Background Paper on E-cigarettes (Electronic Nicotine Delivery Systems)

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EXECUTIVE SUMMARY

- E-cigarettes are evolving rapidly and being marketed like cigarettes were in the 1950s and 1960s
    - Marketing is back on television and radio
    - Aggressive placement in convenience stores (next to candy) and in other stores (next to medications)
- Youth are rapidly adopting e-cigarettes
    - E-cigarettes contain candy flavors (e.g., cherry, chocolate, turkish delight)
    - High levels of dual use
    - Youth who use e-cigarettes are heavier (not lighter) smokers
    - Youth who use e-cigarettes are much less likely to have stopped smoking (OR 0.1-0.2)
    - The temporal and causal relationships between e-cigarette use and smoking have not been determined
- E-cigarettes have not been proven to help people quit smoking
    - Longitudinal population studies show that e-cigarette use is associated with a lower odds of quitting
    - The randomized trial comparing e-cigarettes to nicotine patch shows that in the context of low level behavioral support, the quit rate for those using e-cigarettes is low and similar to those using a nicotine patch
- There is a high level of dual use of e-cigarettes and conventional cigarettes among adults
- The hope that e-cigarettes will reduce harm by delivering "clean" nicotine will not be realized in continuing dual users
    - Continuing to smoke any conventional cigarettes confers essentially the full cardiovascular risk
    - Cancer risk may only be modestly affected because smoking duration is more important than intensity
- E-cigarettes deliver lower levels of toxins than conventional cigarettes, but they still deliver some toxins
- E-cigarettes pollute the air less than conventional cigarettes, but they pollute the air
    - They do not just emit "harmless water vapor"
- People passively exposed to e-cigarettes aerosol absorb nicotine (measured as cotinine), with one study showing levels comparable to passive smokers
- There is little research on direct health effects
    - One study shows short-term pulmonary effects
    - Evidence of cytotoxicity in animal and human *in vitro* test systems
- While the original e-cigarette companies were competing with conventional cigarette companies, all the major cigarette companies are now in the e-cigarette business

- E-cigarette companies are using the same political and public relations strategies as cigarette companies (most notably organizing users, similar to how the cigarette companies organized smokers)
- E-cigarette policy making in many countries is dominated by assumptions about their use (utility as a smoking cessation aid or for harm reduction) that are not supported by the evidence available to date

At minimum, these policies should be implemented immediately:

- Prohibit the use of e-cigarettes anywhere where the use of conventional cigarettes is prohibited
- Apply the same restrictions on e-cigarette advertising and promotion as apply to conventional cigarettes
- Ban the use of characterizing flavors in e-cigarettes
- Prohibit claims that e-cigarettes are effective smoking cessation aids until such time as there is convincing scientific evidence that such claims are true for e-cigarettes as they are actually used in the general population.
- Regulate e-cigarettes to set standards for product performance in order to minimize risks to users and bystanders

Because the product, the market, and the associated scientific evidence surrounding e-cigarettes are all evolving rapidly:

- All legislation and regulations related to e-cigarettes should allow for flexibility to adapt regulations expeditiously in response to new science, including evaluation of different models for regulating e-cigarettes, as it accumulates
- No country or subnational jurisdiction should be compelled to permit the sale of e-cigarettes
- Legislation and regulations regarding e-cigarettes need to take into account the fact that, unlike conventional cigarettes and other tobacco products and medicinal nicotine replacement therapies, e-cigarettes can be altered by users to change the nicotine delivery and be used to deliver other drugs
- There should be transparency in the role of the e-cigarette and tobacco companies in advocating for and against legislation and regulation, both directly and through third parties
- FCTC Article 5.3 should be respected when developing and implementing legislation and regulations related to e-cigarettes

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This document served as one input for discussion on ENDS at the WHO Study Group on Tobacco Product Regulation (TOBREG) meeting in Rio in December, 2013. The interpretation of results and recommendations in the present document represent the opinions of the authors and not necessarily WHO or TOBREG.

BACKGROUND

E-cigarettes (also known as electronic nicotine delivery systems or ENDS) are a class of products intended to deliver nicotine-containing aerosol (incorrectly commonly called “vapor”) to a user by heating a solution typically comprised of propylene glycol and/or glycerol (glycerin), nicotine and flavoring agents (Figure 1). E-cigarettes without nicotine are also available. The first of these devices that started the trend in use we describe in this report was invented by a Chinese pharmacist, Hon Lik, in 2003. The U.S. patent application for the device states that the product is "An electronic atomization cigarette that functions as substitutes (sic) for quitting smoking and cigarette substitutes." (Patent #8,490,628 B2) E-cigarette sales have risen rapidly since they entered the marketplace in2007.(Pauly et al., 2007, Cobb et al., 2010) These products are marketed as healthier alternatives to tobacco smoking, useful in quitting smoking and reducing cigarette consumption, and a method for circumventing smokefree laws and enabling users to "smoke anywhere."(Grana and Ling, in press) Interest in the products has been increasing(Ayers et al., 2011) and an exponential rise in sales over the past 3 years (2010-2013) has been due, at least in part, to widespread advertising via television commercials and print advertisements, that often feature celebrities, for the most popular brands, including those owned by tobacco companies.(Felberbaum, 2013)

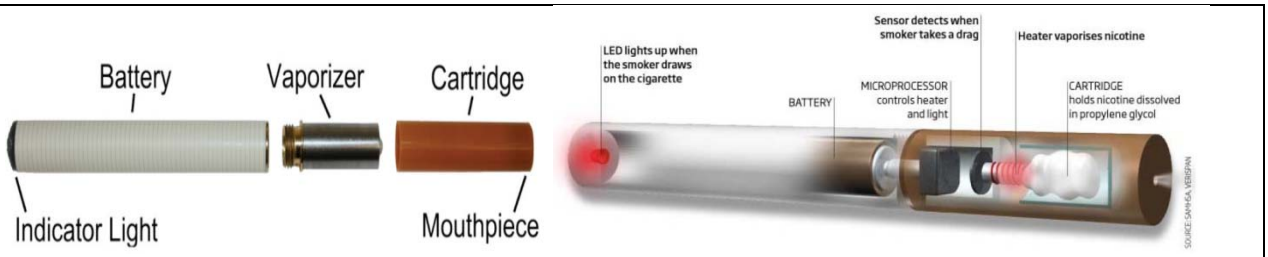

Figure 1. Diagrams of electronic cigarette design

In 2009, the WHO Study Group on Tobacco Product Regulation (TobReg) addressed the emerging regulatory issues pertaining to e-cigarettes. TobReg noted that there was very little published scientific evidence on the health effects of e-cigarettes, or their efficacy for smoking cessation (stated in TobReg Report 955)(World Health Organization, 2009) and that there was not sufficient evidence to support the cessation and health claims made by companies and those in the public health community who were advocating e-cigarettes for harm reduction. The report states (p.7), "In addition to nicotine dependence, the sensory effects of the product, social and

marketing forces and perceptions of harmfulness and potential benefits should be considered in examining the initiation, patterns of use and development of addiction."(World Health Organization, 2009) Meanwhile, e-cigarette prevalence has increased dramatically (Table 1, bottom of document)

Both the 2009 TobReg Report 955 and the 2012 World Health Organization Framework Convention on Tobacco Control (FCTC) Conference of the Parties report on e-cigarettes (November 2012)(FCTC/COP/5/13, 2012) articulated concerns about how the products may create interference with implementation of the FCTC articles that address non-price measures to reduce demand for tobacco products, particularly Articles 8(protection from tobacco smoke exposure), 9 (tobacco product content regulation), 10 (regulation of tobacco product disclosures), 11 (regulation of tobacco product packaging), 13 (tobacco advertising, promotion and sponsorship), because e-cigarettes mimic tobacco cigarettes, and thus may interfere with limits on the indirect promotion of tobacco use/products. E-cigarettes may hinder protection from exposure to tobacco smoke (Article 8) because, while the limited published research suggests that e-cigarettes emit much less and lower levels of toxicants into the environment than conventional cigarettes, they still subject bystanders to passive exposure (called “passive vaping” in Schripp et al., 2012)(Schripp et al., 2012) E-cigarettes are widely advertised and promoted (often inaccurately) as being exempt from clean indoor air laws. The similar appearance of people using e-cigarettes and those using conventional cigarettes can complicate enforcement of restrictions on smoking conventional cigarettes. Moreover, the e-cigarette aerosol has not been proven safe for inhalation by bystanders. A main concern with the products stated in the 2009 WHO report was lack of data on the safety of the ingredients in the e-cigarette solution, especially the safety of repeated inhalation of a heated mixture of propylene glycol and other chemicals.(World Health Organization, 2009) In 2009, TobReg recommended that if e-cigarettes were to be considered medicines or tobacco products, they would be subject to the labeling and warnings requirements in Articles 10 and 11. The TobReg report placed great emphasis on the products’ potential interference with Article 13, which addresses advertising and sponsorship by industry. Both Articles 8 and 13 can have the effect of denormalizing the use of tobacco products and indirect promotion of tobacco products through limiting exposure to tobacco smoke in public places (Article 8) and thus the modeling of smoking behavior in public and limiting advertising

Table 1. Prevalence of e-cigarette use in various countries as measured by published population-based surveys										
Authors	**Country, sample description, n**	**Ever use among general population (%)**					**Ever use among smokers (%)**			
		2009	2010	2011	2012		2009	2010	2011	2012
Regan et al. 2013	U.S., Adults 18+, n=10587 (2009); n= 10328 (2010), ConsumerStyles nationally-representative survey	0.6	2.7	--	--		Not reported	18.2	--	--
King et al. 2012	U.S., Adults, 18+, HealthStyles survey nationally-representative, mail-back (n=4,184) andonline (n=2505) modes n=6689 in 2010, online only n=4050 in 2011	--	2.1 mail, 3.3 online	6.2 online	--		--	6.8 mail, 9.8 online	21.2 online	--
Pearson et al. 2012	U.S., Adults 18+ , 2 samples									
	Nationally-representative online sample (Knowledge Networks), 2010, n=2649	--	3.4	--	--		--	11.4	--	--
	Legacy Longitudinal Study of Smokers (smokers and former smokers), 2010, n=3648	--	--	--	--		--	6.4	--	--
McMillen et al. 2013	U.S., Adults 18+, nationally-representative samples recruited via 2 survey modes: telephone-based (n=1504) and online (n=1736), Social Climate on Tobacco Control survey, 2010	--	1.8	--	--		--	14.4	--	--
Dockrell et al. 2013	U.K., Adults 18+, nationally-representative online panel (YouGov), 2010: n=12597 adults; 2010 n=12432	--	--	--	--		--	--	--	21.6
Adkison et al. 2013	ITC 4-country survey, Adults 18+,* July 2010-June 2011*									
	U.S. (n=1520)	--	--	--	--			20.4		
	Canada (n=1581)	--	--	--	--			10.0		
	U.K. (n=1325)	--	--	--	--			17.7		
	Australia (n=1513)	--	--	--	--			11.0		

Popova and Ling 2013	U.S., Adults 18+, nationally-representative online sample (Knowledge Networks), current and former smokers, n=1836	--	--	--	--		--	--	20.1	--
Cho et al. 2011	Korea, Adolescents, middle school and high school, n=4,341, national survey in 2008*	0.5*	--	--	--		--	--	--	--
Lee et al. 2013 (in press)	Korea, Adolescents, middle school and high school, grades 7-12, ages 13-18, (Korean Youth Risk Behaviour Study) n=75,643			9.4%						
CDC NYTS 2013	U.S., Adolescents, middle and high school, 2011, 2012 National Youth Tobacco Survey (n's not reported)	--	--	MS: 1.4 HS: 4.7	MS: 2.7 HS: 10.0		--	--	--	--

and sponsorship by tobacco companies (Article 13). These policy measures could be undermined by the permitted use of a cigarette-like product that produces a smoke-like aerosol in public and widespread, unrestricted advertising of such products in ways that have been restricted for cigarettes and other tobacco products by the implementation of Article 13.

There has been rapid e-cigarette product innovation in the marketplace despite many unanswered questions about their safety, efficacy for harm reduction and cessation, and total impact on public health. Several commentaries and editorials have been published in the scientific press debating these issues (e.g.,(Britton, 2013, Benowitz and Goniewicz, 2013, Chapman, 2013, Cobb et al., 2010, Etter, 2013, Wagener et al., 2012)) and the number of scientific studies on e-cigarettes is growing. Both the individual risks and benefits and the total impact of these products occur in the context of the widespread and continuing availability of conventional cigarettes and other tobacco products, with high levels of "dual use" of e-cigarettes and conventional cigarettes at the same time among both adults(Adkison et al., 2013, King et al., 2013, Dockrell et al., 2013, Pearson et al., 2012, Regan et al., 2013) and youth.(Centers for Disease Control and Prevention, 2013) This dual use raises questions about the possible harm reduction benefits. It is important to assess e-cigarette toxicant exposure and individual risk as well as health effects of e-cigarettes as they are actually used in order to ensure safety and to develop evidence-based policies and a regulatory scheme that protects the entire population, children and adults, smokers and non-smokers, in the context of how the tobacco industry is marketing and promoting these products.

This report reviews the literature on e-cigarettes available as of September 2013, as well as an update of tobacco industry involvement in the e-cigarette market, research recommendations, global regulations pertaining to e-cigarettes, and potential options for regulation.

METHODS

Initial searches were conducted via the PubMed electronic database using keywords to identify studies describing electronic cigarettes (electronic cigarette, e-cigarette, electronic nicotine delivery systems). The initial searches yielded 153 studies, of which 125 were identified as relevant to electronic cigarettes (Figure 1). Seventy-eight published papers retrieved from those searches were formally reviewed to meet the aims of the present report. Seventy-five

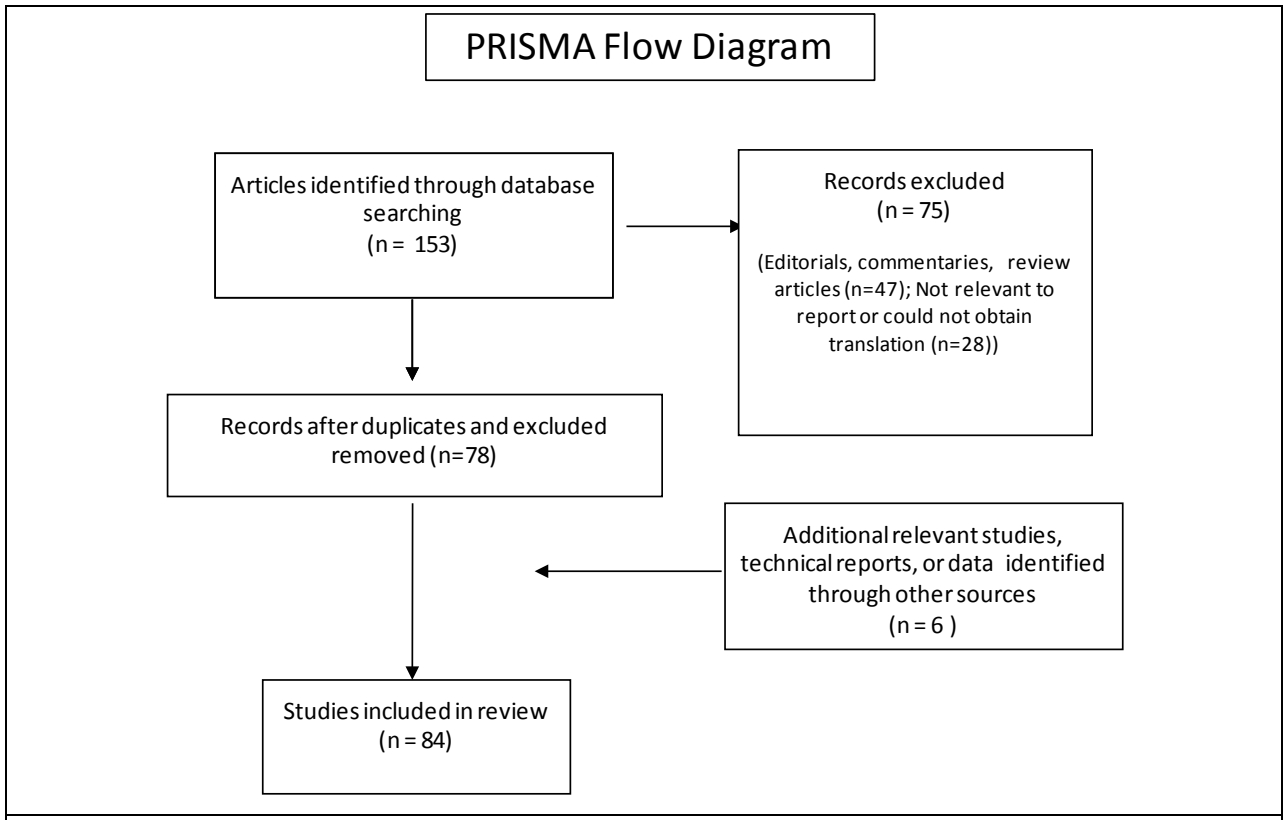

Figure 1. Studies screened and selected for inclusion.

studies were excluded from systematic review were commentaries that did not provide original data, (they are cited to provide background and context.) Searches using the same search terms as above were conducted in the WHO regional databases (electronic cigarette, e-cigarette, electronic nicotine delivery systems). Relevant papers were located in only one database, BIBLIOTECA Virtual em Salude Latin America and Caribbean, and all of the results were already retrieved by the initial searches in PubMed. In addition, the authors, working with WHO, reached out to investigators in the field in an effort to locate studies that had not yet been published (submitted or in press). Each study included in the systematic review was analyzed for content, quality and industry funding (tobacco or e-cigarette companies). After review, each study was categorized according to the main subject headings: marketing and media, prevalence, chemical analyses, biological effects, cessation of conventional cigarettes. Some articles were discussed in other sections of the report: product engineering and product performance and risks to users and bystanders.

Authors also reviewed and included non-peer-reviewed documents, including the World Health Organization Study Group on Tobacco Product Regulation, Technical Report Series 955,(World Health Organization, 2009) a FCTC Conference of the Parties report: “Electronic nicotine delivery systems, including electronic cigarettes. Report by the Convention Secretariat,”(FCTC/COP/5/13, 2012) German Cancer Research Center report, “Electronic Cigarettes – An Overview,”(German Cancer Research Center, 2013)a technical report: “Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?”(Burstyn, 2013) Several published news articles and relevant websites are cited to provide supporting documentation and context to the scientific review.

PRODUCTS (TYPES, ENGINEERING)

E-cigarettes have many names, including electronic cigarettes, ENDS and e-hookah. For the purposes of this report all these products will be referred to as e-cigarettes. Product engineering has been evolving since the first e-cigarettes were documented as arriving on the global market in 2007(Pauly et al., 2007). As of late 2013, there was wide variability in product engineering, including varying concentrations of nicotine in the solution that e-cigarette use to generate the aerosol (also called "e-liquid"), varying volumes of solution in the product, different carrier compounds (most commonly propylene glycol with or without glycerol (glycerin), a wide range of additives and flavors, and battery voltage. Battery voltage differences and unit circuitry can result in great variability in the products' ability to heat and convert the nicotine solution to an aerosol and, consequently, may affect actual nicotine delivery and other chemicals delivered to users and emitted in the exhaled aerosol. Products come in a variety of nicotine strengths (including some without nicotine), usually expressed in mg/ml of solution or percent concentration. Williams and Talbot (2011) measured e-cigarette products' performance across three indicators: airflow rate required to generate aerosol, pressure drop , and aerosol density via three different protocols, finding that air flow and pressure drop required to activate e-cigarette products is quite variable between brands.(Williams and Talbot, 2011) Moreover, the products are "smoked" differently than cigarettes. Hua and colleagues conducted an analysis of 9 videos with tobacco smoking and 64 with e-cigarette "vaping" to assess differences in "smoking" topography between e-cigarette users and conventional cigarette users. Authors found that average length of a puff taken from an e-cigarette was significantly longer than that of tobacco

users (4.3 seconds vs. 2.4 seconds, respectively) and there was a wide range in puffing duration for e-cigarettes (2 to 8.3 seconds).(Hua et al., 2013b)

Quality of product functioning and performance is highly variable and inconsistent,(Trtchounian and Talbot, 2011) and users can modify many of the products. In addition, as the types and design of products and their contents continue to evolve rapidly, it is increasingly difficult to determine what an e-cigarette "is," what it may contain, and what it is delivering to the user and the surrounding environment. The rapid and continual evolution of products makes it difficult to conduct research on the products and generalize study findings to all products because they may become quickly outdated.

The first e-cigarettes were cigarette-shaped, plastic or metal devices comprising three parts: a battery, a reservoir for e-cigarette solution (usually containing nicotine) often with a fibrous material on which the solution is placed, and a heating element (sometimes referred to as an atomizer) which attaches to the battery and converts the liquid into an aerosol (Figure 1). In subsequent models the cartridge was called a cartomizer, which combined the e-liquid reservoir with the wick/fiber and heating element into a single unit (Figure 2). The cigarette-shaped and sized devices are often called “mini” e-cigarettes or "cig-a-likes" by users (who often call themselves “vapers”). There are disposable and rechargeable e-cigarette models (Figure 2). More recent designs are larger models that are pen-shaped and sized with cartomizers (Figure 2) that often hold more nicotine solution to reduce the amount of times a user needs to refill throughout the day. Some cartridges, called clearomizers and "tank systems," hold several ml of e-liquid, are transparent, and allow the user to monitor the level of fluid they contain. There are also much larger capacity and technologically sophisticated tank system devices (Figure 2) that have various mechanical and/or digital display features. One such feature is a larger metal casing for the batteries, which is able to be opened and the batteries replaced according to user preferences. In some tank devices the heating elements and batteries can be replaced with more powerful batteries or lower electrical resistance heaters that allow the user to control how the e-liquid is vaporized (these devices are often referred to as variable voltage devices by users). Furthermore, since the first e-cigarette products appeared on the market, users have been modifying the devices and creating their own; instructions to do so are widely available on the Internet on e-cigarette forum sites and YouTube. A concerning trend that has been occurring at least in the U.S. and is owed largely to the refillable nature of e-cigarettes, is the use of the devices to smoke

Product	Description	Some Brands
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah.	NJOY OneJoy, Aer Disposable, Flavorvapes
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively.	Blu, GreenSmoke, EonSmoke
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs.	Vapor King Storm, Totally Wicked Tornado
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Volcano Lavatube

Figure 2. Examples of different e-cigarette products

marijuana in the form of a liquid and wax dabs (a concentrated form of marijuana, mainly comprising THC).(Givens and Cheng, October 11, 2013, Shuman and Burns, May 24, 2013)

E-liquids are offered in a variety of flavors. A content analysis of 59 e-cigarette websites conducted in 2012,(Grana and Ling, in press) e-cigarettes and the nicotine solution were found to come in tobacco (95%), menthol (97%), coffee (61%), fruit (73%), candy (71%) and alcohol (10%) flavors, as well as more unusual flavors such as “cola” and “Belgian waffle.” Flavor is an important product characteristic in determining who is attracted to a product and the ability to get started on a product. The 2012 US Surgeon General’s Report, Preventing Tobacco Use among Adolescents and Young Adults, found that flavored tobacco products are disproportionately used by youth and initiators (U.S. Department of Health and Human Services, 2012). Since flavors

play a key role in promoting youth tobacco use, cigarettes with these characterizing flavors (with the exception of menthol) have been banned in the U.S. and a flavor ban on nicotine containing products (which includes e-cigarettes) was included in the proposed revision of the EU Tobacco Products Directive (TPD) produced by the European Commission. On 8 October 2013 the EU Parliament deleted this provision, which would allow flavored e-cigarettes (European Parliament, 2013). As of November 2013 there were ongoing negotiations between the European Parliament, the European Council and the European Commission over the final wording of the TPD. To the best of our knowledge, there were no restrictions on flavored e-cigarettes anywhere in the world.

PRODUCT PERFORMANCE AND POTENTIAL RISKS TO USERS AND BYSTANDERS

E-cigarette devices are manufactured mainly in China. There are concerns about risks posed by e-cigarette and e-cigarette solution. Trtchounian and Talbot (2011) examined 6 brands of products for design, content, labeling, quality and product information including warnings.(Trtchounian and Talbot, 2011) Most of the e-cigarette starter kits purchased came with some instructions. Most provided information about the battery and how to connect the parts of the devices, but did not come with a list of product ingredients, or health warning messages. Most of the products leaked when handled and cartridges came with fluid leaked on them, creating the potential for dermal nicotine exposure and potential nicotine poisoning.(Trtchounian and Talbot, 2011)

Propylene glycol and glycerin comprise the main base ingredients of the e-liquid and helps to generate the aerosol used to deliver nicotine and other compounds to the user. This aerosol looks like smoke. There is concern about potential health effects of chronic inhalation of the vaporized base components of the e-liquid.

