a reduction in the number of cigarettes they smoked (66.8%), and almost half reported abstinence from smoking for a period of time (48.8%). The participants that reported using e-cigarettes more than 20 times per day had a quit rate of 70.0%. Of respondents who were not smoking at 6 months, 34.3% were not using e-cigarettes or any nicotine-containing products at the time. The researchers concluded that e-cigarettes are a promising smoking-cessation tool worthy of further study using more rigorous research designs.
- In an Internet study of 81 e-cigarette users in France, Canada, Belgium, and Switzerland, participants answered open-ended questions regarding their use of e-cigarettes, and opinions regarding these products.⁶⁹ Over half of participants (63%) were former smokers; 37% of participants were current smokers. Participants reported using e-cigarettes either to quit smoking, to reduce cigarette consumption, to avoid disturbing other people with secondhand smoke, or to be able to smoke in smoke-free places. There were numerous positive effects associated with e-cigarettes. These included reports that the products are useful in quitting cigarette smoking, and confer the benefits of abstinence from cigarette smoking (less coughing, improved breathing, better physical fitness).

⁶⁸ See Michael B. Siegel et al., *Electronic Cigarettes as a Smoking-Cessation: Tool Results from an Online Survey*, 40(4) AM. J. PREV. MED. 472-475 (2011), available at <http://www.ajpmonline.org/article/S0749-3797%2810%2900792-0/abstract>.

⁶⁹ See Jean-François Etter, *Electronic Cigarettes: A Survey of Users*, 10 BMC PUB. HEALTH 231 (2010), available at <http://www.biomedcentral.com/content/pdf/1471-2458-10-231.pdf> (advocating that further research on e-cigarettes is urgently required, particularly with respect to the efficacy and toxicity of these devices).

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VII. Manufacturers Should Only Have to Demonstrate the Risks and Benefits of Their Unique Product Features and Compliance with Product Standards and Good Manufacturing Practices to Show New Products are Appropriate for the Protection of the Public Health

Assuming that FDA makes a general finding that e-cigarettes, as a class of products, provide a public health benefit and thereby removes the burden of demonstrating the population-level impact of each product from individual companies, AEMSA proposes that FDA create a streamlined PMTA process that focuses on demonstrating the safety on the product on the individual consumer in order to show that the product is appropriate for the protection of the public health. This will be facilitated when FDA discloses science-based industry-specific product standards and Good Manufacturing Practices.

Good Manufacturing Practices or “GMPs” are systems and procedures that are designed to ensure the quality and safe manufacturing of a product. FDA has established GMPs codified in its regulations for food, dietary supplements, drugs and medical devices. With respect to tobacco products, the Tobacco Control Act gives FDA the authority to issue regulations related to tobacco product manufacturing practice in order to protect the public health and to assure that tobacco products are in compliance with the law. Specifically, Section 906(e) of the Act requires that FDA prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing, and storage of tobacco products conform to (i) current GMPs or (ii) hazard analysis and critical control point methodology. Of importance, Section 906(e) also states that the GMP regulations “may differ based on the type of tobacco product involved.”

As noted above, AEMSA is the first and only manufacturers’ trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of e-liquids. One of AEMSA’s primary goals is to provide consumers with higher degrees of confidence that our members’ products are manufactured with professionalism, accuracy and in a safe manner until such time as FDA promulgates GMPs for e-liquids. AEMSA believes that e-liquid manufacturers have the responsibility to:

- Verify the accuracy of nicotine content in e-liquid products;
- Ensure the quality of all ingredients in e-liquid products;
- Prepare e-liquid products in a clean, sanitary and safe environment;
- Ensure e-liquid products are packaged and delivered in a safe manner; and
- Provide a level of transparency into the monitoring and verification process.

These are the core beliefs underlying AEMSA’s manufacturing standards. To assure that the public health is protected and that e-liquids are manufactured in compliance with the

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Tobacco Control Act, FDA should propose for public comment GMPs based on these standards, which will ensure that e-liquids are not contaminated or manufactured in such a way that will result in the products being adulterated or misbranded.

* * *

AEMSA appreciates the opportunity to submit these comments to FDA, and would be glad to discuss these comments at its earliest convenience.

Respectfully submitted,



Jeff Hammel
President
American E-Liquid Manufacturing Standards Association

On behalf of:

AEMSA General Members:

1. 180 Vape – Travis Pharr
2. Azure Vaping – Robert Jack
3. Chuckin' Clouds – Trishcia Braden
4. Ecigcharleston – Joe Atwell
5. EC Blend – Carol Williams
6. Firebrand – Brian Gage
7. Hot Vapes – Tim Roche
8. J Vapes – Jourdan Wheeler
9. Juicy Vapor – Anthony Brancato
10. Madvapes – Scott Church
11. Mister E-Liquid – Dan Lawitzke
12. Molecule Labs – Michael Guasch
13. Mountain Oak Vapors – Steve Nair

14. NicVape – Richard Henning
15. NicQuid – Adam Knudsen
16. Purilum – Bianca Iodice
17. Tampa Vapor – John Synychak
18. Texas Select Vapor – Brett Coppolo
19. The Vapor Bar – Schell Hammel
20. The Vaper's Knoll – Richard Gue
21. Two Peas in a Pod – Orlan Johnson
22. VaporHQ – Adam Black
23. VaporShark – Brandon Leidel
24. Virgin Vapor – Annette Rogers

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3. Konstantinos Farsalinos, M.D.
4. Richard Soltero, Ph.D.

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