As first summarized in the report on electronic cigarettes produced by the German Cancer Research Center in 2013,“Electronic Cigarettes – An Overview,” these chemicals are approved for ingestion in food, cosmetics and some drug preparations by many government regulating agencies (U.S., E.U.(German Cancer Research Center, 2013)). Ingestion is a different mode of administration than inhalation so these safety decisions may not be relevant to e-

cigarette use. Glycerin (also called glycerol), is also approved for use in food and cosmetics, is also not explicitly approved for human inhalation.(German Cancer Research Center, 2013)

Regarding inhalation, a Master Data Safety Sheet, guidance for the industrial use of propylene glycol by Sciencelab.com, Inc., states it can cause eye and respiratory irritation and "Prolonged or repeated inhalation may affect behavior/CNS (with symptoms similar to ingestion), and spleen."(Sciencelab.com Inc., 2013)A major manufacturer of propylene glycol, the Dow Chemical Company, states in its product safety materials that the "inhalation exposure to [propylene glycol] mists should be avoided"(Dow Chemical Company, 2013) and the American Chemistry Council warns against its use in theater fogs due to its potential to cause eye and respiratory irritation.(The American Chemistry Council, July 2001) When heated and vaporized, propylene glycol can form propylene oxide, an IARC class 2B carcinogen.(Laino T et al., 2012) and glycerol forms acrolein, which can cause upper respiratory tract irritation.(U.S. EPA, Henderson TR et al., 1981)

Major injuries and illness have resulted from e-cigarette use, which may be related to lack of basic safeguards in the product design and manufacturing process, as well as the contents of the solution. Tobacco product adverse events can be reported to the Food and Drug Administration (FDA), Center for Tobacco Products (CTP). Chen (2012) summarized the 47 adverse event reports filed with the FDA CTP between 2008 and early 2012 regarding e-cigarettes; finding that 8 of these 47 adverse events were serious health issues with examples including hospitalization due to congestive heart failure, hypotension, pneumonia, chest pain and "possible infant death secondary to choking on e-cig cartridge."(Chen, 2013) Reporting of an adverse event does not indicate causation, but it does raise questions of biological plausibility that need to be addressed. Examples of less serious adverse events include nausea, vomiting and sore throat. Moreover, one e-cigarette company also instructs users to draw on the product differently from a cigarette because they might experience adverse reactions, stating: "If you find yourself smoking your e-cigarette the way you smoke a traditional cigarette, you are doing something wrong. **As a matter of fact, if you vape your e-cig as you smoke your cigarette you will find yourself with a sore throat, sore lungs, an incessant cough and irritation in your mouth and throat.**[bold in original]"(Metro E-cigarette Website)

An18-month old girl in the U.S. became seriously ill after drinking e-cigarette liquid in a refill container that was left in the child's reach and did not come with a child-proof cap.(Shawn

and Nelson, 2013) A child in Israel died of nicotine poisoning from drinking her grandfather's e-cigarette solution.(Winer, May 29, 2013) e-cigarettes have exploded and caught fire, causing serious injury. A man in Florida suffered severe burns and lost half his tongue due to an e-cigarette battery exploding in his face.(CBS NEWS, February 16, 2012) A woman in Atlanta escaped serious injury from an e-cigarette that exploded in her home, starting a fire.(Strickland, 2013) These problems are common enough that e-cigarette internet forums and some retail websites advise that the lithium batteries may explode or overheat when left to charge for long periods of time or in direct heat exposure or if charged with the wrong charger or a powerful electrical source. An e-cigarette forum (www.e-cigarette-forum.com) has a section in which advice is given about the risks of specific battery types.(E-cigarette-forum) Because e-cigarette are not regulated there is no systematic collection of information on these issues, which is likely to result in under-reporting. It is also unknown to what extent these problems could be eliminated by stronger regulatory standards on the product itself.

MARKETING AND MEDIA RESEARCH

While most attention from the biomedical community has been on the e-cigarette device, the aerosol that it delivers to users (and, to a lesser extent, bystanders), and the potential of e-cigarettes for cessation of conventional cigarettes, much of the public discourse and popular understanding about use of e-cigarettes has been determined by how they have been marketed and covered in the news media. In order to understand patterns of product use, it is important to understand the marketing claims promoted to the public about e-cigarettes and how products and marketing is designed to attract different segments of the population (such as never users of nicotine or tobacco products, youth, current smokers, and former smokers). Consumer perceptions of the risks and benefits posed by e-cigarettes, both independent risks and relative to cigarettes and other tobacco products, are important factors in determining uptake and consequently the total public health burden due to tobacco use. For example, claims that e-cigarettes are less harmful than cigarettes may encourage adoption by non-smokers (potentially children) as well as smokers seeking to quit conventional cigarettes. Promotion of e-cigarettes as a convenient alternative to cigarettes when a smoker cannot light up would blunt the effect of smokefree laws on smoking cessation. The explicit promotion of dual use (as has also been done

with snus) for places where people cannot smoke cigarettes (Figure 3) has important implications for the ultimate use patterns and health impact of introducing e-cigarettes into the marketplace.

Grana and Ling (in press) systematically reviewed a sample of single-brand e-cigarette retail websites (n=59) that were online in 2012 to determine the main marketing messages, type

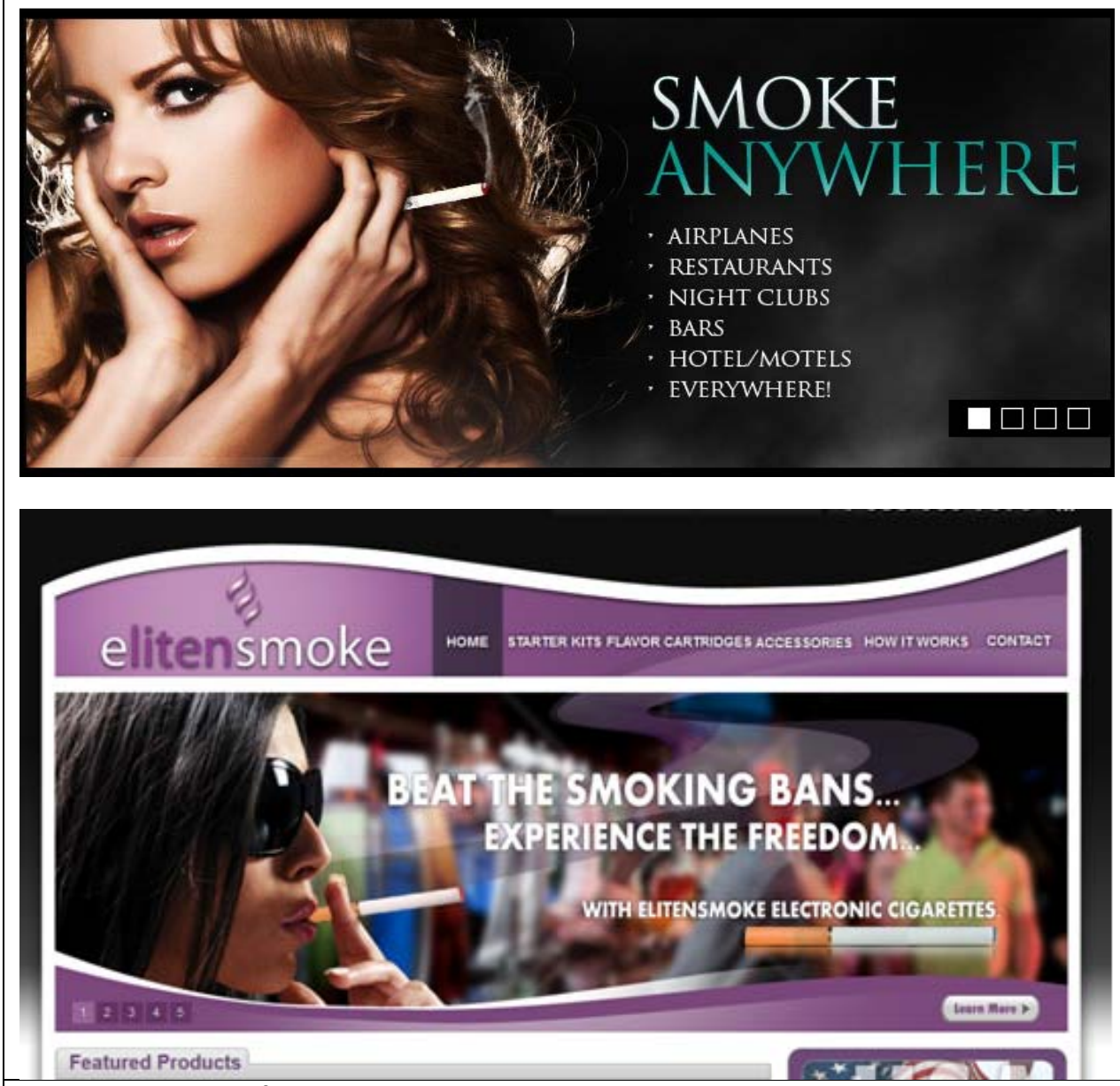

Figure 3. Examples of marketing claims to use e-cigarettes to "smoke anywhere" and "circumvent smokefree laws" (www.smokingeverywhere,com; www.elitensmoke.com) June 2012

of products sold and unique marketing features on the sites.(Grana and Ling, in press) They found that the most popular claims were that the products are healthier (95%), cheaper (93%) and cleaner (95%) than cigarettes, can be smoked anywhere (88%), can be used to circumvent smokefree policies (71%), do not produce secondhand smoke (76%), and are modern (73%). Health claims were also made through pictorial and video representations of doctors, which were present on 22% of sites. Cessation-related claims (ranging from overt statements that one can use the product to quit smoking to indirect claims such as "you'll never want to smoke tobacco cigarettes again") were found on 64% of sites. Claims about effects on bystanders frequently included statements that e-cigarettes emit "only water vapor" that is harmless to others.

Another more subtle way e-cigarettes are presented as a healthier option than conventional cigarettes on e-cigarette-related websites is through information and claims about nicotine.(Tobacco Vapor Electronic Cigarette Association) When mentioning that the products contain nicotine, sites often offer information that nicotine is not the harmful substance in cigarettes. In addition, information about the characteristics of nicotine is presented in a misleading way, with sites presenting nicotine as derived from plants other than tobacco, including eggplant and tomatoes, where the levels are so low that it would require eating pounds a day to take in nicotine in amounts to rival that of nicotine from a secondhand smoke exposure, and also presenting positive aspects of nicotine use on cognition.

Some e-cigarette websites (as well as some scientific commentators)(Phillips and Rodu, Britton, 2013) trivialize the addictive properties of nicotine by comparing it to caffeine. For example, one e-cigarette shop website includes this information in a section called "About the E-Cig:"

> **Is Nicotine harmful?**
>
> Nicotine is not the harmful ingredient in tobacco, it is the smoke that kills: the smoke and combustion artefacts cause lung cancer, heart disease and many other illnesses. Also, everyone tests positive for nicotine in the bloodstream, in very small amounts, since it is a common ingredient in vegetables. A related material, nicotinic acid, is a vitamin Niacin or Vitamin B3 so to say it is universally harmful is obviously untrue. Without the smoke, smoking is likely to be far less harmful, as nicotine may be as harmful as the caffeine in coffee. Nicotine is best avoided by those who are pregnant or have heart disease. You may want to avoid it if you also do not take caffeine or alcohol by drinking coffee, tea, wine or beer. Like these substances, it should probably not be started in the first place. Some people however find their lives are dysfunctional without nicotine, and an electronic cigarette is probably as good a way as any to supply it. www.itisvapor.com, Last accessed November 24, 2013

While nicotine is not the only or most dangerous thing in conventional cigarette smoke, claims that nicotine is harmless is not supported by the scientific evidence as summarized in the 1988 Surgeon General's Report on *The Health Consequences of Smoking: Nicotine Addiction*, addressed this comparison directly:

> Most categories of drugs which have been found to cause widespread drug dependence in the nonlaboratory setting have been tested with animals and humans in laboratory settings. Results of these studies have been reviewed in detail elsewhere Several categories of drugs have been found to be self-administered by humans and animals in the laboratory settings, to meet criteria as positive reinforcers, and to exhibit orderly relations as a function of drug dose, drug pretreatment, and other factors known to affect the intake of dependence-producing drugs. These include alcohol, morphine, pentobarbital, amphetamine, cocaine, and nicotine in the forms of cigarettes and i.v. injection.
>
> Self-administration studies with animals are much more extensive and have also been reviewed in detail elsewhere. In brief, drug self-administration studies in animals in the 1960s showed that a range of drugs including opioids, amphetamines, barbiturates, certain organic solvents, alcohol, cocaine, and nicotine were self-administered. All of these drugs were found to maintain powerful chains of drug-seeking behavior, even when insufficient drug was taken to produce a clinically significant degree of physical dependence. *Drugs that did not serve as reinforcers in these studies included caffeine*…" [emphasis added, citations deleted](U.S. Department of Health and Human Services, 1988)

It is not reasonable to state or imply an equivalence between nicotine and caffeine.

The use of celebrities in product marketing has been occurring since at least 2009.(Grana et al., 2011) In Poland, a popular ad (as of March 2012) featured a famous actor with the tagline 'You can smoke wherever you want.' In the U.S., Katherine Heigl, a famous U.S. actress went on the David Letterman Show, a popular late night program in the U.S. and spent much of her interview discussing her quit attempt with the e-cigarette and even used an e-cigarette on stage with Mr. Letterman (Figure 4). At the time, she had a relationship with the company where a portion of sales of an e-cigarette called the Pitbull were donated to a charity of her choice, Compassion Revolution. The video of the interview with David Letterman was on the site as well as posted on other websites and widely used in many online press releases and advertorials.

Rooke and Amos (2013) conducted a thematic analysis of newspaper and online media coverage about electronic cigarettes in the UK and Scotland from July 2007 to June 2012 (n=119 articles, editorials and columns; 44 from July 2007- June 2010, 75 from July 2010- July

Figure 4. Katherine Heigl smoking an e-cigarette on the set of the David Letterman Show, a popular late-night national television program in the United States, September 2009)

2012).(Rooke and Amos, 2013) Five themes emerged: "healthier choice" (71 articles), "getting around smokefree" (44 articles), "celebrity use" (41 articles), "price" (41 articles), and "risk and uncertainty" (31 articles). They found that the articles published earlier focused on e-cigarettes as a way to circumvent clean indoor air policies, with the healthier choice theme appearing as an aside. Authors noted that the smokefree-themed articles were "rebellious" in tone and presented e-cigarettes as a way to "beat" smoking bans and give users the "freedom to smoke where [they] want." The healthier choice theme increased as a main focus of articles over the years included in the study, with e-cigarettes presented as posing less risk to tobacco cigarettes and potential for use as a smoking cessation aid. Authors noted that the healthier choice claims were often presented as a defense to issues of potential risk and uncertainty about the products, focusing on them as a healthier alternative for smokers and for use in quitting smoking. Potential risks related to lack of product and safety information were usually raised by health officials and included concerns about the poisonous nature of nicotine and risks of accidental overdose or ingestion by children. However, authors note that the "healthier" themed articles also focused on e-cigarettes

as part of "safer cigarette" development by the tobacco industry and as part of the concept of tobacco harm reduction, noting that the coverage "suggested official backing for e-cigarettes and highlighted their 'potential to save lives.'" Stories about celebrity use of e-cigarettes appeared after 2009, focusing on e-cigarettes as the latest stylish, "must-have" item and often emphasizing use of the products to get around smokefree laws and to quit smoking. Coverage often included anecdotes about having tried nicotine replacement therapies (NRT), failing to quit and then trying the e-cigarette, thus implying that e-cigarettes are a more effective form of NRT. Specifically, the Katherine Heigl appearance on the David Letterman television program noted above in Grana et al. (2011) is cited as an example in this article, demonstrating its widespread reach through news and marketing channels and thus the widespread reach of the "cessation aid" message.(Grana et al., 2011)

An innovation that e-cigarette companies have employed since their advent is web-based affiliate marketing (e.g., third-party product promotion that leads to sales, often disguised as a press release or news article). Cobb et al.(2013) performed a forensic analysis of e-cigarette Internet marketing practices in order to track the links between affiliate advertising, affiliate marketing sites and the retailer websites selling the products and to compare the therapeutic (smoking cessation) claims on the affiliate marketing and the seller's website.(Cobb et al., 2013) The analysis revealed that affiliate marketing contained therapeutic claims while the retailer website linked to the affiliate did not. A brief descriptive analysis of 20 websites documented that 12 had affiliate programs, 11 made health claims and 4 made cessation claims.(Cobb et al., 2013) Current legal precedent in the U.S. classifies e-cigarettes as tobacco products unless they are marketed with therapeutic claims and many retail website contain a disclaimer usually in fine print at the bottom of the homepage or in the FAQ section that the products are not intended to treat disease or not intended for smoking cessation.

Another innovation employed effectively by e-cigarette marketers and retailers is the use of social media and viral video sharing. In an analysis of e-cigarette-related Youtube videos (n=396) posted from 2007-2011, Paek et al. (2013) found that 85.2% of videos had a clear sponsorship by e-cigarette companies or their affiliate marketers.(Paek et al., 2013) Despite the industry sponsorship, 79% appeared to be user-generated and only 17% were formal advertisements or news clips. The videos communicated health and smoking cessation claims, with 21.4% presenting e-cigarettes as "less harmful than other tobacco products," 12% claiming

they are “healthy,” and 9.3% “can help you quit smoking;” but non-marketer sites presented significantly more health claims than marketer videos. A high level of information about the product was presented in the videos indicating the use of common retailer marketing tactics (product (68%), price (34%), place (65.5%), brand-specific taste (39.5%) and design (18.9%)). In an analysis of viewer preferences, the number of “likes” on each video was counted at time of download and a hierarchical regression was conducted to determine significant predictors of number of likes. Number of views was the strongest statistically significant predictor of likes ($p<.001$), and more weakly associated variables were "not having an obvious advertising message" ($p=05$), "presented a social benefit" ($p=.05$), and those had a "positive valence" ($p<.01$).

In the only published study as of November 2013 on the effects of viewing e-cigarette television advertising on adult smokers and recent quitters (n=519) in an online convenience sample, Kim et al. (2013) found that after viewing a popular TV commercial for Blu e-cigarettes 75.8% of the sample reported the ad made them think about smoking, 74.3% reported it made them think about quitting and 66% said it made them likely to try e-cigarettes in the future.(Kim et al., 2013) In addition after viewing the ad, participants mean reported urge to smoke was 42.1(SD=1.9) on a 100 point scale from “no urge” to the “strongest urge I have ever experienced”). Persons who had used e-cigarettes (34% of the sample) were statistically significantly more likely to think about smoking cigarettes after viewing the ad than non-users (82.7% and 72.2%, respectively). There were no statistically significant differences in urge to smoke and thinking about quitting for e-cigarette ever-users vs. non-users.

While originally promoted almost exclusively on the internet, marketing activities for e-cigarettes have increased dramatically, with the increasing promotion of e-cigarettes on television in some countries (e.g., U.S., U.K.). In the U.S. television advertising is largely by Lorillard, Inc., a multinational tobacco company based in the U.S. and the first of the cigarette companies to enter the e-cigarette business when it purchased Blu brand e-cigarette in 2012(Esterl, April 25, 2012) and the U.K. brand of e-cigarettes, Sky Cig, in 2013.(Esterl, October 1, 2013) As of late 2013, Lorillard has one of the largest U.S. national TV campaigns, which includes use of celebrities to glamorize e-cigarettes and shows them inhaling and exhaling what looks like smoke. Also, in the U.S., the e-cigarette company NJOY aired a commercial in a regional television market during the 2013 National Football League Superbowl game.(Hodge Jr.

et al., 2013) In the U.K. the commercials range from showing young people out enjoying themselves (SkyCig) to older people who are tired of missing out on major life events due to their smoking (E-Lites), a sentiment more associated with the harm reduction or NRT approach. Jenny McCarthy, a TV host and model, appears in a 2013 Blu advertisement that glamorizes e-cigarette use and emphasizes the romantic opportunity it could create (Figure 5). Moreover, this advertisement is set in a bar which recalls the pairing of cigarettes and alcohol and makes that connection for e-cigarettes, and is likely to appeal to older adolescents and young adults, the population that spends disproportionately more time out in bars trying to develop romantic relationships. Blu also has another actor in its commercials, Stephen Dorff, whose rugged good

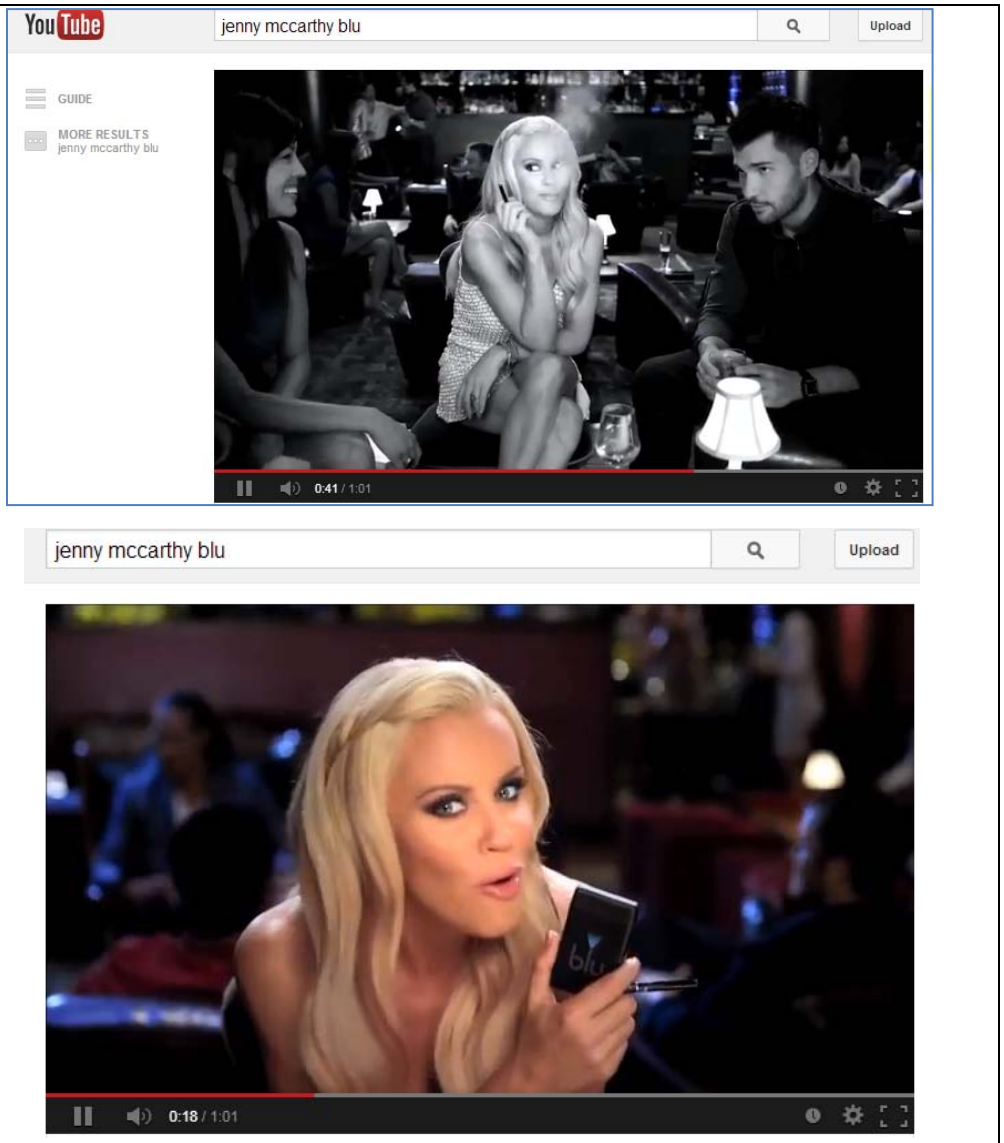

Figure 5. Celebrity Jenny McCarthy in Lorillard's Blu e-cigarette television commercial (as of October 2013)

looks recall the Marlboro Man but in a suit, and e-cigarette brand NJOY uses rebel rockstar Courtney Love.(BluCigs, 2012)

Conclusion

As of 2013, e-cigarette companies (including cigarette companies who have purchased e-cigarette companies) are marketing e-cigarettes using some of the same claims, tactics and media channels – including television and radio -- that were effective at marketing cigarettes to attract young people and deter smokers from quitting before use of these channels to market cigarettes was banned.

The fact that a large majority of e-cigarette retail websites encouraged the use of the products anywhere and everywhere (88%), specifically noting places where cigarette smoking would be banned (71%) and places for socializing, has direct implications for regulation of e-cigarettes and implementation of the FCTC. These messages can be used to undermine the idea of smoking restrictions and existing smokefree laws designed to apply to tobacco smoke. Importantly, it appears that both the e-cigarette companies and tobacco companies are focused on creating positive social norms for the products, encouraging their use "anywhere" and promoting them explicitly to get around smokefree laws (which are effective tobacco control measures), and promoting their use as socially acceptable. The totality of the messaging creates familiarity among smokers by emphasizing the similarity to a cigarette and the smoking experience while simultaneously assuring the smokers and their family and friends (and perhaps kids) that it is entirely different than a cigarette. A 2013 commercial for e-cigarettes, FIN, comes with the tagline “Rewrite the Rules,” and a direct quote from the commercial states, “There was a time when no one was offended by it – that time has come again.”(FIN Electronic Cigarettes, May 25, 2013)

Television and radio have been unavailable to the cigarette and other tobacco companies to market their products in the US (as well as much of the world) since the 1970s. E-cigarette advertising on television and radio is mass marketing of an addictive nicotine product for use in a recreational manner to new generations who have never experienced such marketing. This pervasive marketing may have implications for existing smokers as well as the one published study on this topic indicates that viewing an e-cigarette commercial may induce thoughts about smoking and cue the urge to smoke among adult smokers.(Kim et al., 2013)

PREVALENCE

Adults

International Samples

The Eurobarometer survey in 2012 (n=27 countries, n=26,751) assessed awareness, attitudes toward and prevalence of ever-using e-cigarettes in the European Union.(TNS Opinion & Social, 2012) Male and younger aged respondents had the greatest awareness of e-cigarettes. The greatest awareness was in Finland (92%) and Greece (90%) while the lowest was in Sweden (34%). In general, more Europeans in this survey were unsure if they think e-cigarettes were harmful to health (38%) or think that they are not harmful to health (35%) than thinks they are harmful to health (27%). Seven percent of European Union respondents have tried e-cigarettes at least once, with the highest rate of trial in Bulgaria (11%), Latvia (10%), Denmark (9%), Poland (9%) and the Czech Republic (9%) and highest rate of regular use in Greece, Denmark and Romania (each 2%).

Adkison and colleagues (2013) estimated rates of e-cigarette use and perceptions of the products in 2010 among current and former smokers in the International Tobacco Control Study conducted in U.K, U.S., Australia and Canada.(Adkison et al., 2013) Likely reflecting the fact that e-cigarettes are freely available in the UK and US and not legal for sale with nicotine in Australia and Canada, the highest rates of awareness were in the U.K.(54%) and U.S. (73%), while rates were lower in Australia (40%) and Canada (20%) (all rates were statistically significantly different). Prevalence of e-cigarette trial (among those aware) was 20.4% in U.S., 17.7% in the U.K., 10% in Canada and 11% in Australia. Across countries use was higher among those of younger age, higher income, reporting nondaily smoking and who perceive e-cigarettes as less harmful than cigarettes. Despite larges differences in awareness among the countries, current use did not differ among the countries (p=0.114). In current smokers, a marker of dependence (cigarettes per day) was not associated with ever e-cigarette use or past 30-day use (p value not provided).

United Kingdom

Dockrell et al (2013) analyzed data from a nationally representative survey of UK adults (2010: n=12597 adults, 2297 smokers; 2012 n=12432, 2093 smokers) finding the prevalence of e-cigarette trial and current use doubled from 2010 to 2012.(Dockrell et al., 2013) Ever use in

2010 was not measured among former smokers or never smokers, only current non-daily or daily smokers. In 2010, 5.5% of smokers had tried e-cigarettes but no longer used them, which increased to 15.0% in 2012. Current use of e-cigarettes among smokers rose from 2.7% in 2010 to 6.7% in 2012. Ever e-cigarette use among former smokers in 2012 was 2.7% and current use 1.1%; ever use among never smokers in 2012 (only measured in that year) was 0.4% and current use was 0.1%. About 33% of ever e-cigarette users continued to use in 2010 and in 2012. In a multivariate model which included only ex- and current smokers, being an occasional (OR=4.32 95% CI: 2.89, 6.48) or daily smoker (OR=7.33 95% CI: 5.66, 9.48) increased odds of ever e-cigarette use compared to ex-smokers, while older age (age ≥35) decreased odds of ever e-cigarette use compared to 18-34 year olds (OR=0.58 95% CI: 0.43, 0.78). In the model for current e-cigarette use, only being an occasional (OR=6.04 95% CI: 2.92, 12.49) or daily smoker (OR=6.68 95% CI: 4.15, 10.77) increased odds of current e-cigarette use. Authors also analyzed data from a 2010 survey of smokers (n=1308) that included a special battery of e-cigarette questions. A majority of respondents reported that e-cigarettes: “might satisfy the desire to smoke” (60%), “might help cut down on cigarettes” (55%), and “they might help me give up smoking entirely (51%).”Perceived disadvantages included “might be too expensive” (53%), “might not satisfy the desire to smoke enough” (39%), and might be mistaken for cigarettes therefore frowned upon in public”(35%). Among e-cigarette triers (n=494, 37.7% of sample), the most common reason for trying e-cigarettes was “as a substitute for smoking where smoking is not allowed” (reported by 49% of daily pack a day smokers, 43% of those smoking 10-19 cigarettes per day, and 31% among those smoking 9 or fewer cigarettes per day, p=0.008). Secondary reasons were to cut down (35%) and to quit smoking (31%). The finding that using e-cigarettes to get around smokefree laws is likely reflected in the dominant pattern of dual use in both 2010 and 2012 prevalence data reported in this study.

Switzerland

Douptcheva et al (2013) reported preliminary data analyses of the Cohort Study on Substance Use Risk Factors (C-SURF), a longitudinal study of Swiss men who are interviewed during enrollment in the army, to examine prevalence and predictors of e-cigarette use.(Douptcheva et al., 2013) Among the entire cohort of young men, aged 19-25, 4.9% of participants reported ever trying e-cigarettes. Use differed by smoking status with 9.3% of

current smokers reporting trying e-cigarettes, 1.6% of former smokers and 0.4% of never smokers. Excluding 144 occasional e-cigarette users, they conducted an analysis of e-cigarette use among daily smokers (n=1233) that compared daily dual users (n=25) to daily smokers who never use e-cigarette (n=1064); they found no statistically significant differences in cigarettes per day, nicotine dependence or past year quit attempts.

United States

Using data from U.S.-based ConsumerStyles survey (which is a mail-back survey of a national sample of adults), Regan et al. (2013) found that awareness of e-cigarettes doubled from 2009 to 2010 (16.4% to 32.2%) and ever use of e-cigarettes increased from 0.6% in 2009 to 2.7% in 2010.(Regan et al., 2013) Ever use was most common among men, younger adults and those with lower socioeconomic status. Ever use was higher among smokers than among the general population in 2010 (18.2% v 2.7%, respectively). Current smokers who had tried e-cigarettes did not differ from non-users in intention to quit or past-year quit attempts.

King et al (2013), analyzed data from a companion dataset to the ConsumerStyles, called HealthStyles, collected in 2010 (mail-based and web-based modalities) and 2011 (web-based mode).(King et al., 2013) They found awareness of e-cigarettes had increased from about 40% to about 58% and ever use had doubled from 3.4% to 6.2% between 2010 and 2011. Ever use was higher in current smokers at both waves (6.8% of the 2010 mail-based sample, 9.8% of the 2010 web-based sample and 21% of the 2011 web-based sample). Ever use among former smokers increased dramatically from 2010 to 2011, from 0.6% in 2010 mail sample and 2.5% in 2010 online sample to 7.4% in the 2011 online sample. Authors note data were weighted to be nationally-representative and the Styles surveys typically yield estimates of smoking prevalence that are almost identical to the nationally-representative National Health Interview Survey.(Regan et al., 2013, King et al., 2013) Moreover, a similar percentage of U.S. adults who were aware of e-cigarettes in 2010 were reported by Regan et al and King et al., as the nationally-representative 2010 data reported in Pearson et al. (Pearson et al., 2012) (32.2% Regan,(Regan et al., 2013) 38.5% and 40.9% in King(King et al., 2013) vs. 40.3% in Pearson(Pearson et al., 2012).

Pearson et al (2012) estimated e-cigarette use prevalence in two studies, the Legacy Longitudinal Study of Smokers (LLSS) and a nationally-representative general population online

survey, both conducted in 2010.(Pearson et al., 2012) Smokers in the LLSS and the nationally online sample were similar on all demographics except age (those in the LLSS were on average younger) and smoking characteristics and desire to quit with the exception that a greater proportion of smokers in the LLSS had made more than one quit attempt (69% v 31%, respectively). Overall awareness in the online nationally-representative sample (n=2649) was 40.2% and ever use was 3.4%, while awareness among smokers was 57% and ever use was 11.4%. Among LLSS cohort (n=3648), awareness was 57.0% and ever use was 6.4%. Moreover in the online sample, almost all current use (past 30-day) of e-cigarettes was among current smokers: 4.1%, compared to 0.5% of former smokers and 0.3% of never smokers. (Current use was not measured in the LLSS.) In addition, although a low percentage of former smokers (2%) had used e-cigarettes, that rate was over twice the rate among never smokers (0.77%).In the online nationally-representative survey the odds of being an e-cigarette user was associated with intention to quit in the next 6 months (adjusted OR = 1.74; 95% CI: 1.02, 2.98), compared to never expecting to quit; but this was not evident in the LLSS cohort.

In a 2010 nationally-representative, mixed-mode survey (telephone-based n=1504, online n=1736; total n=3240), McMillen et al. (2012) assessed the ever use of emerging tobacco products including e-cigarettes among adults in the U.S.(McMillen et al., 2012) Ever use of e-cigarettes among all respondents was 1.8%, with highest rates of use among daily (6.2%), and non-daily (8.2%) smokers. Past 30-day (current) e-cigarette use did not exceed 1% for any of the "emerging tobacco products, which included e-cigarettes, but 19.7% of ever e-cigarette users reported past 30-day use.

Popova and Ling (2013) found that among a nationally representative panel of current and recent former smokers, 20.1% had ever used e-cigarettes.(Popova and Ling, 2013) Ever e-cigarette use was more common in women than men (OR=0.79, 95% CI: 0.63-0.99), persons of Asian ethnicity than white (OR=2.76, 95% CI: 1.03, 7.39), and those aged 18-29 years compared to 60 years or older (OR=2.32, 95% CI: 1.57, 3.42). Among smokers, those with some college education compared to those with a bachelors degree (OR=2.09; 95% CI: 1.13, 3.86) and those with incomes less than $15,000 compared to those with incomes of $60,000 or greater were more likely to be current (past 30-day) e-cigarette users (OR=1.95, 95% CI: 1.17, 3.25). Respondents who had ever tried e-cigarettes were significantly more likely to have tried to quit conventional

cigarettes in the past year and failed than persons who had not tried to quit (OR=1.78, 95% CI: 1.25, 2.53).

U.S. Regional Samples

Choi and Forster (2013) found that among young adults aged 20-28 in the Midwestern US surveyed in 2011, ever use of e-cigarettes was 7.0% and past 30-day use was 1.2%.(Choi and Forster, 2013) Among those aware of e-cigarettes, most believe e-cigarettes are less harmful than conventional cigarettes (52.9%) and 44% believe they can help with quitting smoking. Ever use was more common among 20-24 year olds (25-28 year olds), men, current smokers, and those who believe e-cigarettes are less harmful than conventional cigarettes and can be used for in smoking cessation. In a focus group study more broadly focused on young adult perceptions of novel tobacco products that included e-cigarettes, Choi et al. (2012), found that about 50% of the sample of young adult smokers and non-smokers indicated interest in trying e-cigarettes if offered by a friend.(Choi et al., 2012)

Sutfin and colleagues (2013) found that among college students in North Carolina surveyed in 2009, ever use of e-cigarettes was 4.5% while past 30-day use was 1.5%, with highest use among current smokers.(Sutfin et al., 2013) Importantly, they found that 12% of e-cigarette users were never smokers. E-cigarette use was not associated with intention to quit smoking.

A cross-sectional study of Hawaiian daily smokers (n=1567) conducted from 2010-2012, examined e-cigarette use prevalence and associations with quitting attitudes and behaviors.(Pokhrel et al., 2013) Thirteen percent of participants reported having ever used e-cigarette to quit smoking (authors did not assess any other reason for using the products). Smokers who had used e-cigarettes to quit were younger, more highly motivated to quit, had greater self-efficacy for quitting, and reported a longer recent quit duration than smokers who had not used e-cigarettes to quit. In the multivariate logistic regression analyses, greater quit motivation (OR = 1.14; 95% CI: 1.08, 1.21), quitting self-efficacy (OR = 1.18; 95% CI: 1.06, 1.36) and having ever used FDA-approved therapies (OR = 3.72; 95% CI: 2.67, 5.19) were significantly associated with greater likelihood of having used e-cigarettes to quit smoking, whereas age (OR=0.98; 95% CI: 0.97, 0.99) and Native Hawaiian ethnicity (OR = 0.68; 95% CI: 0.45, 0.99) were inversely associated with greater likelihood of using e-cigarettes for quitting.

Convenience Samples of Users: Prevalence, User perceptions

There have also been several studies with convenience samples that may provide information about motivations for using e-cigarettes, attitudes and behavior. Due to study methodology, these studies were likely biased toward recruitment of persons motivated to quit and enthusiastic about e-cigarettes, limiting the generalizability of the findings.

In an online survey of 81 users of cessation websites and e-cigarette forums conducted in 2009, authors found that most respondents perceived the products as less harmful than cigarettes and used the products to quit smoking or to cut down on conventional cigarette smoking.(Etter, 2010) In a subsequent study conducted in 2010, Etter and Bullen (2011) surveyed 3587 adults from several countries that were recruited from e-cigarette forums and smoking cessation websites, and employed a similar questionnaire as Etter 2010.(Etter and Bullen, 2011b, Etter, 2010) Most respondents were former smokers (71%) at time of survey, using a nicotine e-cigarette (97%) and an average of 120 puffs/day. Top reasons for using e-cigarettes were: perceive them as less toxic than tobacco (84%), to help with quitting or relapsing (77%), to ameliorate cravings for and withdrawal from cigarettes (67%) for use in situations where smoking is restricted (39%) .(Etter and Bullen, 2011b) A subset of this sample who gave their email address for follow-up (n=779) completed a one-month (n=477) and a one-year follow-up (n=367) survey.(Etter and Bullen, 2013)As at baseline, a majority of participants at follow-up were former smokers (72%). Seventy-six percent of participants reported using e-cigarettes daily (17% were never users of e-cigarettes), and users took an average of 150 puffs/day and most commonly reported using 16 mg/ml nicotine strength e-liquids. A majority of people who were e-cigarette users at baseline remained e-cigarette users at one month and one year (98% at one month and 89% at one year among daily users. The relapse rate among former smokers who daily e-cigarette users at baseline was 6% by one-month follow-up and 6 percent by one- year follow-up. Of the daily smokers at baseline, 91% were still using e-cigarettes daily at one-month follow-up and 72% were using daily at one-year follow-up. Almost all of the former smokers using e-cigarettes daily at baseline were still using e-cigarettes daily at follow-up (99% at one-month and 92% at one-year). E-cigarette uptake was seen at follow-up among never-users of e-cigarettes at baseline (15% at one -month and 13% at one-year). Twenty-two percent of smokers (occasional and daily) at baseline had quit smoking at one-month and 46% had quit at one year. Authors note that respondents were older, higher income, more likely to be former smokers and

to report daily e-cigarette use compared to non-respondents. Daily smokers retained at follow-up reported higher motivation to quit smoking.

Two of the earliest studies were conducted with attendees of meetings in the U.S. of electronic cigarette enthusiasts and retailers. McQueen et al. (2011) conducted in-person interviews (n=15) with attendees of Vapefest and a MidWest Vapers Group meeting.(McQueen et al., 2011) Respondents were described as experienced e-cigarette users, many of whom were former smokers who had unsuccessfully tried to quit in the past with approved smoking cessation therapies and reported finding e-cigarettes "a vast improvement."Respondents reported perceived benefits of e-cigarette use to include that it is cheaper, has health benefits, less offensive odor, and women reported using nicotine and non-nicotine e-cigarettes to control weight and "snacking." Respondents reported finding the use of Internet forums "invaluable" to find products and assess quality of the diverse range of products. Some interviewees had begun selling the products in the previous 6 months and some indicated they were "unpaid evangelists" who had set up websites for visitors to gain information about e-cigarettes, tips for caring for and modifying the devices, and a way for visitors to purchase the products. Participants reported that the time required to learn how to use an e-cigarette device and how to "vape" with the devices, as well as device defects, present barriers to converting smokers to e-cigarette users. Participants reported starting with a cigarette-shaped device filled with tobacco or menthol e-liquid to maintain familiarity with cigarettes and then moving on to a device with a "larger and/or higher voltage battery" that can vaporize a larger amount of liquid to produce "throat hit" and tapering nicotine over time. They were enthusiastic about the products and supportive of research, particularly on the safety and efficacy of the products.

In another study, Foulds et al. recruited 104 Vapefest attendees at to respond to a survey administered in person that included questions about demographics, e-cigarettes and tobacco history, and beliefs about e-cigarettes.(Foulds et al., 2011) They found that 73% of users started with intention to quit smoking and 88% reported being "ex-smokers," with an average of 9 quit attempts before using e-cigarettes. Two-thirds had tried previously to quit by using FDA-approved cessation devices and 99% felt the e-cigarettes helped with quit attempt. Only 8% used the most widely sold brands, suggesting most built their own devices or bought non-name brand products over the Internet.

Siegel et al. (2011) obtained a list of purchasers of Blu brand electronic cigarettes from the company and invited them to complete a survey 6 months after making their first purchase (5000 purchasers, 4.5% response rate, sample n=222) in 2010.(Siegel et al., 2011) They found that 31% reported they were not smoking tobacco cigarettes at the 6 month survey timepoint. This study is limited by selection bias (purchasers of one particular product) and very low response rate (4.5%).

In 2011, Dawkins et al., (2012) conducted an online survey of 1347 adults recruited from an electronic cigarette retail website.(Dawkins et al., 2013) Participants were 70% men, mean aged 43 years, 96% white (72% European), and most (72%) used a "tank" type of e-cigarettes with nicotine-filled solution (1% reported using no-nicotine). Seventy-four percent of respondents who had used an e-cigarette reported not smoking for at least a few weeks. Results show that users perceive e-cigarettes as healthier than smoking and pleasant to use. In an analysis of self-reported ex-smokers, "'time to first vape' was significantly longer than 'time to first cigarette' ($p<0.001$)."

Goniewicz and colleagues (2012) surveyed Polish e-cigarette users recruited from online forums and retail sites in 2010 (n=179) and found that a majority of e-cigarette users were cigarette smokers when they initiated e-cigarette use (86%).(Goniewicz et al., 2012) Participants reported using the products as a less harmful alternative to smoking (41%) or to quit smoking (41%) and 66% reported no conventional tobacco cigarette smoking at the time of the survey. Fourteen percent of the sample were never smokers before they tried e-cigarettes. Twenty percent of that group reported they now also smoke tobacco cigarettes, suggesting e-cigarette use can be a gateway to smoking and dual use.

Farsalinos et al. (2013) conducted one-time interviews with Greek e-cigarette users (n=111) who were biochemically confirmed abstinence from conventional cigarettes (by level of blood carboxyhemoglobin) to characterize their experience with using e-cigarettes as a complete substitute for conventional cigarettes for at least one month.(Farsalinos et al., 2013b) Participants were recruited from a hospital where the researchers work and from e-cigarette forums, 84% men, and formerly heavy smokers. Although, 35% of participants initiated e-cigarette use with a cigarette-like e-cigarettes, most participants reported using devices with eGo batteries (90.9%) or "variable voltage" "mod" devices (9.1%) during their attempt at complete substitution. Forty-two percent reported that they achieved complete substitution in the first month of using the devices,

reported being abstinent for a median of 6 months (IQR: 4-11) and e-cigarette use for a median of 8 months (IQR: 4-13). With regard to the level of nicotine in the cartridges or e-liquid they used, all participants reported starting by using a nicotine level higher than 5mg/ml, with a large majority (74%) using 15mg/ml or higher and 16.2% reported having to increase the nicotine level in their device to help them completely substitute e-cigarettes for conventional cigarettes. Participants reported using a median of 18mg/ml (IQR: 18-18) nicotine concentration "to stop smoking" and then reducing the nicotine level used in their device after achieving complete substitution. In a logistic regression, controlling for nicotine level used to stop smoking, duration of e-cigarette use was statistically significantly associated with having reduced the nicotine level used in the device. Participants rated their dependence on smoking (when they smoked) as higher (79/100) than their current dependence on e-cigarettes (59/100).

In the Czech Republic, Kralikova et al (2012), surveyed 1738 (86% response rate) people they identified as currently smoking or buying conventional cigarettes in 2012.(Kralikova et al., 2013, Cho et al., 2011) Forty-six point seven percent had heard of e-cigarettes but never tried them, 23.9% had tried them once, 16.6% had tried them repeatedly, and 9.7% reported using them regularly. Of the 50% of respondents who had ever tried an e-cigarette, 18.3% reported regular use and 14% reported using them daily. A positive initial experience with e-cigarette use was much higher among those who use e-cigarettes regularly compared to those who only tried them once (68.5% v 15.2%, respectively). Of those who tried only once or repeatedly, “not satisfying” was the top reason given by both groups followed by “poor taste.”In depth analyses were conducted for the sample of regular users (n=158). Among regular users, reasons for trying e-cigarettes were to cut down (39%), use where smoking is not allowed (28%) and to quit smoking (27%) (5.3% gave another reason). Regular users who reported that e-cigarettes helped them cut down (n=93) smoked on average 9.7 (SD=6.5) cigarettes per day, while those who did not report that e-cigarettes helped them cut down (N=61) smoked 13.1 (SD=7.0) cigarettes per day ($p<.005$). Most non-reducers said they used the e-cigarettes to circumvent smokefree laws.

Youth

In a survey of Korean adolescent respondents to the 2008 Health Promotion Fund Project survey (n=4,341), 10.2% of students were aware of e-cigarettes.(Cho et al., 2011) Overall, only 0.5% of students reported having tried an e-cigarette, but there were significant differences in use

by gender (0.91% among males, 0.18% among females, p<0.001) and having ever used conventional cigarettes (2.0% among ever cigarette users, 0.15% among never cigarette users, p<0.001)

A subsequent study of adolescent (aged 13-18) respondents to the 2011 Korean Youth Risk Behaviour Survey (n=75,643) found that prevalence of e-cigarette use had greatly increased in just 3 years to 9.4% ever use and 4.7% past 30 day use.(Lee et al., 2013) Use was also much higher among respondents who used conventional cigarettes: 8.0% ever e-cigarette use among current smokers, 1.4% ever e-cigarette use among non-smokers or former smokers and 3.6% current (past 30-day) use among smokers, 1.1% current use among non-smokers or former smokers). The relationship between e-cigarette use and current (past 30 day) smoking, quit attempts, and no longer using cigarettes was analyzed with logistic regression.(Lee et al., 2013) They found that after adjusting for demographics, current cigarette smokers were much more likely to use e-cigarettes than non-smokers. Among current cigarette smokers, those who smoked more frequently were more likely to be current e-cigarette users. Odds of being an e-cigarette user was 1.58 times (95% CI: 1.39-1.79) higher among students who had made a quit attempt than those who had not. Students no longer using cigarettes were rare among current e-cigarette users (OR 0.10, 95% CI: 0.09-0.12).

In the U.S., Pepper et al, 2013 found high levels of awareness of e-cigarettes (67%) but little use among a sample of 228 adolescent males who participated in an online survey in 2011 (less than 1 percent had tried an e-cigarette).(Pepper et al., 2013) However, in the multivariate logistic regression only current smoking was strongly associated with increased willingness to try an e-cigarette (OR=10.25, CI: 2.88, 36.46). In the bivariate logistic regression, holding a negative opinion of “the typical smoker” was associated with less willingness to try an e-cigarette (OR=0.58, 95% CI: 0.43, 0.79). These findings demonstrate that adolescent boys who use cigarettes are also susceptible to using e-cigarettes and that negative perceptions of being a smoker may be protective against e-cigarette smoking.

Camenga and colleagues (2013) assessed current (past 30-day) e-cigarette use among high school students in 2 high schools in Connecticut and New York (U.S.) (Camenga et al., 2013) Three cross-sectional waves of data were included in analyses (February 2010 (n=1719), October 2010 (n=1702) and June 2011 (n=1345). Analyses showed that past 30-day e-cigarette use increased from 0.9% in February 2010 to 1.7% in October 2010 to 2.3% in June 2011, and

dual use with cigarettes increased from 0.8%, 1.4% to 1.9%, respectively. At all 3 times, the majority of e-cigarette use was dual use with conventional cigarettes (87.5% in February 2010, 82.8% in October 2010 and 83.9% in June 2011). In separate multivariate models for each wave, current cigarette smokers had a statistically significant increased odds of past 30-day e-cigarette use (adjusted for demographics, school and location).

The first national estimates of e-cigarette use among U.S. youth from the National Youth Tobacco Survey document rapid growth of e-cigarette use of e-cigarette use among middle school and high school students in the U.S. from 2011-2012.(Centers for Disease Control and Prevention, 2013) Among middle school youth (grades 6-8), prevalence of ever trying an e-cigarettes doubled from 1.4% in 2011 to 2.7% in 2012. Similarly, current use (past 30-day use) rose from 0.6% to 1.1%. Among high school youth, ever use doubled from 4.7% in 2011 to 10.0% in 2012, with current use rising from 1.5% in 2011 to 2.8% in 2012. Notably, dual use with cigarette smoking accounts for most of the past 30-day e-cigarette use among middle school youth (61.1%) and high school youth (80.5%). Initiation of nicotine exposure with e-cigarettes is evidenced by the fact that 20% of middle school youth who had tried an e-cigarette and 7.2% of high school youth who had tried an e-cigarette had not tried a conventional tobacco cigarette yet.

Dutra and Glantz (in press) further examined e-cigarette use and conventional cigarette smoking using the 2011 NYTS data w (n=18,644).(Dutra and Glantz, in press) This is a cross-sectional study, which presents associations and does not permit causation. Among experimenters with conventional cigarettes (>1 puff, <100 cigarettes), ever e-cigarette use was associated with higher odds of ever smoking (>100 cigarettes; (OR=7.68, 95% CI [5.45-10.83]) and current smoking (OR=7.44, [5.39-10.27]). Current e-cigarette use was associated with increased odds of ever smoking (OR=7.27 [3.99-13.25]) and current smoking (OR=6.68 [3.82-11.68]). Among experimenters, ever use of e-cigarette was also associated with a decreased odds of abstinence from cigarette smoking (past 30-day (OR=0.22 [0.16-0.30]), 6-month (OR=0.22 [0.16-0.29]), and 1-year (OR=0.22 [0.15-0.32]). Similarly, current e-cigarette use was also associated decreased odds of smoking abstinence in the past 30-days (OR=0.15 [0.08-0.28]), 6-month (OR=0.17 [0.07-0.40]), and 1-year (OR=0.15 [0.07-0.34]). Among ever smokers (>100 cigarettes), ever e-cigarette use approached significance for the odds of abstaining from smoking in the past 30 days in 2011 (OR=0.55 [0.31-1.01]). Thus, in this cross-sectional population-based

study, e-cigarette use was associated with higher odds of ever or current cigarette smoking and lower odds of abstinence from conventional cigarettes.

Goniewicz studied e-cigarette use among 20,240 students enrolled at 176 high schools and universities in Poland.(Goniewicz and Zielinska-Danch, 2012) Surveys were administered September 2010 to June 2011. 23.5% of Polish teens aged 15-19 had ever used e-cigarettes and 8.2% reported past 30-day use. Among 20-24 year olds attending universities, 19.0% had ever used an e-cigarette and 5.9% reported past 30-day use. In the whole sample, 3.2% of never smokers had tried an e-cigarette.

E-cigarette use has been assessed in 2 countries via the Global Youth Tobacco Surveys (GYTS) in 2011 and 2012. Results from analyses of the GYTS data for Latvia (2011), revealed that 9.1% of 13-15 year olds are current e-cigarette users (10.3% boys and 7.7% girls). Analyses of the GYTS in Finland (2012) showed that 17% of 13-15 year olds have ever used e-cigarettes (20% boys and 14% girls) and 4.7% are current e-cigarette users (4.2% boys and 5.2% girls).(Reddy, November 12, 2013)

Conclusion

Awareness of and e-cigarette trial has at least doubled among both adults and adolescents, in the countries where data are available from 2008 to 2012. In the U.S., awareness is more prevalent among men, but trying e-cigarettes is more prevalent among women. Almost the same percent of European Union and US adult respondents to national surveys reported having tried e-cigarettes (7% in 2012 vs. 6.2% in 2011, respectively).(TNS Opinion & Social, 2012, King et al., 2013) All population-based studies of adult use show the highest rate of e-cigarette use among current smokers, followed by former smokers, with little use among nonsmokers, although e-cigarette trial and use rose in all of these categories over the past few years (Table 1; note Eurobarometer report did not assess e-cigarette use by smoking status). Therefore epidemiologic, population-based studies indicate that, across countries, e-cigarette are most commonly being used concurrently with conventional tobacco cigarettes, referred to as dual use. Moreover, in some of the European studies (e.g., U.K., Swiss, Czech) the most common reasons given to try e-cigarettes was to use them in places where smoking is restricted and to cut down on smoking, followed by to help with quitting.(Dockrell et al., 2013, Douptcheva et al., 2013, Kralikova et al., 2013) Few of the population-based studies reported on variables that

could be related to self-selection to use e-cigarettes among smokers in the samples, such as dependence, motivation to quit, and previous use of smoking cessation therapies; however, in the studies that did report on such variables, there was mixed evidence to support associations between e-cigarette use and those factors.(Regan et al., 2013, Pearson et al., 2012, Pokhrel et al., 2013, Lee et al., 2013)

Studies of users recruited through e-cigarette-related venues (websites, festivals and purchaser lists) reveal that the motivations for using e-cigarettes are primarily to cut down or reduce smoking and to quit smoking, and show some successful quitting.(McQueen et al., 2011, Goniewicz et al., 2012, Dawkins et al., 2013, Etter and Bullen, 2011b, Farsalinos et al., 2013b, Siegel et al., 2011) These studies indicate that persons motivated to try e-cigarettes have also tried other smoking cessation methods. These studies are limited by self-selection bias inherent in the e-cigarette and smoking cessation-related recruitment methods, which may attract more enthusiastic users and successful quitters.

The data on e-cigarette use among adolescents is more limited but, like adults, shows rapid increases in awareness and use in 5 countries (U.S., Poland, Latvia, Finland and Korea), with higher rates of trial and current use in European countries than the U.S. or Korea.(Reddy, November 12, 2013, Lee et al., Goniewicz and Zielinska-Danch, 2012, Centers for Disease Control and Prevention, 2013, Dutra and Glantz, in press) As with adult population-based studies, data suggest that e-cigarette use is most appealing and prevalent among youth who are also experimenting with or current users of tobacco cigarettes. Dual use with conventional cigarettes is the predominant pattern of e-cigarette use - 61% in middle school students and 80% among high school students. Among middle school youth, 20% of those who had tried e-cigarettes had never tried a tobacco cigarette, which raises the concern that some youth could be initiating nicotine addiction with e-cigarettes. Although it is unclear if e-cigarette use among youth leads to tobacco smoking, this possibility should be strongly considered given the widespread availability of combustible tobacco products including cigarettes, little cigars, cigarillos, bidis as well as smokeless tobacco products. These results indicate rapid market penetration of e-cigarettes among youth, with trial among high school students (10.0%) in 2012 even higher than the 2011 rate for adults, 6.2%.(King et al., 2013) Moreover, although youth who had tried to quit were more likely to use e-cigarettes, most adolescent e-cigarette users are

dual users with conventional smoking, suggesting that e-cigarettes are not leading to abstinence from smoking among adolescents.

These findings are troubling for what they suggest about the trajectory of developing tobacco use. In a longitudinal cohort study of Swedish adolescents that examined trajectories of tobacco use, adolescents who initiated tobacco use with both cigarettes and snus had a significantly elevated risk of progression to current smoking at 18 years old compared to snus initiators (OR= 2.54 (95% CI: 1.68-3.91).(Galanti et al., 2008) A study of U.S. Air Force recruits sheds light on the trajectory of use with different product initiation. Of those who were never smokers when they entered basic training, 5.1% were current users and 2.5% past users of smokeless tobacco. At one-year follow-up the recruits who were current or ever smokeless tobacco users were over 2 times more likely to have started smoking than nonusers.(Haddock et al., 2001) Post et al. (2010) examined tobacco use and nicotine dependence in Swedish adolescents and found that dual users reported the greatest odds of endorsing the dependence symptoms.(Post et al., 2010) These adolescent dual users also had the highest level of endorsing withdrawal symptoms when trying to quit.

ANALYSES OF E-CIGARETTE E-FLUID AND AEROSOL

Chemical Constituents

In 2009, the U.S. Food and Drug Administration (FDA) released a statement that analyses of ENDS products revealed the presence of tobacco-derived impurities and one cartridge contained a toxic contaminant used in antifreeze (diethylene glycol).(Food and Drug Administration, 2009) Two studies from FDA scientists presented analyses of e-cigarette product constituents.(Hadwiger et al., 2010, Trehy et al., 2011) Trehy et al. (2011) conducted an analysis of 4 e-cigarette products for nicotine and minor tobacco alkaloids in liquids and in aerosol generated from the e-cigarettes.(Trehy et al., 2011) Minor alkaloids refer to alkaloids found in tobacco other than nicotine which are present in much smaller quantities than nicotine. The products that were purchased included NJOY, Smoking Everywhere, CIXI and Johnson Creek e-liquid. (It is not clear in which year the products were purchased.) The puffing procedure was 100 ml puffs taken every 60 seconds for 30 puffs. They found that the amount of nicotine measured in the aerosol was impacted by the temperature to which the solution was heated, with repeated heating of the liquid in short intervals (triggered by short puff intervals) enhancing

nicotine release. Thus the amount of nicotine delivered to the user is likely to be dependent on temperature achieved by the heat source and inter-puff interval performed by the user. The analysis of nicotine content of cartridge e-liquid from three of the brands revealed poor concordance of labeled and actual nicotine content, including two labeled as having 0mg nicotine that had nicotine in them. Analysis of the refill solutions from the U.S. e-liquid company Johnson Creek showed good agreement (100-110% of advertised content) between labeled and actual content. Liquids tested from one manufacturer contained minor tobacco alkaloids, including myosmine, anatabine, anabasine and in some cases cotinine and beta nicotyrine. It is likely that these alkaloids were extracted along with nicotine from tobacco as part of the manufacturing process. The analysis of simulated e-cigarette use found that individual puffs contained from 0 µg to 35µg nicotine per puff. Assuming a high nicotine delivery of 30 µg/puff, it would take about 30 puffs to deliver the 1 mg of nicotine typically delivered by smoking a conventional cigarette. A Marlboro cigarette was tested and found to deliver 152-193µg/puff, so 6 or 7 puffs would deliver 1 mg. The levels of minor alkaloids in aerosol were below the limit of detection for both e-cigarettes, although levels could be measured from the smoke of a Marlboro. Two products from CIXI labeled as Cialis and Rimonabant flavor contained amino-tadalafil and rimonabant, medicines to treat erectile dysfunction and a cannabinoid (THC) receptor antagonist, respectively.(Hadwiger et al., 2010) These studies demonstrates inconsistency in nicotine amount compared to labeled content of these e-cigarette products and indicate that in this study, the nicotine in a puff of the highest nicotine e-cigarette contained 20% of the nicotine than contained in a puff of a conventional cigarette. Actual nicotine delivery from an e-cigarette would likely be impacted by users' smoking behavior.

Goniewicz et al. (2012) analyzed 16 brands of e-cigarette products, and 20 samples across brands.(Goniewicz et al., 2013) They measured nicotine content in e-liquid and used an adapted smoking machine to measure the nicotine content in 300 puffs of aerosol generated from each product. The amount of nicotine measured in the e-liquid extracted from the cartridges varied from labeled nicotine content by more than 20% in 9 of 20 samples. Similarly, a 20% difference in marked content vs. actual content was found in 3 of 15 e-cigarette refill liquid samples. Across products, nicotine content ranged from 0.5 mg (SD=0.1) to 15.4 mg(SD=2.1).

Cameron et al. (2013) analyzed 7 e-cigarette solutions (e-liquids) to determine concordance between advertised or labeled and actual nicotine content.(Cameron et al., 2013)

Among the 7 samples of e-liquid, 2 were labeled as containing 24mg/ml of nicotine and 5 were not marked with a specific nicotine content, but as "low," "medium," "high" and "super high." For samples with only strength descriptors, expected concentrations were obtained from information on the brands' websites (low=6-14mg/ml, medium=10-18mg/ml, high and super high=25-36mg/ml). They found that, while all the samples contained nicotine, only 2 were in the expected range and 4 were lower than specified.

Goniewicz et al (2013) analyzed the aerosol from 12 brands of e-cigarettes for toxic and carcinogenic compounds, including carbonyls, volatile organic compounds, tobacco-specific nitrosamines.(Goniewicz et al., 2013 (online first)) They also compared results from the e-cigarette aerosol to the puffs from a medicinal nicotine inhaler. They found varying levels of carbonyls (e.g., formaldehyde, acetealdehyde and acrolein), volatile organic compounds (e.g., toluene) and tobacco-specific nitrosamines present in the e-cigarette aerosol. E-cigarette products varied widely in toxicant content per 150 puffs averaged across sampling timepoints (e.g., formaldehyde range: 3.2-56.1 µg; acrolein: 0-41.9 µg, TABLE 2). The levels of toxicants in the aerosol were 9-450 times lower than the same volume cigarette smoke, supporting the idea that e-cigarette aerosol is much less hazardous than cigarette smoke (Table 2). Goniewicz et al. also compared the e-cigarette aerosol to the aerosol delivered by the nicotine inhaler, a medicine marketed but not widely used to aid smoking cessation. Depending on brand, some toxicants were found in the e-cigarette aerosol at higher levels than the nicotine inhaler (e.g.,o-methylbenzaldehyde and formaldehyde). Five of the 11 toxicants measured were not detected in the nicotine inhaler at all, including acrolein, toluene, p,m,-xylene, NNN, and NNK. They also report the presence of trace amounts of three metals (cadmium, nickel, and lead) in the e-cigarette aerosol as well as in the nicotine inhaler. Whether the levels of toxicants in e-cigarette aerosol indicate an actual health risk compared to the nicotine inhaler is unknown, but toxicant deliveries from both were far lower than from conventional cigarettes.

Kim et al. (2012) developed a liquid chromatography-tandem mass spectrometry method for analyzing TSNAs in electronic cigarette replacement fluids.(Kim and Shin, 2013) They applied their method to 105 refill fluids from 11 different companies in the Korean market. They specifically quantified NNN, NNK, NAT, and NAB, and they present data on total TSNAs in each product. They found nearly a three order of magnitude variation in TSNA concentrations among e-cigarette refill fluids, with total TSNA concentration ranging from 330 µg/ml to 8600

TABLE 2. Levels of toxicants in e-cigarette aerosol compared to nicotine inhaler and cigarette smoke			
Toxicant	Content in nicotine inhaler mist per 15 puffs*	Range in content in aerosol from 12 e-cigarettes samples per 15 puffs*	Range in content in conventional cigarette micrograms (µg) in mainstream smoke from 1 cigarette
Formaldehyde (µg)	0.2	0.2-5.61	1.6-52
Acetaldehyde (µg)	0.11	0.11-1.36	52-140
Acrolein (µg)	ND	0.07-4.19	2.4-62
o-methylbenzaldehyde (µg)	0.07	.13-.71	--
Toluene(µg)	ND	ND-0.63	8.3-70
p,m-xylene (µg)	ND	ND - 0.2	--
NNN (ng)	ND	ND - 0.00043	0.0005-0.19
NNK (ng)	ND	ND-0.00283	0.012-0.11
Cadmium (ng)	0.003	ND - 0.022	--
Nickel (ng)	0.019	0.011-0.029	--
Lead (ng)	0.004	0.003-0.057	--
* 15 puffs was selected to approximate the same nicotine delivery of 1 conventional cigarette; µg=microgram, ng=nanogram ND=Not Detected -- = Not measured Data were taken from Tables 3 and 4 in Goniewicz et al. 2013.(Goniewicz et al., 2013 (online first))Lowest and highest values reported in each table were used for the range presented for each toxicant			

µg/ml. Their data demonstrate significant variability in TSNA composition and quantity among different e-cigarette brands and illustrate the importance of screening numerous products to obtain an overview of product variability.

E-cigarettes do not burn or smolder, so aerosol emitted into the environment is exhaled by the user. Schripp et al. (2012) analyzed the aerosol exhaled by users to determine the presence of toxicants and address the question of secondhand aerosol exposure.(Schripp et al., 2012) Three studies are described. In the first, a smoker puffed 6 puffs from an e-cigarette separated by 60 seconds each time in an $8m^3$ stainless steel chamber with an air exchange rate of 0.3/hr. This puffing regimen in the chamber was repeated with 3 e-liquids (0mg nicotine, apple flavor, 18mg nicotine, apple flavor, 18mg nicotine, tobacco flavor) and one tobacco cigarette. In the second protocol, aerosol from three different types of e-cigarettes puffed for 3 seconds each was pumped into a 10 L glass chamber with an air exchange rate of 3/hr. In the third protocol an

e-cigarette consumer exhaled one e-cigarette puff into a glass chamber. Three e-cigarette devices were used for these experiments – two that used a "tank" system which is directly filled with e-liquid and one that used a cartridge with a cotton fiber on which to drip the e-liquid. Authors found that aerosol from the $8m^3$ chamber analysis contained low levels of formaldehyde, acetaldehyde, isoprene, acetic acid,2-butanodione (MEK), acetone and proponal (Table 3). Analyses of the aerosol in the second protocol (10-l glass chamber) revealed high levels of 1,2-propanediol (propylene glycol), 1,2,3-propanetriol, diacetin (from flavorings), traces of apple oil (3- methylbutyl-3-methylbutanoate), and nicotine. When e-cigarette aerosol was directly pumped into a glass chamber, propylene glycol was the predominant element, with lower levels of others. Nicotine release was 0.1 to 0.2 µg/puff.

Pellegrino et al. (2012) analyzed the chemical composition of the e-liquid and resulting aerosol generated from one Italian brand, of e-cigarettes, Aria, both the nicotine and non-nicotine versions. The e-liquid and aerosol in both nicotine and non-nicotine e-cigarettes was primarily comprised of propylene glycol and glycerol (glycerin) and low levels of flavoring agents and).

Table 3. Concentrations of selected compounds in a test chamber of exhaled e-cigarette aerosol and conventional cigarette secondhand smoke (reproduced from Table 4 of (Schripp et al., 2012))(Schripp et al., 2012)

Table 4 Concentrations ($\mu g/m^3$) of selected compounds during the 8-m^3 emission test chamber measurement of e-cigarette A and conventional cigarette using Tenax TA and DNPH

			E-cigarette			Conventional cigarette
Compounds	CAS	Participant blank	Liquid 1	Liquid 2	Liquid 3	
1,2-Propanediol	57-55-6	<1	<1	<1	<1	112
1-Hydroxy-2-propanone	116-09-6	<1	<1	<1	<1	62
2,3-Butanedione	431-03-8	<1	<1	<1	<1	21
2,5-Dimethylfuran	625-86-5	<1	<1	<1	<1	5
2-Butanone (MEK)	78-93-3	<1	2	2	2	19
2-Furaldehyde	98-01-1	<1	<1	<1	<1	21
2-Methylfurane	534-22-5	<1	<1	<1	<1	19
3-Ethenyl-pyridine[a]	1121-55-7	<1	<1	<1	<1	24
Acetic acid	64-19-7	<1	11	13	14	68
Acetone	67-64-1	<1	17	18	25	64
Benzene	71-43-2	<1	<1	<1	<1	22
Isoprene	78-79-5	8	6	7	10	135
Limonene	5989-27-5	<1	<1	<1	<1	21
m,p-Xylene	1330-20-7	<1	<1	<1	<1	18
Phenol	108-95-2	<1	<1	<1	<1	15
Pyrrole	109-97-7	<1	<1	<1	<1	61
Toluene	108-88-3	<1	<1	<1	<1	44
Formaldehyde[b]	50-00-0	<1	8	11	16	86
Acetaldehyde[b]	75-07-0	<1	2	2	3	119
Propanal[b]	123-38-6	<0.2	<0.2	<0.2	<0.2	12

[a]Quantified on the basis of toluene response.
[b]DNPH method.

nicotine (in the nicotine e-cigarettes

McAuley et al (2012) conducted a published risk assessment of e-cigarettes funded by the Consumer Advocates for Smoke-free Alternatives Association, CASAA, a pro- e-cigarette advocacy group.(McAuley et al., 2012) Key details about the protocol for conducting their risk assessment are not described, as there are obvious problems with the study that do not warrant its review in this report. In fact, a technical report(Burstyn, 2013) (below) reviewing the existing data on e-cigarette constituents that was also funded by CASAA excluded this study due to its poor quality, stating:

> Although the quality of reports is highly variable, if one assumes that each report contains some information, this asserts that quite a bit is known about composition of ENDS liquids and aerosols. The only report that was excluded from consideration was work of McAuley et al.[23] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially trustworthy, but those related to PAH are not since it is incredible that cigarette smoke would contain fewer polycyclic aromatic hydrocarbons (PAH; arising in incomplete combustion of organic matter) than aerosol of e-cigarettes that do not burn organic matter [23]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy.(Burstyn, 2013)

Other problems with the analysis and findings include the fact that they did not detect any benzo(a)pyrene in the conventional cigarette smoke despite the fact that it has been established for over 50 years that benzo(a)pyrene is an important carcinogen in cigarette smoke. The most unreliable conclusion in the paper (on page 855, second column, 11 lines from the top) is that “neither vapor from e-liquids or cigarette smoke analytes posed a condition of ‘Significant Risk’ of harm to human health via the inhalation route of exposure." Given the authors' analysis found that conventional cigarettes did not pose significant risk, there is likely a fatal error in the data, analysis, or both. This paper's conclusions about e-cigarette toxicity does not appear credible as it concludes that cigarettes are not dangerous to inhale.

In the technical report funded by CASAA examining the constituents in e-cigarette cartridges and liquid, Burstyn (2013) employs occupational threshold limit values (TLVs) to evaluate the potential risk posed by various toxins at various levels in e-cigarettes.(Burstyn, 2013) In reviewing the evidence of risk due to propylene glycol or glycerine exposure the report

states that assuming a high level of consumption around 5-25ml of solution a day could produce levels of exposure to propylene glycol and glycerin to justify concern. The author noted that the assessment is limited by "the quality of much of the data that was available for [the] assessment was poor." Based on calculated levels of inhalation, the author concludes that

> …there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (contaminants plus declared ingredients), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.(Burstyn, 2013)

TLVs are an approach to assessing health effects for occupational chemical exposures that are generally much higher (often orders of magnitude higher) than levels considered acceptable for ambient or population-level exposures.(Employing an occupational standard to evaluate risk to the general population is the same approach to risk assessment as those conducted for secondhand smoke by those affiliated with the tobacco industry, which concluded that secondhand tobacco smoke could not produce any adverse health effects.) Occupational exposures also do not consider exposure to sensitive subgroups, such as people with medical conditions, children and infants, who might be exposed to secondhand e-cigarette emissions, most notably nicotine.

Particulate Matter

Particle size is an important determinant of where inhaled particles will be deposited in the respiratory system and the resulting adverse health effects of particulate exposure (U.S. EPA http://www.epa.gov/pm/). All particles less than or equal to 10 microns in aerodynamic diameter (i.e., PM_{10}) reach the respiratory system and potentially cause health problems in the circulatory and respiratory systems (http://www.epa.gov/pm/health.html). Those whose diameter falls between 2.5 and 10 microns are considered the “inhalable coarse fraction” and impact the large central airway. Fine particles with an aerodynamic diameter are defined as particles less than equal to 2.5 microns and are termed $PM_{2.5}$. Ultrafine particles (also called nanoparticles) are particles less than or equal to 0.1 micron (0.1 micron = 100 nm). (For reference, conventional cigarette smoke particles have a median size of 200-400 nm.) For ultrafine particles between

approximately 10 and 300 nm in diameter, roughly 10 – 50% are deposited in the furthest reaches of the lungs – the alveoli (FIGURE 4, below). Ultrafine liquid particles would coalesce with lung fluid to form a film, and constituents would be absorbed after deposition, as for larger particles. Solid ultrafine or nano-particles (carbonaceous or metal) can penetrate the epithelium and reach circulation. Once in the bloodstream they can be deposited around the body and be absorbed directly into cells through endocytosis. There is also evidence of extrapulmonary translocation of ultrafine particles with various potential toxic effects(Oberdorster et al., 2005) (Oberdorser et al. 2005) including translocation to the central nervous system.(Elder et al., 2006)Frequent low or acute high levels of exposure to fine and ultrafine particles can contribute to pulmonary and systemic inflammatory processes and increase the risk of cardiovascular and respiratory disease and death (Pope et al., 2009, Brook et al., 2010)and respiratory problems.(Mehta et al., 2013)

Because of these health concerns, the U.S. EPA has standards for ambient concentrations of both $PM_{2.5}$ and PM_{10}: http://www.epa.gov/air/criteria.html.Ambient particles can be variable and chemically complex and the specific components responsible for toxicity are generally not known.(Ostro et al., 2007) In particular, the relative importance of particle size and particle composition to toxicity is not known. Given these uncertainties, it is not clear to what extent the ultrafine particles delivered by e-cigarettes will have similar health effects and toxicity as ambient fine particles such as those generated by conventional cigarette smoke or secondhand

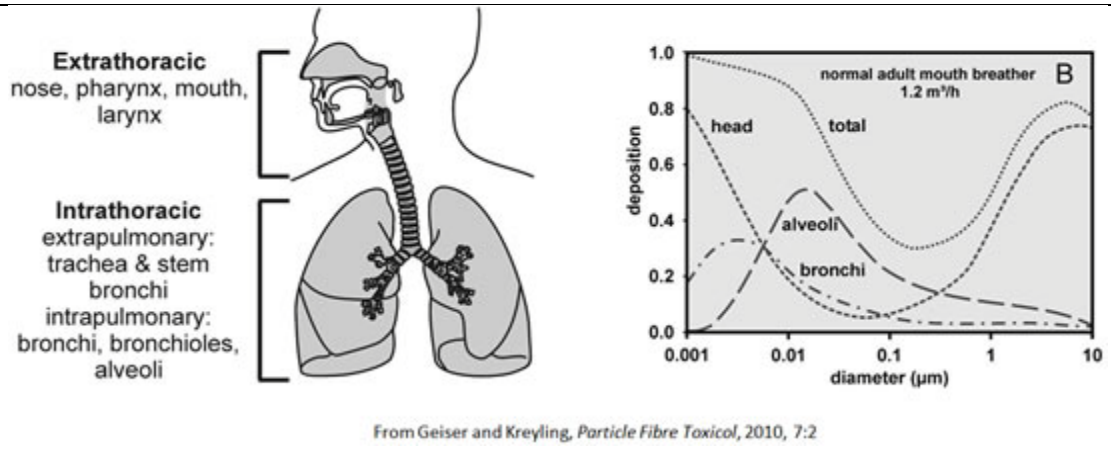

FIGURE 4. Particle deposition in the human body by size (reproduced from Geiser and Kreyling, 2010)(Geiser and Kreyling, 2010)

smoke; e-cigarette particles could be more, less or of equal toxicity as other particles of similar size.

Schripp et al. (2012) observed particles in exhaled e-cigarette aerosol, around and below 100 nm.(Schripp et al., 2012), the range of sizes that are efficiently deposited to alveoli (Figure 4). The number of particles was observed to decrease as a function of time with specified time intervals, 1, 5, 10 minutes in both the $8m^3$chamber and the glass 10 liter chamber, perhaps due to deposition in the container. Exhaled e-cigarette aerosol contained mostly propylene glycol and smaller amounts of related VOCs, apple oil (flavorant) and nicotine. The authors conclude that *"'passive vaping' must be expected from the consumption of e-cigarettes."* Like secondhand cigarette smoke, levels of these chemicals in real environments where e-cigarettes are being used will depend on the density of users and properties of the ventilation system.

Pellegrino et al. (2012) compared pollution levels in a chamber of particulate matter from a nicotine-containing e-cigarettes and a non-nicotine e-cigarettes and a conventional cigarette via evaluation of the concentration of suspended particulate (TSP) and particles sized $\leq$ 10, 7.5, 2.5 and 1 µg.(Pellegrino et al., 2012) All measurements to determine TSP was taken over a 3 minute periodwith "a portable laser operated aerosol mass analyser (Aerocet 531, Metone Instruments Inc, USA) in an air volume of $11m^{3"}$. The e-cigarettes were attached to a device which drew 4 puffs per minute over the 3 minutes, but it was unclear from a description of the methods whether the conventional cigarette was left burning for the study period of 3 minutes or the same number of puffs were elicited. (The very high levels of TSP after 3 minutes, around 900 µg $/m^3$, suggests that the conventional cigarettes were allowed to burn continuously.) It is also not clear whether the authors were comparing mainstream e-cigarette aerosol with total or sidestream conventional cigarette smoke. Authors found greater concentrations of larger compared to smaller particles in e-cigarette and cigarette emissions. The authors also reported much larger particles than the other particle size studies. Particle concentrations were much higher (15 times) in air polluted by cigarette smoke than either nicotine or non-nicotine e-cigarettes for all sizes of particles. There are several methodological concerns about this study and the results are very different from the other papers on this topic.(Fuoco et al., 2014, Ingebrethsen et al., 2012, Schripp et al., 2012, Zhang et al., 2013, Williams et al., 2013)

Zhang et al. (2103) examined the size of e-cigarette aerosol particles and likely deposition in the human body. They examined e-cigarette aerosol produced by a single brand of

e-cigarettes (BloogMaxXFusion) using both propylene glycol and vegetable glycerin-based liquids.(Zhang et al., 2013) They generated the aerosol by using a smoking machine that was altered to take 25ml aerosol samples for analysis. In order to assess the likely deposition of particles in the human respiratory system, they used two factors: particle size and lung ventilation rates (one for a "reference worker" one for a "heavy worker," 1.2 m^3/hr and 1.688 m^3/hr, respectively). They found that e-cigarettes and tobacco cigarettes produce aerosols with similar particle size, with some particles in the nanoparticle range. Their human deposition model estimated that 73-80% of particles are distributed into the exhaled aerosol, while 7%–18% of particles would be deposited in alveoli resulting in arterial delivery and 9%–19% would be deposited in the head and airways, resulting in venous delivery.(Zhang et al., 2013) As expected, the heavy worker model showed more alveolar delivery across puffs compared to the reference worker who would have more head and airway delivery.(Zhang et al., 2013) In total, about 20-27% of particles are estimated to be deposited in the circulatory system and into organs from e-cigarette aerosol, which is comparable to the 25-35% for conventional cigarette smoke.

Ingebrethsen et al. (2012) (authors employed at RJ Reynolds tobacco company) conducted a study of particle size in e-cigarette aerosol using three methods (spectral transmission, electric mobility, and gravimetric).(Ingebrethsen et al., 2012) and found the aerosol particles to average 250–450 nm in size, which is comparable to conventional cigarettes. Testing two brands of e-cigarettes (one disposable, one rechargeable) and one tobacco cigarette, authors found that the geometric mean particle size ranged from 238 to 387 nm, and was similar for e-cigarettes and tobacco cigarettes. (The authors did not describe the composition of the e-liquids, which can potentially affect particle size and concentration.)

Fuoco et al. examined particle number concentration and distribution as well as a volatility analysis of the e-cigarette aerosol generated from 3 different devices(2 rechargeable and 1 disposable) using 4 different refill e-liquids with varying levels of nicotine and flavorants. The authors used state-of-the art methods to measure particle number concentration and size distribution (condensation particle counter and a fast mobility particlesizer spectrometer, respectively). Comparisons of particle number concentration in the aerosol from different nicotine content e-liquids, revealed that the higher the nicotine content in the e-liquids the higher

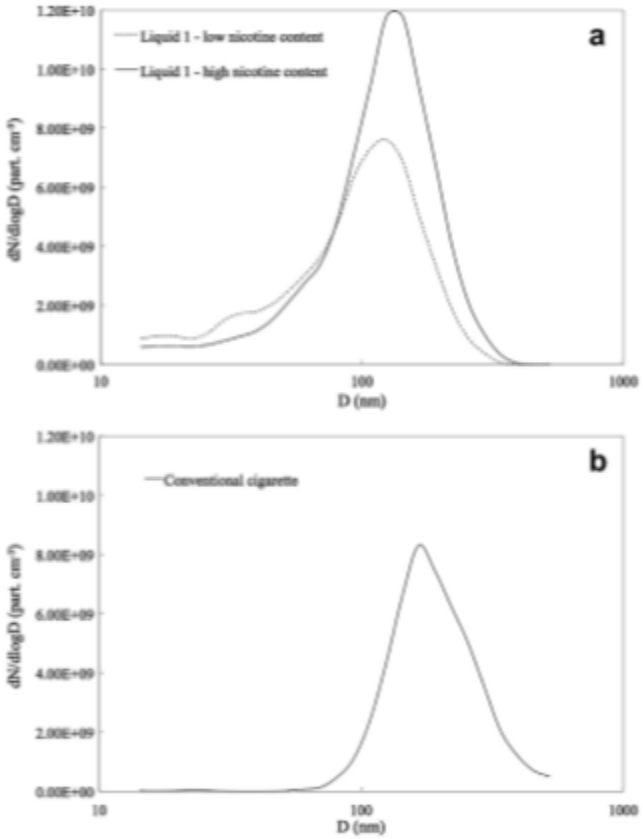

Fig. 3. Particle number distribution measured through the FMPS 3091 (after thermodilution at 37 °C) of the mainstream aerosol from the Liquid 1 (a) and from the conventional tobacco cigarette (b).

Figure 5. Particle number distribution from a) mainstream aerosol in e-liquid 1 and from b) conventional cigarette (reproduced from Figures 3 in Fuoco et al., 2013(Fuoco et al., 2014))

the particle number in the resulting aerosol with little effect on the particle size distribution. Longer puffing time resulted in more particles. Flavor was not associated with differences in particle number or size distribution. The particle size distribution (with modes around 120-165nm range) was similar to conventional cigarettes, with some e-cigarettes delivering more particles than conventional cigarettes.The particle size distributions were similar to that found in Schripp et al. and Ingebrethesen et al. (Figure 5)

Metals in e-cigarette liquid and aerosol were studied by Williams et al (2013) who performed various laboratory analyses on 22 dissected cartomizers (the atomizer and cartridge combined into a single component).(Williams et al., 2013) They examined metal content and quantity in both e-liquid (from cartomizers) and the corresponding aerosol using electron microscopy and energy dispersive x-ray spectroscopy. Both the e-liquid and the Poly-fil fibers

that are used to absorb the e-liquid for heating and conversion to an aerosol andcome into contact with heating elements in the cartomizers, contained heavy metals (tin, nickel, copper, lead, chromium).(Williams et al., 2013) Tin, which appeared to originate from solder joints, was found in the form of both particles and tin whiskers in cartomizer fluid and Poly-fil. E-cigarette fluid containing tin was cytotoxic to human pulmonary fibroblasts.(Williams et al., 2013) E-cigarette aerosol also contained other metals. Levels of nickel were measured that were 2-100 times *higher* than found in Marlboro cigarette smoke. The nickel and chromium possibly originated from the heating element, which conventional cigarettes do not have. Some nickel, tin and chromium in the aerosol were in the form of nanoparticles (<100 nm). This study analyzed e-cigarette models that employ Poly-fil fiber to contain the e-liquid, which is not used in some "tank" systems, where liquid surrounds a heating element or wick. It is likely that the engineering features, including the nature of the battery and the heating temperature of the liquid, the type of heating element and reservoir, will influence the nature of particles that are produced, how many and at what size. These metal nanoparticles can deposit into alveolar sacs in the lung, potentially causing local respiratory toxicity and/or becoming translocated into the circulation.

Cytotoxicity

Bahl et al (2012) screened 41 e-cigarette refill fluids obtained from 4 companies (year of purchase not reported) for cytoxicity (measured as the ability to kill half of the cells in a culture using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay procedure) to three cell types: human pulmonary fibroblasts, human embryonic stem cells, and mouse neural stem cells.(Bahl et al., 2012) The latter two cells types were chosen as early prenatal and early postnatal models. A hierarchy of cytotoxicity was determined based on e-cigarette liquid that killed 50% of the cells (IC_{50}) for the human embryonic stem cells, which were the most sensitive of the three cell types tested. Results showed that: (1) cytoxicity varied among products with some being highly toxic and some having low or no cytoxicity, (2) nicotine did not cause cytotoxicity, (3) all companies had some products that were non-cytotoxic and some that were highly cytotoxic, (4) one company had products that were non-cytotoxic to pulmonary fibroblasts but cytotoxic to both types of stem cells, (5) cytotoxicity was related to the concentration and number of flavorings used. The finding that the stem cells were more sensitive

than the differentiated adult pulmonary fibroblasts cells suggests that adult lungs are probably not the most sensitive system to the effects of exposure to e-cigarette aerosol. These findings also raise concerns about pregnant women who use e-cigarette or are exposed secondhand e-cigarette aerosol.

In a study funded by FlavorArt e-cigarette liquid manufacturers, Romagna and colleagues (2013) compared the cytotoxicity of aerosol produced from 21 flavored (12 tobacco flavored and 9 fruit or candied flavored; all contained nicotine) brands of e-cigarette liquid to smoke from a reference conventional tobacco cigarette.(Romagna et al., 2013) Samples were analyzed for cytotoxicity using an embryonic mouse fibroblast cell line (3T3) via the MTT assay according to UNI ISO 10993-5 standards, which defines cytoxicity as a 30% decrease in viability of treated cells vs. untreated controls. Only aerosol from coffee-flavored e-liquid produced a cytotoxic effect average of 51% viability at 100% concentration of solution). They concluded that e-cigarette aerosol is much less toxic than cigarette smoke and could be useful products in tobacco harm reduction.

Farsalinos et al. (2013) analyzed the aerosol generated by e-cigarettes and a conventional cigarette for cytotoxicity to cultured rat myocardial cells.(Farsalinos et al., 2013a) Study authors tested 20 refill solutions from 5 manufacturers containing 6 to 24mg/ml of nicotine; 17 tobacco flavored, 3 fruit or candy flavors), a "base" only solution (50% propylene glycol and 50% glycerol)and smoke from a cigarette (0.8mg nicotine, 10mg tar, 10 mg carbon monoxide) in an e-cigarette cartridge and atomizer with a low-voltage battery (3.7 volts) attached and one with a high voltage battery (4.7 volts) attached (the high voltage battery contained an "electronic circuit by which the voltage applied to the atomizer can be adjusted"). The aerosol extract, base only and cigarette smoke solutions were tested on cardiac myoblasts (H9c2) at 100% and 4 dilutions (50%, 25%, 12.5%, 6.25%)and cytotoxicity was measured after a 24 hour incubation period by the ISO 10993-5 <70%. The aerosol from 3 refill fluids was cytotoxic at 100% and 50% dilution, two were tobacco flavored and one was cinnamon cookie flavored. Cigarette smoke was cytotoxic at 100% and all dilutions except 6.25%.

Conclusion

The studies of what is in e-cigarettes are limited by the selection of a handful of products tested (from the hundreds on the market) and by puffing protocol which may or may not reflect

actual users puffing behavior. Considering these limitations, the published research demonstrates a lack of standards for e-cigarettes, mislabeled nicotine content and wide variability in e-cigarette constituents and toxicants.(Trehy et al., 2011, Goniewicz et al., 2013, Hadwiger et al., 2010, Cameron et al., 2013) The e-liquid that is aerosolized in e-cigarette devices is not uniform in ingredient content and proportion; some do not even include nicotine. Studies have detected varying levels of nicotine content from labeled amounts, and the presence of volatile organic compounds, tobacco-related carcinogens, metals and chemicals. For the carbonyl compounds (formaldehyde) and the VOCs, the data show much lower levels than a cigarette but higher levels than the nicotine inhaler.(Goniewicz et al., 2013 (online first)) In addition, the data in Table 2 demonstrate that, depending on brand and sample, an e-cigarette possibly delivers several toxins which were not detected in the nicotine inhaler (the reference for this study). Some of the chemicals, particularly some flavoring agents, in e-cigarette aerosol are cytotoxic to human and rat cells, particularly human embryonic cells. Several chemicals that have been found in e-cigarette aerosol and e-liquid are on California's official list of known human carcinogens or reproductive toxicants,, including nicotine, acetaldehyde, formaldehyde, nickel, lead, toluene.(California Office of Environmental Health Hazard Assessment (OEHHA), November 8, 2013)

Studies that have measured the diameter of the particles comprising e-cigarette aerosol have detected small (<10microns in diameter), fine (<2.5microns in diameter) and ultrafine/nanoparticles (<1 micron in diameter).(Williams et al., 2013, Schripp et al., 2012, Zhang et al., 2013) The size of particles is important for how they can deposit in the body's bloodstream, cells and organs. The smaller the particle size, the easier it is for chemicals to enter the bloodstream and cells, potentially effecting damage or changes. Very small particles mostly get inhaled and exhaled. However some fraction of these particles, at least of certain types, may be absorbed directly. Medium sized particles (cigarette smoke size) are optimal to impact and release their constituents into the airways, and then be absorbed.

The particle size distribution and number of particles delivered by e-cigarettes is similar to that of conventional cigarettes, with most of the particles in the ultrafine range (modes around 100 -200 nm). The particle delivery appears to depend on nicotine level in the e-cigarette liquid, with more particles delivered in higher nicotine e-cigarettes, but not as impacted by the presence of flavors. Users exhale some of these particles, which exposes bystanders to "passive vaping."

Like cigarettes, e-cigarette particles are small enough to reach deep into the lungs and cross from lungs into blood and be absorbed into body tissues.

Based on the data from all these studies one would expect that e-cigarette aerosol could be inhaled into the deep lung, similarly to a tobacco cigarette. The particle concentrations ($10^9/cm^3$) were also similar for e-cigarette and conventional tobacco cigarettes.

At minimum, these studies show that e-cigarette aerosol is not merely "water vapor" as is often claimed in the marketing for these products. Based on these studies, the e-cigarettes tested have much lower levels of most toxicants – but not particles -- than conventional cigarettes. The thresholds for human toxicity of potential toxicants in e-cigarette aerosol are not known, and the possibility of health risks to primary users of the products and those exposed passively to the product emissions must be considered.

BIOLOGICAL EFFECTS

Nicotine Absorption

Vansickel et al. (2010) conducted a study with 32 healthy smokers to examine nicotine absorption from e-cigarettes, cardiovascular effects on craving and withdrawal after using an e-cigarette.(Vansickel et al., 2010) (Results with a subset of these participants were published in *Tobacco Control* as a research letter prior to this study being published and reported similar findings.(Eissenberg, 2010)) Participants with no prior e-cigarette use were asked to participate in each of 4 product use protocols (own brand of cigarette, 18mg NJOY “NPRO” e-cigarette, 16mg Crown Seven “Hydro” e-cigarette, and sham-unlit cigarette) separated by 48 hours and after 12 hours of abstinence from tobacco smoking. The flavor of e-cigarette cartridge was matched to the type of tobacco cigarette usually used by the participant (e.g., menthol or non-menthol). Biological measures were blood plasma nicotine and expired air carbon monoxide (CO); heart rate and subjective measures of craving and withdrawal were also assessed. They found that 5 minutes of puffing on both e-cigarettes and sham cigarette resulted in little or no change from baseline in blood plasma nicotine levels but the expected increased occurred with own brand of tobacco cigarettes (18.8ng/ml) (Figure 6 reproduced from their article). After 5 minutes of puffing, heart rate increased reliably for own cigarette brand only, from 65.7(SD=10.4) to 80.3(SD=10.9) beats per minute. Neither e-cigarette product nor sham smoking increased expired air CO concentration, but own cigarette brand smoking increased CO

as expected. E-cigarette use, with or without nicotine, decreased some nicotine/tobacco abstinence withdrawal symptoms, including cigarette craving, although not to as great an extent as smoking a conventional cigarette. This study shows that smokers could experience some modest relief of some withdrawal symptoms and positive subjective effects with e-cigarette use despite minimal systemic delivery of nicotine.

In a cross-over trial, (Bullen et al 2010) 40 adult smokers were randomized to the following groups at different times: e-cigarette (Ruyan V8) 16mg nicotine, 0mg e-cigarette, Nicorette inhalator, or their usual cigarette for four days (with three days in between test

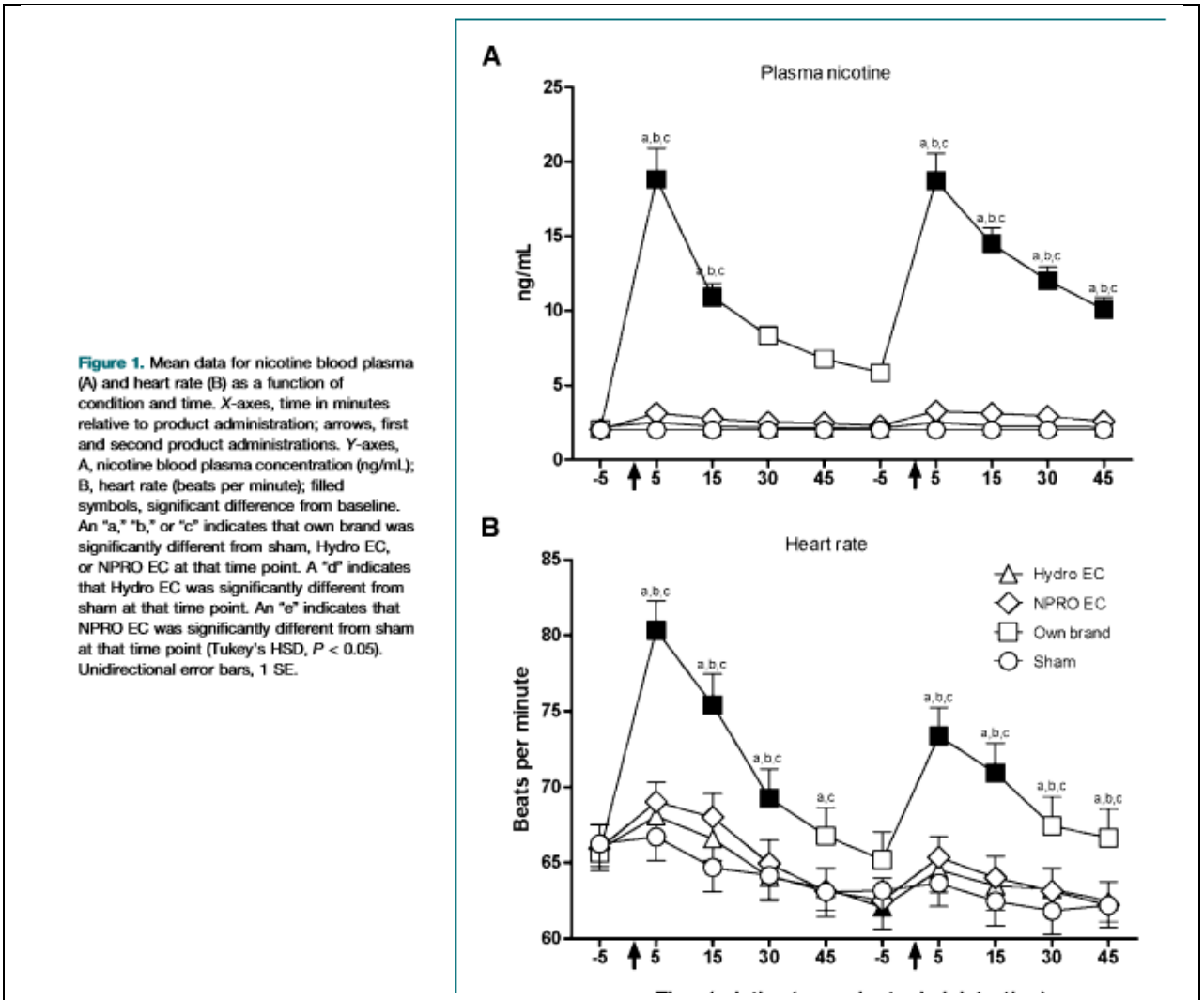

Figure 1. Mean data for nicotine blood plasma (A) and heart rate (B) as a function of condition and time. *X*-axes, time in minutes relative to product administration; arrows, first and second product administrations. *Y*-axes, A, nicotine blood plasma concentration (ng/mL); B, heart rate (beats per minute); filled symbols, significant difference from baseline. An "a," "b," or "c" indicates that own brand was significantly different from sham, Hydro EC, or NPRO EC at that time point. A "d" indicates that Hydro EC was significantly different from sham at that time point. An "e" indicates that NPRO EC was significantly different from sham at that time point (Tukey's HSD, $P < 0.05$). Unidirectional error bars, 1 SE.

Figure 6. Levels of blood plasma nicotine concentration and heart rate over time by condition in participants in a 4-arm cross-over study (reproduced from Vansickel et al. (2010))(Vansickel et al., 2010)

rounds).(Bullen et al., 2010) The 16mg e-cigarette resulted in similar serum level of nicotine as the Nicorette inhalator in a similar amount of time (1.3ng/ml at 19.6 min and 2.1ng/ml at 32.0 min, respectively), with the inhaler taking longer to reach peak levels. However, both the e-cigarette and the nicotine inhaler achieved much lower peak serum nicotine levels with a longer time to peak concentration compared to a tobacco cigarette, which increased serum nicotine to 13.4ng/ml at 14.3 min. The 16mg e-cigarette and nicotine inhalator reduced desire to smoke over the 60 minute puffing period more than the 0mg e-cigarette (Figure 7 reproduced from their paper). Both 16mg e-cigarette and the nicotine inhalator reduced the desire to smoke and withdrawal symptoms, with no statistically significant differences. Respondents reported a similarly low level of "satisfaction" with both the 16mg e-cigarette and the nicotine inhalator (approximately 3 on a 10 point scale, exact number not reported), but rated the 16mg e-cigarette as more "pleasant to use" than the inhalator by 1.49 units on a 10 point visual analog scale (VAS) scale (p=0.016).The cross-over design is a strength of the study as it tests the effects of each condition within the same person. However, authors noted that the 16mg e-cigarette failed to deliver nicotine to one-third of participants and participants reported failure of the device to

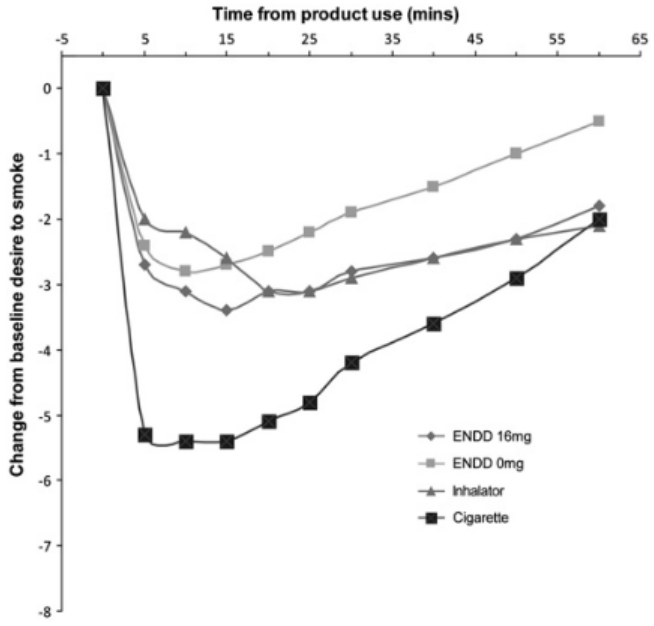

Figure 2 Change in desire to smoke from baseline over the first hour after each product use.

Figure 7. Change in desire to smoke among participants in a 4-arm cross-over trial of 16mg and 0mg nicotine e-cigarette use, inhalator and conventional cigarette (Reproduced from Bullen et al. (2011)(Bullen et al., 2010)

function and produce aerosol (which the authors noted that they discussed with the e-cigarette company supplying the products). This study may also be limited by lack of a “practice period” for participants to become familiar with how to use the e-cigarette or nicotine inhalator, as participants had never used them and only 2 participants had ever used the nicotine inhalator. (This study was funded by the e-cigarette manufacturer, Ruyan Group Holdings Limited through Health New Zealand Ltd., a company owned by one of the authors, M. Laugesen.)

Vansickel and Eissenberg (2013) conducted a second study of nicotine delivery and craving suppression, this time in former smokers who were experienced e-cigarette users (n=8; at least 3 months of regular use) and brought their own e-cigarette device for use during a single, 5-hr. session.(Vansickel and Eissenberg, 2013) For the first part of the protocol, plasma nicotine, heart rate and subjective effects were assessed at baseline and 5 and 15 minutes after users took 10 puffs (at 30 second intervals) followed by a one-hour ad lib puffing session, where blood was sampled every 15 minutes and during a 2-hour rest (no puffing) session where blood was sampled every 30 minutes. Seven of the eight participants used e-cigarette devices that "did not resemble tobacco cigarettes, contained cartomizers, and housed higher voltage and/or longer lasting batteries "than the cigarette-sized e-cigarette products used in the authors' previous work.(Vansickel et al., 2010) Most of the participants used 18 mg/ml nicotine solution (n=6), 1 used 24mg/ml and one used 9mg/ml. Mean blood plasma nicotine level reached 10.3 ng/ml (SEM = 2ng/ml)during the 10-puff protocol, which was much higher than previous studies and comparable to that delivered by conventional cigarette smoking. Blood plasma levels reached an even higher mean after one-hour of ad lib puffing (Figure reproduced form the original article below). During ad lib puffing, heart rate increased from an average of 73.2(SD=2.0beats/min to 78(SD=1.9) within the first 5 minutes and remained elevated throughout the hour, consistent with the expected effects of nicotine. Nicotine withdrawal symptoms (e.g., restlessness) were relieved over the 75minute puffing period (Figure 8, reproduced from their article).(Vansickel and Eissenberg, 2013) Overall, these results show effective nicotine delivery inexperienced users, using their own cartomizer style e-cigarette (with higher battery power than the first generation cigarette-like e-cigarette), with nicotine deliveries comparable to conventional cigarettes, and subjective effects on withdrawal symptoms suggest the e-cigarette relieves symptoms of nicotine physical dependence.

Dawkins et al (2013) assessed nicotine delivery in a study intended to replicate the methodology described above in Vansickel and Eissenberg (2013) in a study funded by SkyCig e-cigarette company.(Dawkins and Corcoran, 2013) Participants (n=14, 6 current smokers, 8 ex-smokers) who were recruited via the SkyCig company website, used at least one 18mg/ml e-cigarette cartridge per day for a minimum of 1 month, were almost all men (3 women), and had a mean age of 37 years. Authors reported difficulty in obtaining samples from half of the participants due to various reasons and consequently only 7 of the 14 participants were able to provide complete blood samples (none of the 3 women were able to provide samples at all time points). Among the 7 participants with complete data, from baseline to 10 minute after taking 10 puffs of the 18 mg/ml e-cigarette, blood plasma nicotine concentration increased from an average concentration of 0.74 ng/ml to 6.77 ng/ml and reached a maximum average peak of 13.91 ng/ml

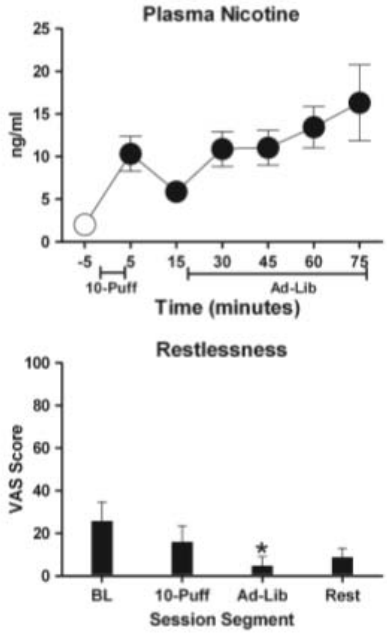

Figure 1. Top panel: *M* (±1 *SEM*) plasma nicotine (assay's limit of quantitation = 2 ng/ml; Breland, Kleykamp, & Eissenberg, 2006) levels at baseline (−5) and during the 10-puff and 1-hr ad lib puffing periods. Filled symbols indicate a significant difference from baseline. Bottom panel: *M* (+1 *SEM*) response to a visual analogue scale item assessing "restlessness" (0–100 scale) at baseline and the end of the 10-puff, ad lib, and rest periods. An asterisk indicates a significant difference from baseline. Data are from eight electronic cigarettes (EC) using participants who abstained from ECs for at least 12 hr before session. Paired *t* tests were used to compare means, $p \leq .05$.

Figure 8. Plasma nicotine concentration and level of restlessness before, during and after e-cigarette use (Reproduced from Vansickel and Eissenberg (2013))(Vansickel and Eissenberg, 2013)

after the 60 minute ad lib session. Participants' tobacco withdrawal symptoms were reduced significantly after e-cigarette use (both the 10 minutes and 60 minute puffing periods).

In another study, Dawkins and colleagues (2013) (Dawkins et al., 2012) also tested the effect of e-cigarette use on withdrawal symptoms, craving and cognition in 86 smokers who had no prior e-cigarette use. (This study was funded by SkyCig e-cigarette company and e-cigarettes were provided by The Electronic Cigarette Company). Participants were randomized to engage in 5 minutes of ad lib puffing on an 18mg/ml "White Super" brand e-cigarette, a 0mg/ml (placebo) "White Super" e-cigarette, or to hold an e-cigarette for 5 minutes without puffing on it and measurements were taken at baseline (time 1), after 5 minutes (time 2) and after 20 minutes (time 3). Authors found that desire to smoke decreased from time 1 to time 3 for both the nicotine and placebo e-cigarette groups compared to the just hold group; declining statistically significantly more in men vs. women. With regard to withdrawal symptom reduction, there were differences in symptoms reduction between men and women. Among men in the nicotine e-cigarette group, symptoms of anxiety, restlessness, poor concentration and irritability were statistically significantly reduced from time 1 to time 3 compared to the participants in placebo e-cigarette and the just hold conditions, but only poor concentration and depression were reduced among women compared to just hold condition. Authors conclude that perhaps nicotine is more important for reducing withdrawal symptoms for men than women. There was no statistically significant difference in performance on the letter cancellation task among the three groups; however those in the nicotine group demonstrated better performance on the Brown-Peterson memory test compared to those in the placebo e-cigarette and just hold condition.(Dawkins et al., 2012)

Nides et al. (2013) examined nicotine delivery and the potential for reduction and cessation among adult smokers provided NJOY King disposable cigarettes over a one-week period (e-cigarettes contained 26 mg nicotine in 0.5 ml of solution each, i.e., 52 mg/ml) (study funded by NJOY e-cigarette company).(Nides et al., 2014) Participants were 25 healthy adult smokers not currently ready to quit smoking (in the next 30 days), mean age 43 years, 66% male, on average smoked 20 cigarettes/day, 45% never e-cigarette users, 7% used more than 10 e-cigarettes in their lifetime. They attended 3 lab visits: visit 1 to screen for eligibility), visit 2 for training which included instructions on how to use the e-cigarettes, provision of a 10-day supply of e-cigarettes (menthol or regular, depending on user preference) and instruction to use them ad

libitum), and visit 3, a follow-up one-week after the training visit. At the screening visit, participants were also instructed to keep a log of cigarettes smoked per day which they returned at visit 2 and at visit 2 were instructed to keep a log of cigarettes smoked and e-cigarette puffs taken per day (using a manual counting device) until visit 3 when they turned in that log. At visit 3, participants came in (abstinent from nicotine for previous 12 hours) and their plasma nicotine, carbon monoxide, heart rate, craving and withdrawal and perception of the products were measured. Blood nicotine levels after 5 minutes of use (10 puffs with 30 seconds between puffs) reached a mean of 3.5 ng/ml (range 0.8-8.5 ng/ml), heart rate increased and craving was reduced by 55% and CO did not increase. During the trial week, most used the e-cigarette daily and participants took a median of 59 puffs each day (range 1.7-400 puffs), 89% decreased cigarettes per day by an average of 39%. Participants rated the e-cigarettes as highly satisfying in terms of looking like a cigarette, safety, ease of use, use to cut down on cigarettes and use to quit smoking. Most common adverse events rated as study-related were "local irritation of the mouth, throat or airways, specifically throat irritation, followed by cough, dry throat, burning sensation on lips," all of which were rated by participants as mild, except one who discontinued use due to throat irritation.

Etter (2011) reported on saliva cotinine levels in experienced e-cigarette users recruited through the smoking cessation and e-cigarette forum websites described in Etter and Bullen 2011.(Etter and Bullen, 2011a) Participants in the original study completed an online questionnaire and 196 participants were mailed saliva collection materials, of which 31 mailed back saliva samples. Thirty participants were former smokers and 1 reported currently trying to quit and smoking 1 cigarette per day. The sample was mean age 41 years, 65% men and reported using 18mg/ml nicotine concentration e-liquid, 5 refills per day and taking a median of 200 puffs per day. Median cotinine among the ex-smokers was 322ng/ml. Investigators concluded that cotinine levels among e-cigarette users were higher the levels reported among those using NRT and similar to the levels reported among smokers.

Abuse Liability

Vansickel et al 2012 conducted a study of the abuse liability of an 18mg e-cigarette (Vapor King brand) with 20 current, daily smokers.(Vansickel et al., 2012) They tested several aspects of abuse liability during a series of four within-subject sessions, 1 of which allowed for

product sampling to familiarize users with the device and 3 of which involved the “multiple choice procedure,” (MCP) a validated procedure in which participants sample a drug and then make two or more choices between it and another drug, or a series of monetary values. The first session involved 6, 10-puff bouts with each puff separated by 30 seconds and each 10-puff bout separated by 30 minutes. During the MCP sessions, participants chose between 10 e-cigarette puffs and varying amounts of money, 10 e-cigarette puffs and a varying number of own brand conventional cigarette puffs, or 10 conventional cigarette puffs and varying amounts of money. The monetary value at which users chose money over the 10 product puffs was considered the "crossover value," or for e-cigarette and conventional cigarette choice condition crossover value was when participants chose conventional cigarette puffs over the e-cigarette puffs. The crossover values were higher for conventional cigarettes compared to e-cigarettes (average of $1.06(SD=$0.16) for 10 e-cigarette puffs and average of $1.50(SD=$0.26) for 10 conventional cigarette puffs ($p<0.003$). E-cigarettes delivered a similar level of nicotine as a cigarette, but more slowly and required a greater number of puffs than cigarettes to achieve the same nicotine level, and reduced withdrawal symptoms. The authors concluded that e-cigarettes deliver nicotine, can reduce withdrawal symptoms and appear have lower abuse potential compared to conventional cigarettes.

Conclusion

The early studies of nicotine absorption found that e-cigarettes delivered a lower level of plasma nicotine than conventional cigarettes(Vansickel et al., 2010, Bullen et al., 2010), while more recent studies demonstrated that when users are experienced and using their own product and engaged in more puff intervals nicotine absorption is similar to that of conventional cigarettes.(Vansickel and Eissenberg, 2013)(Dawkins et al., 2013) As indicated in the Nides et al (2013) study as well, differences in nicotine delivery may be due to a combination of characteristics of the devices and user vaping topography. However, despite the greater efficiency at nicotine delivery in the more recent study by Vansickel et al. (2013) and range of delivery, such as in Nides et al. (2013) all of these studies show that e-cigarettes regardless of nicotine delivery, e-cigarettes can modestly alleviate some symptoms of withdrawal and produce positive subjective appraisal of the e-cigarettes as pleasant to use. Moreover, the one study examining abuse liability found that at least one model of cigarette-shaped 18mg e-cigarette

appeared to have a lower abuse liability than cigarettes.(Vansickel et al., 2012) In the trial comparing nicotine inhalator to e-cigarettes,(Bullen et al., 2010) the nicotine inhalator delivered a similar amount of nicotine as the 16mg e-cigarette, however authors noted that the e-cigarette malfunctioned and did not deliver any nicotine in a third of participants, which did not occur with the nicotine inhalator. These results highlight the need for product regulation in terms of the potential drug delivery and effects, as well as device quality and labeling. Only a few brands and models of e-cigarettes were tested in these studies, limiting the generalizability of the findings to other products.

HEALTH EFFECTS

Vardavas et al. (2012) conducted a study examining pulmonary function after acute *ad lib* puffing of an e-cigarette (Nobacco, medium, 11mg) in a group of healthy cigarette smokers(n=30).(Vardavas et al., 2012) All participants were asked to use the same e-cigarette device (>60% propylene glycol, 11 mg/ml nicotine) as desired for 5 minutes. Participants refrained from smoking tobacco cigarettes for 4 hr prior to study. On another day, 10 participants selected randomly from the 30 participants were asked to sham-smoke an e-cigarette device with the cartridge removed. Three lung function measures were assessed: spirometry, dynamic lung volumes and resistance and expired nitric oxide (NO). E-cigarette use had no effect on spirometric flows (such as FEV1/FVC) but did significantly increase airway resistance (18%) and decrease expired NO (16%). Sham e-cigarette use had no significant effect, as expected. Acute increases in airway resistance, although modest in size, raise concern that more prolonged e-cigarette use could have greater effects, particularly in people with reactive airways disease (asthma). This study is limited by small sample size, the short period of tobacco use abstinence before the protocol was executed, the short length of exposure to e-cigarette aerosol and the lack of comparison to smoking conventional tobacco cigarettes. In addition, smokers in general have high airway resistance with dynamic testing and lower expired NO, likely due to oxidant stress. Despite these limitations, this study suggests that e-cigarette use constricts lung peripheral airways, possibly due to the irritant effects of propylene glycol, which could be of concern particularly in people with chronic lung disease such as asthma, emphysema or chronic bronchitis.

Flouris et al. (2013) assessed the short term effects of active and secondhand e-cigarette and conventional tobacco cigarette use on serum cotinine and pulmonary function in 15 cigarette smokers and 15 never smokers.(Flouris et al., 2013) A single brand of e-cigarettes made in Greece and a single e-liquid (> 60% propylene glycol; 11 mg/ml nicotine) was used. The authors attempted to compute how many e-cigarette puffs would deliver the same amount of nicotine as a conventional cigarette using a number of assumptions, some of which are not valid. For example, authors assume that the smoking machine yield of each person's cigarette indicates amount of nicotine delivered to the smoker, yet neither for conventional cigarettes or e-cigarettes is there evidence of correlation between machine-tested yield and actual systemic delivery. The passive exposure study was conducted in a $60m^3$ chamber. The ventilation (air exchange rate) was not specified. The secondhand cigarette smoke was generated with a target air CO of 23 ppm which is extremely high but which simulates exposure in a very smoky bar. E-cigarette aerosol was generated using a pump that operated for the same duration as the cigarette smoking and aerosol was released into the room. The study limitations include using only type of e-cigarette, studying people who were not regular e-cigarette users, studying a specified puffing (vs *ad lib*) regimen, using extremely high passive exposure conditions, and studying short term pulmonary effects in healthy people (as opposed to asthmatics, who would be expected to be more sensitive to a lung irritant).The authors found a similar rise in serum cotinine with active tobacco cigarette or e-cigarette use immediately after active use (mean increase about 20ng/ml). The passive exposure the serum cotinine increase was similar for e-cigarette and tobacco cigarette exposure (averaging 0.8ng/ml for the tobacco cigarette and 0.5ng/ml for the e-cigarette). These results show that in cigarette smokers, some e-cigarette devices deliver similar amounts of nicotine as tobacco cigarette smoking. With very heavy passive exposure there is also similar systemic exposure to nicotine from tobacco and e-cigarettes among bystanders. Active cigarette smoking resulted in a significant decrease in expired lung volume (FEV1/FVC) but not with active e-cigarette or with passive tobacco cigarette or e-cigarette exposure.

Flouris et al. (2012) studied the effects of passive e-cigarette aerosol on white blood cell count. The paper presents additional analyses of data collected in the same study described by Flouris et al 2013,(Flouris et al., 2013)this time with a different biomarker outcome.(Flouris et al., 2012) The effects of tobacco cigarettes and e-cigarettes, both with active use and passive exposure, on white blood cell count were examined. White cell count increases acutely and

chronically following cigarette smoking, the latter reflecting a chronic inflammatory state that is associated with future risk of acute cardiovascular events. As expected, active conventional cigarette smoking and exposure to secondhand conventional cigarette smoke increased the total white blood cell count as well as granulocyte and lymphocyte counts. Active e-cigarette use and passive exposure to e-cigarette aerosol did not result in a statistically significant increase in these biomarkers over one hour of exposure. This study suggests that the increase in white cell count is mediated more by tobacco combustion products than by nicotine. The figure provided in the paper suggests that the change, if any, is very small, and possibly not of clinical significance. Since the protocol is the same as Flouris et al 2013 (respiratory effects),(Flouris et al., 2013) the same limitations apply.

Hua and colleagues (2013) sought to determine the health impact of electronic cigarettes, using an infodemiological approach.(Hua et al., 2013a) They collected information posted on three electronic cigarette forums: Electronic Cigarette Forum, Vapers Forum and Vapor Talk. Posts were reviewed for reports of both positive and negative health impact. Data were then analyzed with Cytoscape. There were 405 symptoms reported, with the majority negative (326 negative, 78 positive and 1 neutral). These effects encompassed twelve anatomical regions/organ symptoms. The majority of the symptoms affected the mouth and throat, and the respiratory system. Overall, examples of potentially serious negative health effects included: increased blood pressure and asthma attack. Some of the symptoms reported appeared opposite, such as increased and decreased blood pressure, indicating that users of the product may be differently affected or that these events are random occurrences and not related to e-cigarette use, as these are self-reported data with no formal analysis of causality.

McCauley and colleagues reported a case of a serious adverse event deemed to be due to e-cigarette use.(McCauley et al., 2012)A42 year old woman who reported the following symptoms: fevers, dyspnea, and productive cough that had lasted for seven months. The patient was found to have exogenous lipoid pneumonia, a lung disease caused by the deposition of oil in the lung tissue. The symptoms coincided with when she began using e-cigarettes. Because no other behavior or exposure could explain her symptoms and because they resolved after she stopped using e-cigarettes, the patient was diagnosed with “exogenous lipoid pneumonia due to e-cigarette use.”

Conclusion

Only a few studies have directly investigated the health effects of exposure to e-cigarette aerosol. Studies have examined effects of acute, short-term e-cigarette use in people who were also cigarette smokers.(Flouris et al., 2013, Flouris et al., 2012, Vardavas et al., 2012) The few studies examining potential effects of second hand aerosol on non-users have tested short-term e-cigarette aerosol exposure conditions, which may not be realistic for indoor spaces where there could be exposure to e-cigarette aerosol for several hours, such as airplanes, bars, and aerosol lounges. One study describes the self-reported health-related events and symptoms reported on e-cigarette forums,(Hua et al., 2013a)another a case of a lung disease due to e-cigarette use(McCauley et al., 2012)and as reviewed above, there have been adverse events reported to the U.S. FDA.(Chen, 2013)Taken together these studies provide a very limited perspective on the health effects from e-cigarettes. Studies are limited to the few products that have been tested, but some do demonstrate the ability for e-cigarette aerosol exposure to result in biological effects. Long-term biological effects are unknown at this time because e-cigarettes have not been in widespread use long enough to assess these effects.

EFFECTS ON CESSATION OF CONVENTIONAL CIGARETTES

As noted above e-cigarettes are promoted as devices to assist in smoking cessation and many adults who use e-cigarettes are doing so because they believe that they will help them quit smoking conventional cigarettes. The assumption that e-cigarettes will be as effective, or more effective, than pharmaceutical nicotine replacement therapy has also motivated support for e-cigarette use among some public health researchers and policy makers and (as discussed later) formed the basis for public policies on the regulation of e-cigarettes.

Population-based studies

There are two longitudinal studies of the association between e-cigarette use and quitting conventional cigarettes (Table 4) and one cross-sectional study.(Popova and Ling, 2013)

In Adkison et al. (2013) (ITC 4-Country Study noted above) authors presented a longitudinal analysis of data from current and former smokers over 2 times separated by one year.(Adkison et al., 2013) E-cigarette users had a statistically significant greater reduction in cigarettes per day from the first time to the second, one year later (e-cigarette users: 20.1cig/day

Table 4. Longitudinal Studies of the Association between e-cigarette use and cessation of conventional cigarette smoking		
Study	**Location and study design**	**Odds of quitting OR, (95% CI)**
Adkison et al. (2013)	U.S., U.K., Canada, Australia (ITC), surveyed at 2 waves, one year apart	One-year follow-up: 0.81 (0.43-1.53)*
Vickerman et al. (2013)	U.S. quitline callers surveyed at enrollment and 7-months post	Seven-months post enrollment in the quitline: 0.50 (0.40-0.63)**
*Odds ratios obtained by contacting authors **Computed by authors of this report based on the numbers reported in the paper		

to 16.3 cig/day; non-users: 16.9 cig/day to 15.0 cig/day). Although 85% of e-cigarette users reported they were using the product to quit smoking at the initial wave, e-cigarette users were no more likely to have quit one year later than non-users (OR=0.81, 95% CI: 0.43-1.53; p=0.52).

Vickerman et al. (2013) collected data about e-cigarette use among quitline callers from 6 U.S. states assessed at 7-months post enrollment.(Vickerman et al., 2013) About 31% reported they had ever tried e-cigarettes in their lifetime and the majority of those who have ever tried them used them for less than one month (67.1%) and 9.2% were using them at 7-month survey (34.6% response rate). Respondents' main reason for using e-cigarettes was tobacco cessation (51.3%), but it is not known whether the ever use occurred as part of a quit attempt in the past 7 months. Nevertheless, those who reported using e-cigarettes were statistically significantly less likely to quit than those who had not used e-cigarettes (21.7% among callers who used for one month or longer, 16.6% among those who used less than one month and 31.4% among never-users; $p<0.001$).(Vickerman et al., 2013) The unadjusted odds of quitting were statistically significantly lower for e-cigarette users compared to non-users (OR=0.50, 95% CI: 0.40-0.63) (computed from the data in the Table 2 in the paper.(Vickerman et al., 2013))

The association between e-cigarette use and conventional smoking cessation has also been examined in one population-based cross-sectional study. Popova and Ling (2013) like earlier research, found that an important reason that adults tried e-cigarettes (as well as other smokeless products) was to help them quit smoking conventional cigarettes. However, the use of e-cigarettes was not associated with being a successful quitter (adjusted OR 1.09; 95% CI 0.72-1.65) but was associated with being an unsuccessful quitter (OR=1.78, 95% CI 1.25-2.53) compared to people who had never tried to quit. This evidence is from a cross-sectional study

(i.e., a snapshot in time) rather than following the same people over time (a longitudinal study), so it does not allow for causal conclusions.

Clinical trials

Four clinical trials have attempted to examine the efficacy of e-cigarettes for smoking cessation (2 with very small samples).(Polosa et al., 2011, Caponnetto et al., 2013b, Caponnetto et al., 2013a, Bullen et al., 2013, Polosa et al., 2013) In 3 of the studies all groups were using an e-cigarette product, some with and some without nicotine; there was no comparison group not using e-cigarettes.(Polosa et al., 2011, Polosa et al., 2013, Caponnetto et al., 2013a, Caponnetto et al., 2013b) The other study compared efficacy of e-cigarettes to a standard of care regimen with 21mg nicotine patch (Bullen 2013). None of the trials were conducted with the level of behavioral support or counseling that accompanies most pharmaceutical trials for smoking cessation.

Polosa et al. (2011) conducted a proof-of-concept study conducted in Italy in 2010 with smokers18-60 year old not intending to quit in the next 30 days were offered 'Categoria' e-cigarettes and instructed to use up to 4 cartridges (7.4mg nicotine content) per day as desired to reduce smoking and to keep a log of cigarettes smoked per day, cartridges used per day and adverse events.(Polosa et al., 2011) (Polosa notes he served as a "consultant for the Arbi Group Srl., the manufacturer of the 'Categoria' e-cigarette used in the study, beginning in February 2011.") Six-month follow-up was completed with 68% (27/40) of participants. At 6-month follow-up, 13 were using both e-cigarettes and tobacco cigarettes, 5 maintained exclusive tobacco cigarette smoking and 9 stopped using tobacco cigarettes entirely and continued using e-cigarettes (Polosa et al., 2011). Cigarette consumption was reduced by at least 50% in the 13 dual users (25 cig/day at baseline to 6 cig/day at 6-months, $p<0.001$). Most common adverse events reported during the trial were throat irritation, dry cough and mouth irritation, followed closely by headache, nausea and dizziness. Participants reported they would recommend the e-cigarettes to a friend yet noted the need for better manufacturing practices as they were frustrated by problems they had operating their devices.

Polosa et al. continued follow-up of this sample at 18 and 24-months post baseline with 23 subjects who could be follow-up (58% of the original 40 enrolled).(Polosa 2013) Among the 23 participants who completed a 24-month visit, 18 continued to smoke; a greater than 50%

reduction in cigarettes per day occurred in 11 of the participants with a statistically significant reduction from an average of 24 to 4 cigarettes per day (p=0.003) and 7 participants reduced by less than 50% (p=0.06). Five participants had quit tobacco cigarettes at 24 months. During the follow-up phase the specific model of the brand of e-cigarettes used in the study was discontinued thus participants were not using that by the last follow-up. Five participants were not using the e-cigarettes provided (it was unclear if they were using another product) but abstinent from smoking and 3 relapsed. Four obtained other e-cigarettes and continued to use them until the end of the study (all were refillable devices and classified as "heavy reducers" by the authors. Study limitations include use of a product that was noted for poor quality during the trial and lack of a comparison or control group, which could make it difficult to determine if quit rates achieved were not due to chance.

A similar study was conducted by Caponnetto et al (2013) with 14 smokers with schizophrenia not intending to quit in the next 30 days.(Caponnetto et al., 2013a)Participants were provided the same “Categoria” e-cigarettes and carbon monoxide, product use, number of cigarettes smoked, and positive and negative symptoms of schizophrenia were assessed at baseline, week-4, week-8, week-12 week-24 and week 52. Sustained 50% reduction in the number of cigarettes per day smoked at week-52 in 7/14 (50%) participants and median of 30 cig/day decreased to 15 cig/day (p = 0.018). Sustained abstinence from smoking occurred with 2 participants (14.3%) by week 52. Most common side effect was dry cough followed by nausea, throat irritation, and headache. Positive and negative aspects of schizophrenia were not increased after smoking cessation in those who quit. The most common outcome was dual use of e-cigarettes with conventional cigarettes. Study findings are not generalizable to smokers with mental illness due to very small sample size and lack of a control group.

Caponnetto et al. (2013) also conducted a randomized, quasi-controlled trial (n=300) to examine efficacy of different strength e-cigarettes for smoking cessation and reduction in three study arms: 12 weeks of treatment with the 7.2mg nicotine e-cigarette, a 12-week nicotine tapering regimen (6 weeks of treatment with a 7.2mg e-cigarette and 6 weeks with 5.4mg e-cigarette), and 12 weeks of treatment with a non-nicotine e-cigarette.(Caponnetto et al., 2013b) Reduction occurred in the median value of cigarettes per day at all study visits among all three treatment arms. At one-year follow-up the reduction in median level of cigarettes per day among participants in the 7.2 mg nicotine e-cigarette group was 19 to 12 cig/day; the tapered e-cigarette

group was 21 to 14 cig/day and the non-nicotine e-cigarette group was 22 to 12 cig/day. Differences in reductions between groups were not significant after week 8 assessment. There was no statistically significant difference in 6-month or one year quit rate among the three conditions (one year rates: 4% for placebo e-cigarette users, 9% for low nicotine e-cigarette users and 13% for high nicotine e-cigarette users) (Capponetto 2013). The authors noted that those who initiated quitting in the first few weeks of the study stayed quit, while those who did not remained dual users throughout the study. In addition, 26% of quitters continued to use e-cigarettes at 1 year. A problem noted in the paper was a lack of product quality (the authors noted the devices malfunctioned often and new ones had to be sent out frequently over the course of the treatment period).

Bullen et al (2013) conducted the first randomized controlled clinical trial of e-cigarette compared to medicinal nicotine replacement therapy in Auckland, New Zealand.(Bullen et al., 2013) Adult smokers who wanted to quit (n=657) were randomized using a 4:4:1 ratio to the 3 study arms (16mg e-cigarette n=289, 21mg NRT patch n=295, no-nicotine e-cigarette n=73).(Bullen et al., 2013) Voluntary telephone counseling was offered to all subjects. Participants had visits at baseline, week 1 (quit day), 12 weeks to 6 months. Fifty-seven percent of participants in the nicotine e-cigarette group reduced their cigarettes per day by≥50% by 6 months compared to 41% in the patch group (p=0.002) and 45% in the non-nicotine e-cigarette group (p=0.08). Those randomized to the nicotine patch group were less adherent to the treatment (46%) than the 16mg e-cigarette group (78%) and the no-nicotine e-cigarette group (82%). It is possible that study methodology may have biased against success in the nicotine patch group. E-cigarettes were provided by mail for free to participants randomized to either the nicotine or no-nicotine e-cigarette group. Participants in the patch group were provided with usual care for quitline callers in New Zealand, where they are mailed cards redeemable for nicotine patches at a pharmacy at a very reduced rate of about $4 USD for 12 weeks of nicotine patches and were also provided with monetary vouchers to compensate for the $4 they had to pay for the patches at time of card redemption. While the protocol for providing the patches represented reasonable “usual care” for New Zealand, where everyone calling the local quitline has the option of receiving a voucher for NRT that can be redeemed at a local pharmacy, the fact that participants randomized to e-cigarettes were sent the e-cigarettes directly whereas participants randomized to NRT only received vouchers that they had to take to a pharmacy to

redeem may have biased the results against the NRT if the study were viewed as a head-to-head comparison of e-cigarettes and NRT for cessation. There were no statistically significant differences in biochemically-confirmed (breath CO) self-reported continuous abstinence from quit day to 6 month follow-up between nicotine e-cigarette (7.3%), nicotine patch (5.8%), and non-nicotine e-cigarette (4.1%). Considering the nicotine patch group as the standard of care, the quit rates in the Bullen study are much lower than quit rates seen for nicotine patches in clinical trials that offer more intensive behavioral support.(Stead et al., 2008) Another limitation with respect to interpreting this study for e-cigarettes broadly is that the product used had poor nicotine delivery.

Conclusion

In the population-based longitudinal studies of the effects of e-cigarette use on cessation of conventional cigarettes, several strengths and limitations should be noted. A strength of the Adkison et al. (2013) and Vickerman et al. (2013) studies is the assessment of why participants were using e-cigarettes. In Adkison et al. (2013), 85% of e-cigarette users, and in Vickerman 66.5% of e-cigarette users, indicated they were using the product to quit or switch "to replace other tobacco," which limits the possibility that lack of effect on quitting is observed due other motivations for using the device. Although quitline callers represent a small population of smokers motivated to quit, these data present a real-world estimate of the potential effectiveness of using e-cigarettes to quit in a population of motivated to quit. However, this study had a low response rate (34.6%) and may be subject to recall bias as e-cigarette use and perceptions were only assessed at 7-month follow-up. As participants are not randomly assigned to use e-cigarettes in the real world, a strength of the Vickerman et al. (2013) study is that it provides information on smoking characteristics, including measures of tobacco dependence, which could potentially be a source of self-selection bias. In the Vickerman study those who tried e-cigarettes did not statistically significantly differ from non-users in cigarettes per day or time to first cigarette, although they were more likely to have tried to quit 2 or more times. However, it is as yet unclear to what extent self-selection is occurring and contributes to quit success or failure.

The quit rates produced in Caponnetto et al. (2013) for the non-nicotine e-cigarette was 4%, tapered nicotine e-cigarette was 9% and 7.4mg e-cigarette was 13%; past 30-day abstinence at one year was not statistically significantly different.(Caponnetto et al., 2013b) Similarly, in

Bullen et al. (2013), the quit rates for 16mg e-cigarette, 21mg nicotine patch and 0mg e-cigarette showed no statistically significant differences in continuous abstinence quit rates at 6 months (7.4%, 5.8%, 4.1% respectively). Neither study found effects of e-cigarette use on quitting, beyond what is seen in unassisted or low-assistance studies of smokers using NRT to quit.(Hughes et al., 2003) Neither the Caponnetto et al. (2013) and the Bullen et al. (2013) randomized trials demonstrated a statistically significant difference in quit rates between nicotine e-cigarette and non-nicotine e-cigarette, but this could be due to low statistical power.(Bullen et al., 2013, Caponnetto et al., 2013b) In determining the effectiveness of a smoking cessation therapy, active drug is considered efficacious when it outperforms its placebo form, therefore the evidence to date demonstrates that e-cigarettes would not be considered efficacious as nicotine replacement to produce cessation. However, it is possible that e-cigarettes even without nicotine act as substitutes for the sensory and behavioral effects of conventional cigarettes. If this is the case the non-nicotine placebo e-cigarettes would be considered an active treatment condition in that e-cigarettes as discussed previously have been shown to reduce withdrawal symptoms.(Bullen et al., 2010, Eissenberg, 2010, Dawkins and Corcoran, 2013, Vansickel et al., 2010) Important limitations of the current research include lack of a control group not using e-cigarettes, the use of e-cigarettes that deliver relatively low levels of nicotine and the provision of minimal to no behavioral counseling. Another important limitation of studies assessing effectiveness of e-cigarettes for smoking cessation is that because they are not approved as a cessation therapy there are no therapeutic instructions for using them as replacements or to quit smoking (e.g. dosage tapering, duration of use, how to combine them with behavioural strategies, guidance for discontinuation).

In contrast to the assumption that e-cigarettes would function as a better form of NRT, population-based longitudinal studies that reflect real-world e-cigarette use found that e-cigarette use is not associated with successful quitting.(Adkison et al., 2013, Vickerman et al., 2013) The one clinical trial examining the effectiveness of e-cigarettes (both with and without nicotine) compared to the medicinal nicotine patch found that e-cigarettes are no better than nicotine patch and all treatments produced very modest quit rates without counseling.(Bullen et al., 2013) Although more participants liked using the e-cigarette compared to patch and would recommend it to a friend trying to quit,(Bullen et al., 2013) taken together these studies suggest that e-cigarette are not associated with higher quit rates in the general population of smokers.

HEALTH IMPLICATIONS OF CIGARETTE REDUCTION IN THE CONTEXT OF DUAL USE

Reductions in cigarettes per day were observed in these several of the clinical studies(Caponnetto et al., 2013b, Bullen et al., 2013, Polosa et al., 2011) and in one population-based study(Adkison et al., 2013) among those who did not quit. In the cigarette reduction analyses presented in some of the studies, many participants were still smoking about half a pack cigarettes/day at the end of the study.

An individual's cigarette smoking behavior, including both total duration of cigarette consumption, (i.e., years of cigarette use), and intensity of cigarette use, (i.e., number of cigarettes smoked per day) influences the risk of negative health effects.(Godtfredsen et al., 2003) Duration was addressed in a 2013 study of adults in the United States, in which those who stopped smoking cigarettes at younger ages had lower age-adjusted mortality compared to those who continued to smoke later into adulthood.(Jha et al., 2013) Findings regarding decreased smoking intensity; however, have been less consistent, with some studies showing lower mortality with reduced daily cigarette consumption(Gerber et al., 2012) and others not finding a significant overall survival benefit.(Tverdal and Bjartveit, 2006) Use of electronic cigarettes by cigarette smokers to cut down on number of cigarettes smoked per day is likely to have small if any beneficial effects on overall survival if it results in continued use of cigarettes, even in smaller amounts, concurrently with electronic cigarettes, as low intensity cigarette exposure still confers substantially increased mortality risks.

Even if smokers reduce cigarette consumption while using e-cigarettes there is unlikely to be much, if any, cardiovascular benefit because of the highly nonlinear dose-response relationship between exposure to fine particles and the and risk of cardiovascular disease.(Pope et al., 2009, Barnoya and Glantz, 2005)(As discussed earlier in this report, e-cigarettes deliver similar loads of fine particles as conventional cigarettes, both in terms of numbers and size distributions.) Light smoking, even 1-4 cigarettes per day, is associated with markedly elevated cardiovascular disease risk(Bjartveit and Tverdal, 2005).

Both smoking duration and intensity determine cancer risk.The relative risk of death from lung cancer among U.S. adults increases with total number of years smoked and more cigarettes smoked per day.(Thun et al., 2013) Similar results have been seen in risks for other malignancies, with greater smoking duration, intensity, and cumulative smoking dose associated

with greater odds of pancreatic cancer(Lynch et al., 2009) and associations between increased smoking duration and intensity and esophageal cancer.(Pandeya et al., 2008) The relative risk of both lung cancer and bladder cancer levels off after a certain number of cigarettes/day,(Vineis et al., 2000) suggesting that above a certain intensity, the specific levels of exposure may not cause significant differences in risk for these cancers. Doll and Peto (1978) found a dose-response relationship between duration of smoking and number of cigarettes smoked per day and risk of lung cancer, with models suggesting the impact of duration to be greater than that of intensity.(Doll and Peto, 1978) Using participants from the Cancer Prevention Study II, Flanders et al. found a greater increase in lung cancer mortality with greater duration of cigarette smoking compared to greater intensity of smoking.(Flanders et al., 2003) Taken together, these data suggest that lung cancer mortality increases more with additional years of smoking compared to additional cigarettes smoked per day and smoking more cigarettes per day for fewer years may pose less lung cancer risk than fewer cigarettes per day for many years. While use of electronic cigarettes to cut down on cigarettes without complete abstinence may result in the latter scenario and thus a reduction in morbidity, particularly with respect to lung cancer, this trend has not been shown with overall mortality.

Thus, if dual use of electronic cigarettes and cigarettes results in reductions in the number of cigarettes smoked per day for current smokers, might mitigate some of the malignancy risk associated with smoking, but the effect will be less than proportional to the reduction in cigarette consumption because of the (likely larger) importance of duration of smoking. There is not likely to be much cardiovascular benefit absent complete cessation.

TOBACCO INDUSTRY INVOLVEMENT

In 2012 and 2013 major tobacco companies – Lorillard, Reynolds American Inc, (which is 42% owned by British American Tobacco), Altria (Philip Morris), British American Tobacco and Imperial Tobacco -- purchased or developed e-cigarette products. Lorillard, Reynolds and Altria's products are marketed by subsidiary companies: Lorillard Vapor Corporation, R.J.Reynolds Vapor Company, and Nu Mark, LLC., which is owned by Altria. Lorillard acquired e-cigarette companies that produced Blu and SkyCig brands marketed under Lorillard Vapor Corporation.(Esterl, October 1, 2013) As of November 2013, Altria's Mark Ten e-cigarette was in test market in Indiana,(Kress, June 11, 2013) Reynolds' product, the Vuse, was

in test market in Colorado and has planned to continue marketing in Utah as the next phase of national distribution.(Carver, November 18, 2013) BAT markets the Vype in the U.K. Imperial Tobacco Group announced plans to market two e-cigarettes in 2014.(Geller, November 5, 2013) In addition, a smaller tobacco company, Swisher, that makes little cigars and cigarillos, also markets an e-cigarette called the e-Swisher.(Swisher Tobacco Company, 2013)

Tobacco companies are marketing or manufacturing e-cigarettes and some tobacco companies claim to want to participate in "harm reduction," despite no evidence of a strategy to phase out their sale of tobacco cigarettes or other tobacco products. Lorillard CEO Murray Kessler stated in an interview with the *Wall Street Journal* that e-cigarettes will provide smokers an unprecedented chance to reduce their risk from cigarettes.(Esterl, August 27, 2013) Also, in *USA Today* he published an op-ed on September 23, 2013 where he stated: “E-cigarettes might be the most significant harm-reduction option ever made available to smokers.”(Kessler, September 22, 2013) However, Lorillard has gained approval from the US Food and Drug Administration to market a new non-mentholated Newport conventional cigarette, demonstrating the inherent inconsistency in messaging and deeds by expanding their cigarette line while touting their ability to offer a product they claim reduces harm from cigarettes. In this way the cigarette companies get to have it both ways, they purport offer an alternative to their products that cause massive death and disease while continuing to market them. In fact, as noted in the 2010 Surgeon General’s Report, "How Tobacco Smoke Causes Disease,"(U.S. Department of Health and Human Services, 2010) the tobacco industry has used every iteration of cigarette design to undermine cessation and prevention.

Moreover, the tobacco companies address e-cigarette issues as part of their policy agenda. As they did in the 1980's and 1990's,(Samuels and Glantz, 1991) some tobacco companies continue to engage in creating and supporting “smokers rights” groups, seemingly independent groups to interact with consumers directly on political involvement in support of their agenda. Altria and R.J. Reynolds Tobacco Company maintain websites called “Citizens for Tobacco Rights” and “Transform Tobacco;” Figure 7) have e-cigarette news and action alerts featured on the homepages of these websites and include instructions for taking action against bills designed to include e-cigarette use in smokefree laws. In addition, e-cigarette companies engage in similar tactics, using the same political and public relations strategies as the tobacco

Figure 7. Tobacco company advocacy websites; Altria, Inc. website: www.tobaccorights.com; Reynolds American website: www.transformtobacco.com

companies (most notably featuring organized "vapers" like the organized smokers). These strategies were successfully deployed in Europe to convince the European Parliament to substantially weaken the proposed EU Tobacco Product Directive in October 2013.(Higgins, November 9, 2013)

E-cigarette market analysis reports by Goldman-Sachs in 2012 and 2013 noted that despite currently comprising <1% total industry sales, there is the potential for e-cigarettes to account for 15% of US tobacco market profit by 2020.(Hong et al., 2012, Hong et al., 2013) Another equity research report noted that “full conversion” from cigarettes to e-cigarettes has not been achieved and most users are dual users with conventional cigarettes, and going on to note that products would have a longer lifespan because its users would have a longer lifespan.(Herzog et al., July 19, 2013) Importantly, the market analysts remained positive on the long term growth of the tobacco industry with e-cigarettes playing a role, not as a total replacement for the tobacco or nicotine products.

Likewise, after evaluating the cigarette companies’ internal documents and public positions on snus as “harm reduction” in Europe, Gilmore et al. (2013)(Peeters S and Gilmore AB, 2013) found that they were entering the market to protect their cigarette business as long as possible. They saw clear lessons for assessing the companies’ involvements in e-cigarettes:

> While such evidence must be considered alongside the broader body of evidence around snus and the fact it is significantly less harmful than smoked tobacco, collectively these issues suggest that legalisingsnus sales in Europe may have considerably less benefit than envisaged and could have a number of harmful consequences. Perhaps of greater concern, however, given that harm reduction using nicotine products is already an established element of tobacco control and recent research suggests scope for benefit via newer nicotine products, are the recent industry investments in pure nicotine products. These raise two concerns. First, one of competition: should such investments continue, competition between cigarettes and clean nicotine products would decrease, limiting the potential for harm reduction to benefit public health and maintaining the status quo of cigarettes. While a nicotine regulatory authority could ensure that regulation was proportional to harm, it would be powerless to address the issue of competition, so this situation needs close observation. Second, they may enable TTCs [transnational tobacco companies], by presenting themselves as purveyors of nicotine rather than tobacco products, to undermine Article 5.3 of the Framework Convention on Tobacco Control which aims to protect public health policy from commercial and other vested interests of the tobacco industry. Finally, if TTCs are genuinely interested in seeing their cigarette consumers switch to snus (or pure nicotine products), rather than creating new snus/nicotine users and/or dual use opportunities, we would expect to see detailed strategic plans and cigarette sales reduction targets at least for the markets where they intend to introduce these products. However, to this date we have yet to see this. [citations eliminated] (Peeters S and Gilmore AB, 2013)

CURRENTSTATE OF GLOBAL REGULATION (NOVEMBER 2013)

Like e-cigarettes themselves, the policy environment related to e-cigarettes is rapidly developing despite the lack of a sufficient base of scientific evidence to support policy development. Policymakers in many countries are under considerable pressure to provide regulatory guidance regarding e-cigarettes and many policies are based on the assumption that e-cigarettes will contribute to reducing the harms of smoking either by serving as a smoking cessation aid or by replacing combusted cigarettes. However, based on interpretations of the data reviewed above, mounting evidence of dual use and youth initiation of e-cigarette use is of increasing concern and relevance to the evaluation of any hypothesized harm reducing effect.

European Union Draft Tobacco Product Directive

As of November 2013, the policy position on e-cigarettes in the European Union was in flux, with three versions of revisions of the European Union Tobacco Product Directive (EU TPD) under consideration. First, in December 2012 the European Commission issued a draft EU TPD that treated e-cigarettes in a separate class of "nicotine containing products" and as medicinal products if they contain nicotine above a certain threshold.(European Commission, 2012) In June 2013, the Council of the European Union released a draft with changes made by consensus among the Member States that accepted the Commission's overall approach and generally strengthened the regulation of e-cigarettes.(Council of the European Union, June 24, 2013) In particular, the Council cut by half the threshold of nicotine that a product can contain and still be treated as a "nicotine containing product" that is sold as a consumer product. (Any devices delivering more than this threshold would be regulated as a medicine.) In October 2013, the European Parliament approved amendments to the Commission draft that substantially weakened the Commission's authority to regulate e-cigarettes.(European Parliament, 2013) The European Parliament's amendments were based on the explicitly stated premise that, "Given the potential of nicotine-containing products to aid smoking cessation, Member States should ensure that they can be made available as widely as tobacco products." The premise that e-cigarettes are established as effective cessation devices is contradicted by the available data reviewed in this report.

The European Commission Draft(December 2012)

The revisions to the EU TPD released 2012,(European Commission, 2012) proposed to regulate e-cigarettes as medicines or consumer products depending on the levels of nicotine content and delivery. E-cigarettes would be authorized as medicines if they contain at least 2mg of nicotine, 4mg/ml nicotine concentration in the e-cigarette liquid, or deliver a peak plasma nicotine level of 4ng/ml. E-cigarettes that deliver lower levels of nicotine would be authorized to be sold as consumer products with "an adapted health warning." The nicotine content and delivery thresholds were established by considering the nicotine content and delivery of existing nicotine replacement therapies on the assumption that e-cigarettes will perform in similar ways and yield similar success rates for smoking cessation as currently regulated pharmaceutical NRT products.

Article 18 of the EU TPD section on nicotine containing products (NCPs), which includes e-cigarettes, does not account for the widespread variation in products available and product engineering. In contrast to cigarettes or conventional nicotine replacement therapies such as patch, gum, lozenge, there are many different e-cigarette -like products in the current marketplace and many are not sold pre-filled and pre-assembled. Even the most similar product, the medical nicotine inhaler, is standardized for use. It has only one cartridge of one nicotine concentration that only fits in one device. It is unclear how the regulations as proposed will address this variability.

The EU TPD is silent on the marketing of e-cigarette devices that do not contain nicotine, so does not create any restrictions on the marketing or sale of these products, particularly to youth. This is an important omission. Since with e-cigarette products, different components of products are sold separately and can be used with several different liquids with varying or no nicotine content, one way that a company could possibly legally evade regulation under the EU TPD would be to sell nicotine-free e-cigarettes as consumer products then sell the nicotine fluid separately, as is done in New Zealand. It is not clear how the nicotine content standards would apply in this context (e.g., bottles of e-liquid, different sized cartridges that can be used on different devices). Moreover, it is not clear how every piece of these devices would be regulated to ensure that they meet safety standards (whether regulated as medicines or consumer products), or even if they would be allowed to be sold separately.

Another issue the Commission draft of the EU TPD does not address is how products would be allowed to be advertised as medicines. By providing these products with their own definition (that is distinct from cigarettes) and creating a nicotine threshold where some products will be medicines and others will be consumer products, none of the restrictions that have been established policy for marketing tobacco products in the EU will apply. The EU TPD is silent on advertising, relying on current EU policy. E-cigarettes could be marketed on television and radio and using celebrities, sports sponsorships, and product placement that would have strong youth appeals. Furthermore, if marketing differs for those that are authorized as medicines and those that are consumer products, it would cause great confusion since the products look identical and produce identical looking smoke-like aerosol.

The Council of the European Union Proposal (June 2013)

The Council of the European Union accepted the overall approach to regulating e-cigarettes proposed in the Commission draft and strengthened several provisions related to e-cigarettes, most notably by decreasing by half the nicotine levels and concentrations for which medical regulation would apply (changed equal to or exceeding 2mg to 1mg for nicotine levels and equal to or exceeding 4mg/ml to 2mg/ml for nicotine concentration) and deleting the provision pertaining to nicotine delivery (i.e., deleted "products whose intended use results in a mean maximum peak plasma concentration exceeding 4ng of nicotine per ml").(Council of the European Union, June 24, 2013)

The Council also strengthened the ability of Member States to introduce stricter national measures in several areas, including those related to e-cigarettes, when justified for public health reasons (as long as they were proportionate and did not constitute a disguised restriction on trade between Member States).

The EU Parliament Amendments (October 2013)

The European Parliament amendments significantly weakened the Commission's authority to regulate e-cigarettes. The amended EU TPD would allow marketing of all NCPs with a nicotine level of 30 mg/ml or less without any screening for their quality, safety, or efficacy if they are not presented with medicinal or therapeutic claims. (NCPs that exceed 30mg/ml are prohibited.) The 30 mg/ml threshold protects almost all e-cigarette products

currently on the market; 36 mg/ml is typically the strongest concentration offered in cartridges and e-liquid bottles. There are e-liquid preparations for sale in very large quantities that exceed this concentration (100 mg/ml),(Wizard Labs, 2013) but in a content analysis of e-cigarette retail websites in 2012, no product over 36 mg/ml was found.(Grana and Ling, in press) The 30mg/ml level is higher than the nicotine content in any of the e-cigarette devices tested in the studies published to date that are reviewed in this report.

The European Parliament amendments would subject e-cigarettes to pre-market authorization only if they are "presented as having properties for treating or preventing disease" (i.e., "medicinal products"). This position is counter to the assumption Parliament added to the EU TPD that *all* e-cigarette products should be available because of their "potential … to aid smoking cessation." This inconsistency within the European Parliament amendments is evident when the amended TPD notes that "Nicotine-containing products - including e-cigarettes - are sold on the Union market. However Member States have taken different regulatory approaches to address health and safety concerns associated with these products. There is a need for harmonized rules, therefore all nicotine-containing products should be regulated under this Directive as a related tobacco product."

To implement this policy, Article 3.7 provides that:

> The proposal removes current legislative divergence between MemberStates and the differential treatment between Nicotine Replacement Therapies and Nicotine Containing Products, increases legal certainty and consolidates the on-going development in Member States. It also encourages research and innovation in smoking cessation with the aim of maximising health gains.(European Parliament, 2013)

Thus, the draft directive accepts as a premise that NCPs, including e-cigarettes, are "medicinal products" within the meaning of Directive 2001/83/EC because they have properties that are useful "for treating or preventing disease" by aiding smoking cessation. As amended, the EU TPD Article 18 which deals with e-cigarettes seems inconsistent with these provisions since it differentiates between NCPs that are "presented as having properties for treating or preventing disease," which are required to get premarket authorization (under Directive 2001/83/EC under paragraph 2 of Article 18), and all other NCPs, which need only follow the notification procedure set out in Article 17.

Both the Commission's and the European Parliament's proposals for Article 6 (which deals with cigarettes) prohibit "*tobacco products* with a characterising flavor;" however, the

European Parliament's proposal for Article 18 (which deals with e-cigarettes) explicitly states that "flavourings are allowed in the [nicotine containing] products," including e-cigarettes. In other words, under the European Parliament amendments additives which may impart a characterizing flavor that increase product appeal to children (e.g., chocolate, cherry, strawberry, licorice, menthol) are explicitly allowed in e-cigarettes, although they are explicitly prohibited from tobacco products (conventional cigarettes).

The EU TPD requires that "each unit packet and any outside packaging of nicotine-containing products carry the following health warning: 'This product is intended for use by existing smokers. It contains nicotine which is a highly addictive substance.'" The size and placement of the warning is the same as for tobacco products for smoking other than cigarettes and roll-your-own tobacco: 30%-35% of the external area of the unit pack and any outside packaging, depending of the number of a Member State's official languages.

The European Parliament's proposal for Article 18 restricts sales of NCP's according to the legal age for sale of tobacco products in Member States, but in no case under age 18. Additionally, the European Parliament's proposed Article 18 states that all nicotine-containing products must be "available to be sold outside of pharmacies." This means that e-cigarettes or other NCPs that might be marketed "for treating or preventing disease" and are registered as "medicinal products" could be sold outside of pharmacies. The Commission's proposal for Article 18 does not add this language.

The European Parliament's proposal for Article 18 added language that nominally provides for public release of ingredient information on the internet by Member States before e-cigarettes (and other NCPs) are placed on the market, but imposes the requirement on Member States to do so "with due regard to the protection of trade secrets." This explicit added protection for trade secrets could create a loophole that would permit companies to avoid this disclosure requirement by claiming that their ingredient lists are trade secrets, as they have done in response to required submissions for tobacco products to the FDA in the United States.

Both the Commission's and the European Parliament's proposals acknowledge that legislative action at the European Union level is necessary to implement the WHO Framework Convention on Tobacco Control (FCTC), and note the particular relevance of the FCTC's Article 13 on advertising. The European Parliament's proposal explicitly provides that the same "limitations on advertising, sponsorship, audiovisual commercial communication and product

placement for tobacco products as set out in Directive 2003/33/EC and Directive 2010/13/EC" shall apply to e-cigarettes. It also prohibits co-branding of e-cigarettes and tobacco products: "tobacco trademarks, brand names and symbols are not used on nicotine-containing products." The ability to co-brand products with a celebrity's "brand" is unclear. The Commission's proposal for Article 18 regarding nicotine-containing products does not include this specific language.

The definition of passive smoking, "'Passive smoking' means the involuntary inhalation of smoke from the combustion of cigarettes or cigars or from the exhalation of one or more smokers," excludes the so-called "vapor" from e-cigarettes, as it only includes the "combustion of cigarettes or cigars." This omission would thus permit the use of ENDS in places that are currently regulated by laws that prohibit "passive smoking."

Perhaps most significantly, the amendments to the EU TPD eliminated the authority of the European Commission to update the regulations related to ENDS as new information about marketing and use patterns and their direct health effects and effects on cigarette consumption develops in the currently rapidly changing market. Specifically, the requirement that:

> The Commission shall be empowered to adopt delegated acts in accordance with Article 22 to adapt the requirements in paragraphs 3 and 4 taking into account scientific and market developments and to adopt and adapt the position, format, layout, design and rotation of the health warnings.

was deleted and replaced with a weak requirement for monitoring and preparation of a report after 5 years that could recommend changes to the TPD (but not make any actual changes).

This change effectively insulates the e-cigarette companies from any science-based regulations for at least 5 years and likely much longer, since it moves the issue back into the political sphere where the tobacco companies are strongest.(Neuman et al., 2002, Smith et al., 2010)

The Situation as of November 2013

As of November 2013 there were three different versions of the EU TPD on the table: the European Commission proposal (from 2012),(European Commission, 2012) the Council of the European Union general approach version(Council of the European Union, June 24, 2013) which reflects the views of the Member States (from June 2013), and the European Parliament amendments (from October 2013).(European Parliament, 2013) According to the Lisbon Treaty,

the Commission has the right to propose new legislation and the Council (Member States) and European Parliament are co-legislators. The three institutions were seeking to negotiate a compromise in the so-called "informal trilogue." If they reach a compromise it will be adopted in the European Parliament in the first reading; if not the co-decision procedure will be officially started, which will most likely take another 1-2 years.

United Kingdom

The U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) announced a plan to regulate e-cigarettes as medicines. MHRA policy is based on the position that e-cigarettes function like nicotine replacement therapies for smokers wishing to cut down or quit, stating:

> The consistent evidence from a variety of sources is that most electronic cigarettes use is to support stop smoking attempts or for partial replacement to reduce harm associated with smoking. This is comparable to other nicotine replacement products (e.g., gums, patches, inhalator), which are licensed as medicines. The current evidence is that electronic cigarettes have shown promise in helping smokers quit tobacco but the quality of existing NCPs [nicotine containing products, how MHRA labels e-cigarettes] is such that they cannot be recommended for use.(Medicines and Healthcare Products Regulatory Agency, June 12, 2013)

Thus, the MHRA policy appears to be based on three assumptions: (1) harm reduction implemented by shifting cigarette smokers to “cleaner” forms of nicotine delivery is an effective public health; (2) e-cigarettes are a safe and effective form of nicotine replacement; and (3) the widespread introduction of e-cigarettes will increase cigarette cessation and not increase initiation.

The MHRA’s regulatory plans focus on ensuring consistency of nicotine delivery and quality control of the e-cigarette devices. Since March 2011 MHRA reviewed evidence to regarding safety of the devices and e-liquid and their own analysis of four e-cigarette products, finding that existing products on the market are low quality and not assured for safety.(Commission on Human Medicines Working Group on Nicotine Containing Products (NCPs)) Their evidence review found that products have inconsistent nicotine content from labeled values and levels varied for identical products within the same brand and that is just among a selection of brands among the hundreds on the market. The MHRA found diethylene glycol in one product which is likely to be a result of improper processing of propylene glycol. In addition, they found the presence of a toxic contaminant (1,3-bis(3-phenoxyphenooxy) benzene),

which they stated has no plausible reason for being in the products. They concluded that the devices cannot be considered safe or effective nicotine delivery devices as the content and delivery of nicotine differs from brand to brand and even within brand. Moreover, their evidence review acknowledges that low levels of known tobacco-specific carcinogens were found in products, likely from low-quality nicotine extraction processes. All of these findings concur with the published research reviewed in this report.

MHRA noted that their regulation of e-cigarettes as medicines is in accordance with the European Commission's version of the proposed EU TPD, and that they assumed a version of the EU TPDwould be adopted in 2014 and come into effect by 2016. The MHRA specifies that their program seeks to determine four dimensions to establish medicines licensing for e-cigarettes: "the nature, quality and safety of unlicensed NCPs; the actual use of unlicensed NCPs in the marketplace; the effectiveness of unlicensed NCPs in smoking cessation; and modelling of the potential impact of bringing these products into medicines regulation on public health outcomes." It is unclear the specific steps to achieve these aims.

The MHRA does not include any restrictions on e-cigarette marketing. An undated document, "The Regulation of Nicotine Containing Products: Questions and Answers,"(Medicines and Healthcare Products Regulatory Agency, 2013) attempts to address this issue:

> **24. What will be done by the Government to stop manufacturers making their products attractive to young people/children – such as making fruit tasting electronic cigarettes or doing special offers such as two for the price of one?**
>
> Medicines regulation prohibits advertising to children (under 16 years of age).Any licensed medicines would have an age limit – likely to be 18 years of age. One of the reasons for favouring medicines regulation is that it has controls on advertising and promotion and sale and supply. We will look at applications from manufacturers on a case-by-case basis.
>
> If need be, we are able to set particular conditions on the way that products are presented and promoted, especially if they become popular with young people.
>
> At present, we are not aware of any widespread use of e-cigarettes by young people.(Medicines and Healthcare Products Regulatory Agency, 2013)

These assurances provide little or no protection against aggressive marketing of e-cigarettes to youth; the tobacco companies are long-practiced at developing and implementing effective marketing campaigns directed at youth with similar restrictions for decades all over the world. Evidence published after this agency issued their intended policies has shown rapid e-cigarette uptake among adolescents in the US, (with use doubling from 3.4% to 6.8% among all middle school and high school youth from 2011 to 2012, with rates even higher among older youth in high school 4.7% to 10.0%), mostly among current smokers. Similarly, much of the research on the effects of e-cigarette use on smoking cessation summarized earlier in this report was published after the MHRA evidence review(Commission on Human Medicines Working Group on Nicotine Containing Products (NCPs)) was released and provides additional information that contradicts the assumptions upon which these documents were based that should be considered in further designing these regulatory approaches.

As part of what appears to be a broad consensus in the UK that the introduction of e-cigarettes will reduce the harm of smoking, the anti-smoking advocacy group Action on Smoking and Health (ASH) UK has announced that it "does not consider it appropriate to include e-cigarettes under smokefree regulations,"(Action on Smoking and Health, June 2013)supporting one the e-cigarette companies' key marketing messages that e-cigarettes can be used everywhere without the restrictions and social stigma of smoking.(Grana and Ling, in press, McKee, 2013) It is unclear how the UK plans to address the potential interference with enforcement of existing smokefree laws and potential promotion of smoking as these are mimicking products.

United States

In the U.S., as of November 2013, e-cigarette products remained unregulated by any federal authority, particularly the US Food and Drug Administration (FDA). The Sottera Inc. case ruling that was upheld on appeal in U.S. court, found that e-cigarettes could be regulated as tobacco products unless they are marketed with health and therapeutic claims.(D.C. Circuit U.S. Court of Appeals, 2010) The FDA accepted that ruling and issued a letter to stakeholders on April 25, 2011 stating their intent to issue guidance about exercising their deeming authority over e-cigarettes in the future, but, no such deeming authority or guidance had been issued.(FDA, 2011) Frieberg et al. (2012) analyzed the Family Smoking Prevention and Tobacco

Control Act and used existing legal precedent to imagine potential regulatory options in the U.S. for other tobacco products including electronic cigarettes. He posited that the U.S. FDA could extend restrictions on flavors based on evidence for flavored cigarettes as starter products for youth, price restrictions such as free sampling, warning labels, minimum age for purchase, and restrict health claims.(Freiberg, 2012)

The Food and Drug Administration does not have the authority to regulate where e-cigarettes are used; that is the domain of state and local governments, where almost all activity on smokefree laws has occurred. Since e-cigarettes entered the U.S. market in 2008, there has been a rapid increase in the number of municipalities and states that have adopted legislation regulating where e-cigarettes can be used and laws restricting sales to minors. As of November 2013, 25 states have laws restricting sales to minors, 3 states (New Jersey, North Dakota, and Utah) and 100 municipalities restrict use of e-cigarettes in 100% smokefree indoor environments.(American Nonsmokers' Rights Foundation, October 1, 2013) An additional 9 states restrict e-cigarettes in other venues such as school district property, Department of Corrections/prisons, public educational facilities and grounds, and commuter rail systems.(American Nonsmokers' Rights Foundation, October 1, 2013)These figures could be an under count. Many U.S. local and statewide smokefree laws were enacted before the introduction of e-cigarettes and some include language that could be interpreted as including e-cigarettes.

Convention on Tobacco Control (FCTC) Conference of the Parties Report on national e-cigarette policies and regulations

The November 2012 FCTC Conference of the Parties' report by the convention secretariat on e-cigarettes contains data about 33 participating countries" e-cigarette availability and regulatory policies.(FCTC/COP/5/13, 2012) Brazil, Singapore, Canada, the Seychelles and Uruguay ban e-cigarettes from being sold or distributed in their countries. Several countries have two-tiered or three-tiered levels of regulation depending on the product contents and intended use (communicated through company marketing claims and statements). For example, New Zealand and Switzerland allow e-cigarettes without nicotine to be sold, but residents may purchase e-cigarettes and e-liquid with nicotine over the Internet for personal use (may not sell them in the country). Some countries aim to apply a drug delivery device classification for e-

cigarettes with nicotine and that make health claims. For example, in some countries, the regulatory scheme separates e-cigarette products into consumer and medicinal by their nicotine and health claims. If a product contains no nicotine and no health claim it is currently considered a consumer product and allowed to be sold. However, if a product has nicotine in it and is marketed with a health claim, it must go through their drug delivery regulatory scheme to be approved for retail, distribution and advertisement as a medication. Such regulations exist in Hungary, Turkey, Australia, Belgium, New Zealand and Norway where e-cigarette products require pre-market authorization if they contain nicotine and are marketed with a health claim or claim they are intended to be used for smoking cessation. A unique case exists for South Korea, where products *without* nicotine are regulated as quit aid by the Korean Food and Drug Administration and products with nicotine are treated as tobacco products and regulated by Ministry of Finance (Lee et al 2012).

Updated Information

Since the Conference of the Parties report in 2012, several countries updated policies and policy recommendations regarding e-cigarettes. Germany's Supreme Court ruled that e-cigarettes should be treated as tobacco products under the law.(The Local, September 17, 2013)In 2012, Australia had a country-wide policy that e-cigarettes with nicotine and that make therapeutic claimsare subject to regulation as a therapy, but absent those characteristics were unregulated. Since 2012, several states and territories have included e-cigarettes in their current marketing restrictions as applied to products that mimic tobacco products.(Australian Government, 2013)

In contrast to the position ASH UK took in England, the French Health Minister, Marisol Touraine, announced on May 31, 2013 (World No Tobacco Day) that the French government plans to extend existing smoking restrictions to e-cigarettes.(FRANCE 24, May 31, 2013) These restrictions were undertaken to prevent confusion in enforcement of the national smokefree law and prevent modeling of smoking by a product that mimics cigarette smoking. It will also protect bystanders from being exposed to secondhand e-cigarette aerosol. In India e-cigarettes were declared as illegal under Drugs and Cosmetics Act by State Drug Controller in Punjab and the government of India is preparing to ban them.(State Drugs Controlling Authority Food & Drug Administration Punjab India, 2013) In the Philippines, the Food and Drug Administration recently recommended that e-cigarettes should not be used indoors anywhere that smoking is

prohibited.(Food and Drug Administration Philippines, June 26, 2013)Davao is the first city in the Philippines to act on this recommendation and enact a smokefree law that includes e-cigarettes.(Saligumba, Spetember 24, 2012)

OVERALL SUMMARY

While most discussion of e-cigarettes among health authorities has concentrated on the product itself, its potential toxicity and use of e-cigarettes to help people quit smoking, the e-cigarette companies have been rapidly expanding using aggressive marketing messages similar to those used to promote cigarettes in the 1950s and 1960s. Moreover, e-cigarette advertising is on television and radio in many countries that have long-banned similar advertising for cigarettes and other tobacco products. While it may be reasonable to assume that if existing smokers switched completely from conventional cigarettes (with no other changes in use patterns) there would be a lower disease burden caused by nicotine addiction, the evidence available at this time (while limited) points to high levels of dual use of e-cigarettes with conventional cigarettes, little benefit for cessation (either on a population basis or compared to currently regulated nicotine replacement therapy) and rapidly increasing youth initiation with e-cigarettes. Although, some cite a desire to quit smoking by using the e-cigarette, other common reasons respondents give for using the products are to circumvent smokefree laws and to cut down, which may reinforce dual use patterns.

It is unclear what will be the trajectory of the dual use pattern among adults or children, but any uptake in children is very concerning. Nicotine is a highly addictive substance with negative effects on animal and human brain development, which is still ongoing in adolescence.(Dwyer et al., 2008, Liao et al., 2012, Lichtensteiger et al., 1988, Longo et al., 2013) Evidence from published studies examining dual use of smokeless tobacco, snus and conventional cigarettes among youth and adults shows a progression to cigarette smoking and difficulty with quitting among adolescent smokeless tobacco users.(Galanti et al., 2008, Post et al., 2010) Concerns that e-cigarettes could play a similar role in increasing conventional cigarette use are warranted. Furthermore, high rates of dual use may result in greater total public health burden and possibly increased individual risk if a smoker maintains an even low-level tobacco cigarette addiction for many years instead of quitting.

E-cigarette devices and their components should be evaluated for risks posed to consumers by consumer product safety regulatory authorities and consumers should be appropriately warned about risks and proper handling. Although the data are limited, it is clear that e-cigarette aerosol is not "harmless water vapor" as is frequently claimed and can be a source of air pollution. Article 8 of the FCTC focuses on smoke-free policies to afford protections for the public and all workers to breathe clean air. When evaluating the risks of exposure to e-cigarette aerosol, the standard of comparison should not be whether the vapor is better than the toxic chemical mixture in tobacco cigarette smoke (which is already prohibited), it should be whether the product's emissions introduce toxins into clean air, and how they affect existing public health protections. In contrast to the paucity of research on e-cigarettes, there is an extensive scientific literature showing that smokefree policies protect nonsmokers from exposure to toxins and encourage smoking cessation.(U.S. Department of Health and Human Services, 2006) One-hundred percent smoke-free policies have about twice the effect on consumption and smoking prevalence than policies with exceptions or partial coverage.(Fichtenberg and Glantz, 2002) Exceptions for e-cigarettes may similarly decrease the effects of smoke-free policies on smoking cessation, and as noted in the FCTC Conference of the Parties report, use of the products in smokefree environments may also decrease enforcement of Article 13 as e-cigarettes act as cigarette-mimicking products. Introducing e-cigarettes into clean air environments may result in population harm if use of the product reinforces the act of smoking as socially acceptable, and/or if use undermines the effects of smoke-free policies on smoking cessation. Strong smoke-free policies are an integral part of the recognized and proven comprehensive global tobacco control policies.

RESEARCH NEEDS

There are several areas in which additional research would be useful for understanding the effects of e-cigarettes that could guide policymakers and health professionals:

- Systematic surveillance is critical to monitoring trends in use that will determine the net impact of the products on tobacco use.
- Longitudinal studies to determine trajectories of use to obtain better data on patterns of initiation, the stability of dual use behavior and effect on cessation rates and relapse of both conventional cigarettes and e-cigarettes as actually used in the real world.

- Randomized trials of e-cigarettes as part of supervised smoking cessation programs.
- Assessment of the impact of smoking reduction in the context of dual use as a way to promote long-term cigarette abstinence.
- Short- and long-term studies on the health effects of e-liquid aerosol in humans.
- Effects of short- and long-term exposure to fine particles by e-cigarette aerosol
- How e-cigarette advertising is perceived by all segments of the population – youth, naïve nicotine users, smokers and former smokers, both recent and long-term – and how advertising exposure impacts behaviors.
- Studies of the engineering design and functioning of e-cigarettes, including impact of heating temperature, battery size, puffing characteristics and e-liquid composition on the nature of the aerosol and systemic exposure of users to aerosol constituents.
- Policy research on the impact of the different approaches being taken around the world on conventional smoking, e-cigarette use, and the overall burden of nicotine-induced disease.
- Studies of the nature of the reinforcing effects of e-cigarettes, including influences of nicotine content, flavorants and other constituents, and abuse liability.
- Studies to determine optimal nicotine delivery to support transition away from tobacco products but avoid recruitment of new users.

While important research questions, the evidence summarized in this report is adequate to guide policy makers in responding to e-cigarettes. These policies can be refined over time as more research becomes available.

POLICY RECOMMENDATIONS

As noted above, e-cigarettes deliver lower levels of most of the toxins found in cigarette smoke; the main impediment to e-cigarettes making a contribution to reducing the harm caused by cigarette smoking arise from the effects on youth, dual use (among both adults and youth) and renormalization of smoking behavior. The ultimate effect of e-cigarettes on public health will depend on what happens to the tobacco product market, particularly with combustible products. There are conditions in which e-cigarettes could be a public health benefit on a population level:

- No initiation with e-cigarettes

- No youth use of e-cigarettes
- Cigarette smokers switch completely and not continue a dual use pattern of consumption
- Use of e-cigarettes does not negatively impact current cigarette denormalization efforts
- E-cigarettes do not deliver harmful substances besides nicotine
- No youth-oriented marketing
- No secondhand delivery of nicotine

As of November 2013 this situation did not exist. This situation could change if the following policies were implemented:

- Prohibit the use of e-cigarettes anywhere that use of conventional cigarettes is prohibited
- E-cigarettes should not be sold to anyone who cannot legally buy cigarettes or sold in any venues where sale of conventional cigarettes is prohibited
- Ban conventional cigarettes or regulate nicotine to non-addictive levels
- Apply the same restrictions on e-cigarette advertising and promotion as apply to conventional cigarettes
- Ban the use of characterizing flavors in e-cigarettes
- E-cigarettes should not be co-branded with cigarettes or marketed in a way that promotes dual use
- Prohibit claims that e-cigarettes are effective smoking cessation aids until such time as there is convincing scientific evidence that such claims are true for e-cigarettes as they are actually used in the general population
- Regulate e-cigarettes to set standards for product performance in order to minimize risks to users and bystanders

Should these policies be put in place, it is possible that current conventional smokers who will not quit nicotine would shift to e-cigarettes without major dual use or youth initiation to nicotine addiction with e-cigarettes. Absent this change in the policy environment it is reasonable to assume that the behavior patterns that have been observed for e-cigarettes will persist, which makes it unlikely that they will on balance contribute to reducing the harm of tobacco use and could increase harm by perpetuating the life of conventional cigarettes.

Because the product, the market, and the associated scientific evidence surrounding e-cigarettes are all evolving rapidly:

- All legislation and regulations related to e-cigarettes should allow for flexibility to adapt regulations expeditiously in response to new science, including evaluation of different models for regulating e-cigarettes, as it accumulates
- No country or subnational jurisdiction should be compelled to permit the sale of e-cigarettes
- Legislation and regulations regarding e-cigarettes need to take into account the fact that, unlike conventional cigarettes and other tobacco products and medicinal nicotine replacement therapies, e-cigarettes can be altered by users to change the nicotine delivery and be used to deliver other drugs
- There should be transparency in the role of the e-cigarette and tobacco companies in advocating for and against legislation and regulation, both directly and through third parties
- FCTC Article 5.3 should be respected when developing and implementing legislation and regulations related to e-cigarettes

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